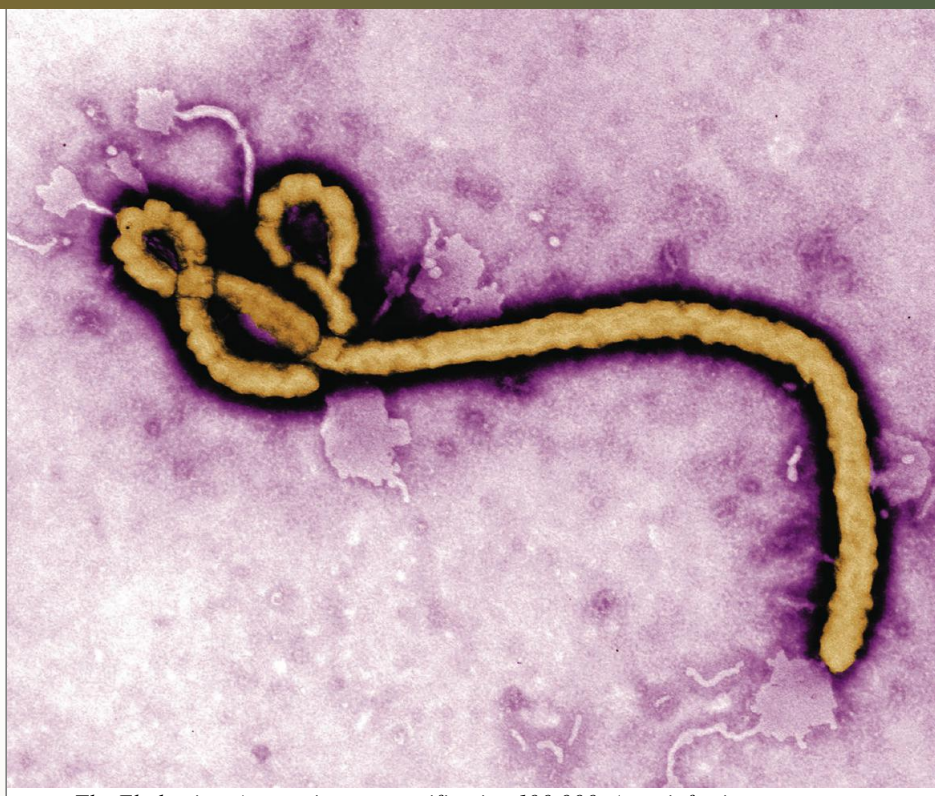
The Immune System

CHAPTER 18



The Ebola virus (approximate magnification 100,000×), an infectious pathogen in humans.

You have learned about numerous organ systems in previous chapters, some of which, such as the digestive system, consist of anatomically connected organs. By contrast, the **immune system** consists of a diverse collection of disease-fighting cells found in the blood and lymph and in tissues and organs throughout the body. **Immunology** is the study of the physiological defenses by which the body (the host) recognizes itself from nonself (foreign matter). In the process, foreign matter, both living and nonliving, is destroyed or rendered harmless. In distinguishing self from nonself, immune defenses (1) protect against infection by **pathogens**—viruses and **microbes** including bacteria, fungi, and eukaryotic parasites; (2) isolate or remove foreign substances; and (3) destroy cancer cells that arise in the body, a function known as **immune surveillance**.

Immune defenses, or immunity, can be classified into two categories, innate and adaptive, which interact with each other. **Innate immune responses** defend against foreign substances or cells without having to recognize their specific identities. The mechanisms of protection used by these defenses are not unique to the particular foreign substance or cell. For this reason, innate immune responses are also known as nonspecific immune responses. **Adaptive immune responses** depend upon specific recognition by lymphocytes of the substance or cell to be attacked. For this reason, adaptive immune

responses are also called specific immune responses. Innate and adaptive immune responses function together. For example, components of innate immunity provide instructions that activate the cells that carry out adaptive responses.

The pathogens with which we will be most concerned in this chapter are bacteria and viruses. These are the dominant infectious agents in the United States and other industrialized nations. On a global basis, however, infections with parasitic eukaryotic organisms are responsible for a huge amount of illness and death. For example, several hundred million people now have malaria, a disease caused by infection with protists of the *Plasmodium* genus.

Bacteria are unicellular organisms that have an outer coating (the cell wall) in addition to a plasma membrane but no intracellular membrane-bound organelles. Bacteria can damage tissues at the sites of bacterial replication, or they can release toxins that enter the blood and disrupt physiological functions in other parts of the body.

Viruses—such as the Ebola virus depicted in the chapter-opening photo—are essentially nucleic acids surrounded by a protein coat. Unlike bacteria, viruses are not living organisms and lack the enzyme machinery for metabolism and the ribosomes essential for protein synthesis. Consequently, they cannot multiply by themselves but must exist inside other cells and use the molecular apparatuses of those cells. The viral nucleic acid directs the host cell to synthesize the proteins required for viral replication, with the required nucleotides and energy sources also supplied by the host cell. The effect of viral habitation and replication within a cell depends on the type of virus. After entering a cell, some viruses (the common cold virus, for example) multiply rapidly, kill the cell, and then move on to other cells. Other viruses, such as the one that causes genital herpes, can lie dormant in infected cells before suddenly undergoing the rapid replication that causes cell damage. Finally, certain viruses can transform their host cells into cancer cells.

Of the general principles of physiology described in Chapter 1, one that is fundamental to the immune system is the principle that homeostasis is essential for health and survival. Indeed, illness can often be thought of as a disruption in one or more homeostatic processes. A key way in which the immune system regulates homeostasis is via cell-to-cell signaling. As you read this chapter, therefore, consider also how this general principle of physiology applies: Information flow between cells, tissues, and organs is an essential feature of homeostasis and allows for integration of physiological processes. ■

18.1 Cells and Secretions Mediating Immune Defenses

We begin our survey of the human immune system with an overview of some of the key cells and cellular secretions that make up the innate and adaptive immune responses. The appearance and production of immune cells were introduced in Section A of Chapter 12 and should be reviewed at this time.

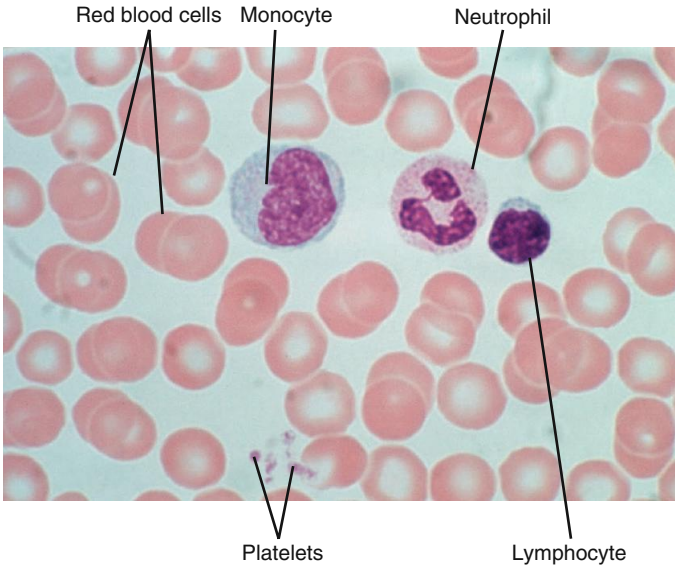
Immune Cells

The cells of the immune system are the various types of white blood cells collectively known as **leukocytes;** representative histological appearances of some of these can be seen in the human blood smear in **Figure 18.1** (also refer back to Figure 12.2). Unlike erythrocytes, leukocytes can leave the circulatory system to enter the tissues where they function. Leukocytes can be classified into two groups based upon the type of stem cell from which they differentiate: myeloid cells and lymphoid cells.

The myeloid cells include the **neutrophils, basophils, eosinophils,** and **monocytes.** Their functions will be described later. Other immune cells derived from myeloid precursor cells include **macrophages;** these are found in virtually all organs and tissues, their structures varying somewhat from location to location. They are derived from monocytes that pass through the walls of blood vessels to enter the tissues and transform into macrophages. In keeping with one of their major functions, the engulfing of particles and pathogens by **phagocytosis** (the form of endocytosis whereby a cell engulfs and usually destroys particulate matter), macrophages are strategically placed where they will encounter their targets. For example, they are found in large numbers in the various epithelia in contact with the external environment, such as the skin and internal surfaces of respiratory and digestive system tubes. In several organs, they line the vessels through which blood or lymph flows.

There are also populations of myeloid-derived cells that are not macrophages but exert certain macrophage-like functions such as phagocytosis. These are termed **dendritic cells** because of the characteristic extensions from their plasma membranes at certain stages of their life cycle (not to be confused with the dendrites found on neurons). They are highly motile and are found scattered in almost all tissues but particularly at sites where the internal and external environments meet, such as the digestive tract. Upon activation, dendritic cells process phagocytosed pathogens and migrate through the lymphatic vessels to secondary lymphoid organs where they activate resident immune cells there.

Mast cells are found throughout connective tissues, particularly beneath the epithelial surfaces of the body. They are derived



AP|R **Figure 18.1** A light micrograph of a human blood smear showing the histological appearance of a few types of leukocytes along with numerous red blood cells and platelets.

from the differentiation of a unique set of bone marrow myeloid cells that have entered the blood and then left the blood vessels to enter connective tissue, where they differentiate and undergo cell division. Consequently, mature mast cells—unlike basophils, with which they share many characteristics—are not normally found in the blood. The most striking anatomical feature of mast cells is their very large number of cytosolic vesicles, which secrete locally acting chemicals such as **histamine,** an amine derived from the amino acid histidine. Among its many functions, histamine helps stimulate the innate immune response.

The second group of leukocytes, lymphoid cells, include several types of **lymphocytes,** including **B lymphocytes** (**B cells**), **T lymphocytes** (**T cells**), **natural killer** (**NK**) **cells,** and **plasma cells.** Plasma cells are not really a distinct cell type but differentiate from B lymphocytes during immune responses. The major functions of all of these cells will be described shortly.

The sites of production and functions of the major immune cells are briefly listed in **Table 18.1** for reference and will be described in subsequent sections. For now, we emphasize two points. First, lymphocytes serve as recognition cells in adaptive immune responses and are essential for all aspects of these responses. Second, neutrophils, monocytes, macrophages, and dendritic cells have a variety of activities, but particularly important is their ability to secrete inflammatory mediators and to function as **phagocytes.** A phagocyte denotes any cell capable of phagocytosis.

Immune Cell Secretions: Cytokines

The cells of the immune system secrete a multitude of protein messengers that regulate host cell division (mitosis) and function in both innate and adaptive immune responses. **Cytokine** is the collective term for these messengers, each of which has its own unique name. Cytokines are produced not by distinct specialized glands but, rather, by a variety of individual cells. The great majority of their actions occur at the site at which they are secreted, the cytokine acting as an autocrine or paracrine substance. In some cases, however, the cytokine circulates in the blood to exert hormonal effects on distant organs and tissues involved in host defenses.

Cytokines link the components of the immune system together. They are the chemical communication network that allows different immune system cells to "talk" to one another. This is called *cross talk,* and it is essential for the precise timing of the functions of the immune system. Most cytokines are secreted by more than one type of immune system cell and also by certain nonimmune cells (for example, by endothelial cells and fibroblasts). This often produces cascades of cytokine secretion, in which one cytokine stimulates the release of another, and so on. Any given cytokine may exert actions on an extremely broad range of target cells. For example, the cytokine interleukin 2 influences the function of most cells of the immune system. There is great redundancy in cytokine action; that is, different cytokines can have very similar effects.

This chapter will be limited to a discussion of a few of the important cytokines and their major functions, which are summarized for reference in **Table 18.2**.

18.2 Innate Immune Responses

Innate immune responses defend against foreign cells or matter without having to recognize specific identities. These defenses recognize some *general* molecular property marking the invader as foreign. One common set of identity tags is often found in particular classes of carbohydrates or lipids that are in microbial cell walls. Plasma membrane receptors on certain immune cells, as well as a variety of circulating proteins (particularly a family of proteins called complement), can bind to these carbohydrates and lipids at crucial steps in innate responses. This use of a system based on carbohydrate and lipid for detecting the presence of foreign cells is a key feature that distinguishes innate responses from adaptive ones, which recognize foreign cells mainly by specific proteins the foreign cells produce.

The innate immune responses include the response to injury or infection known as *inflammation,* and a family of antiviral proteins called interferons. Before turning to those responses, however, we briefly describe how the body surface itself presents a barrier to infection.

Defenses at Body Surfaces

Though not immune *responses,* the first lines of defense against pathogens are the barriers offered by surfaces exposed to the external environment, because very few pathogens can penetrate the intact skin. Other specialized surface defenses are the hairs at the entrance to the nose and the cough and sneeze reflexes. The various skin glands, salivary glands, and lacrimal (tear) glands have a more active function in immunity by secreting antimicrobial chemicals. These may include antibodies; enzymes such as lysozyme, which destroys bacterial cell walls; and an iron-binding protein called lactoferrin, which prevents bacteria from obtaining the iron they require to function properly.

The mucus secreted by the epithelial linings of the respiratory and upper gastrointestinal tracts also contains antimicrobial chemicals; more importantly, however, mucus is sticky. Particles that adhere to it are prevented from entering the blood. They are either swept by ciliary action up into the pharynx and then swallowed, as occurs in the upper respiratory tract, or are phagocytosed by macrophages in the various linings. Finally, the acid secretion of the stomach can also kill pathogens, although some bacteria can survive to colonize the large intestine where they provide beneficial gastrointestinal functions.

Inflammation

Inflammation is the local response to infection or injury. The functions of inflammation are to destroy or inactivate foreign invaders and to set the stage for tissue repair. The key mediators are the cells that function as phagocytes. As noted earlier, the most important phagocytes are neutrophils, macrophages, and dendritic cells.

In this section, inflammation is described as it occurs in the innate responses induced by the invasion of pathogens. Most of the same responses can be elicited by a variety of other injuries—cold, heat, and trauma, for example. Moreover, we will see later that inflammation accompanies many *adaptive* immune responses in which the inflammation becomes amplified.

The sequence of local events in a typical innate inflammatory response to a bacterial infection—one caused, for example, by a cut with a bacteria-covered splinter—is summarized in **Figure 18.2**. The familiar signs of tissue injury and inflammation are local redness, swelling, heat, and pain.

The events of inflammation that underlie these signs are induced and regulated by a large number of chemical mediators, some of which are summarized for reference in **Table 18.3** (not all of these will be described in this chapter). Note in this table

TABLE 18.1 Cells Mediating Immune Responses

Name	Site Produced	Functions
Leukocytes (white blood cells)		
Neutrophils	Bone marrow	Phagocytosis Release chemicals involved in inflammation (vasodilators, chemotaxins, etc.)
Basophils	Bone marrow	Carry out functions in blood similar to those of mast cells in tissues (see below)
Eosinophils	Bone marrow	Destroy multicellular parasites Participate in immediate hypersensitivity reactions
Monocytes	Bone marrow	Carry out functions in blood similar to those of macrophages in tissues (see below) Enter tissues and transform into macrophages
Lymphocytes	Mature in bone marrow (B cells and NK cells) and thymus (T cells); activated in peripheral lymphoid organs	Serve as recognition cells in specific immune responses and are essential for all aspects of these responses
B cells		Initiate antibody-mediated immune responses by binding specific antigens to the B cell's plasma membrane receptors, which are immunoglobulins Upon activation, are transformed into plasma cells, which secrete antibodies Present antigen to helper T cells
Cytotoxic T cells (CD8 cells)		Bind to antigens on plasma membrane of target cells (virus-infected cells, cancer cells, and tissue transplants) and directly destroy the cells
Helper T cells (CD4 cells)		Secrete cytokines that help to activate B cells, cytotoxic T cells, NK cells, and macrophages
NK cells		Bind directly and nonspecifically to virus-infected cells and cancer cells and kill them Function as killer cells in antibody-dependent cellular cytotoxicity (ADCC)
Plasma cells	Peripheral lymphoid organs; differentiate from B cells during immune responses	Secrete antibodies
Macrophages	Bone marrow; reside in almost all tissues and organs; differentiate from monocytes	Phagocytosis Extracellular killing via secretion of toxic chemicals Process and present antigens to helper T cells Secrete cytokines involved in inflammation, activation and differentiation of helper T cells, and systemic responses to infection or injury (the acute phase response)
Dendritic cells	Almost all tissues and organs; microglia in the central nervous system	Phagocytosis, antigen presentation
Mast cells	Bone marrow; reside in almost all tissues and organs; differentiate from bone marrow cells	Release histamine and other chemicals involved in inflammation

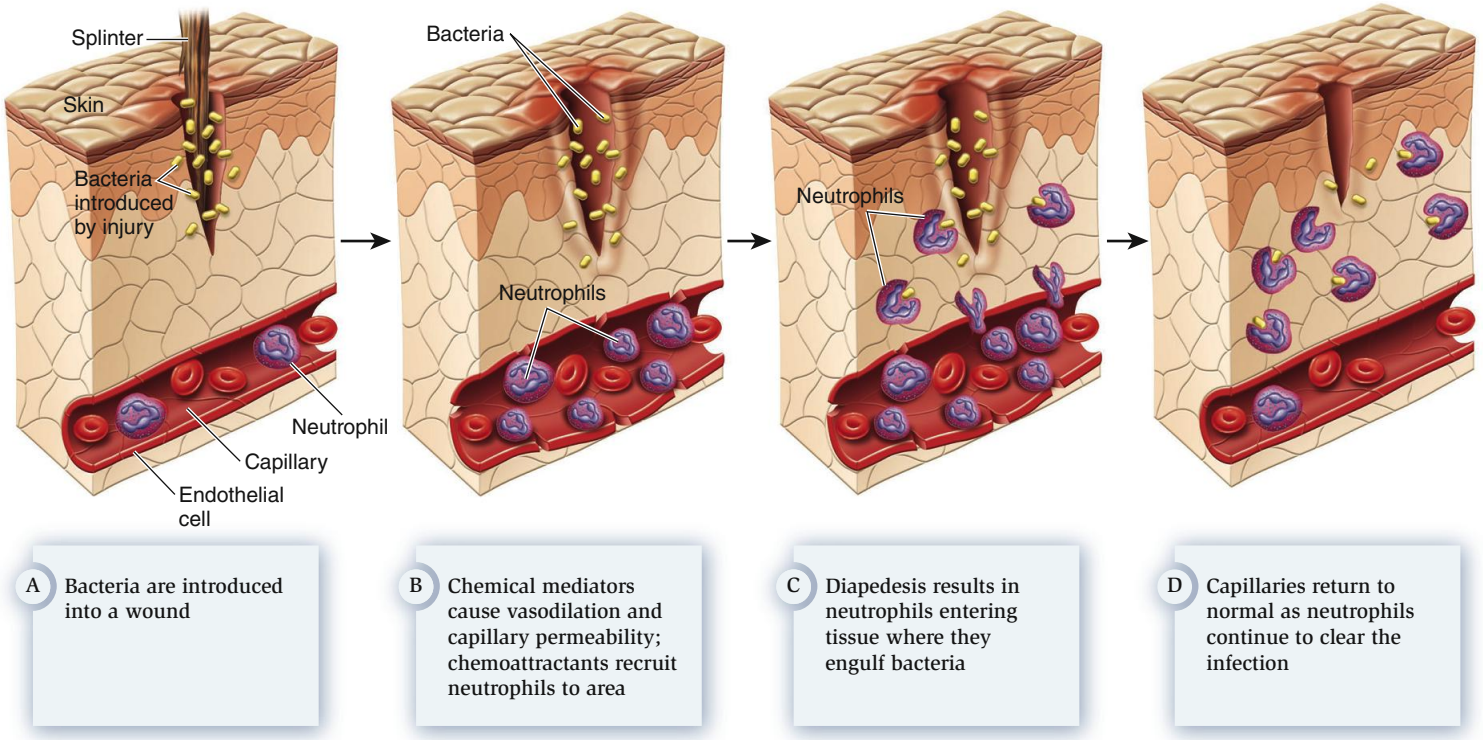
TABLE 18.2 Features of Selected Cytokines

Cytokine	Source	Target Cells	Major Functions
Interleukin 1, tumor necrosis factor-α, and interleukin 6	Antigen-presenting cells such as macrophages	Helper T cells; certain brain cells; numerous systemic cells	Stimulate IL-2 receptor expression; induce fever; stimulate systemic responses to inflammation, infection, and injury
Interleukin 2	Most immune cells	Helper T cells; cytotoxic T cells; NK cells; B cells	Stimulate proliferation Promote conversion to plasma cells
Interferons (type I)	Most cell types	Most cell types	Stimulate cells to produce antiviral proteins (innate response)
Interferons (type II)	NK cells and activated helper T cells	NK cells and macrophages	Stimulate proliferation and secretion of cytotoxic compounds
Chemokines	Damaged cells, including endothelial cells	Neutrophils and other leukocytes	Facilitate accumulation of leukocytes at sites of injury and inflammation

that some of these mediators are cytokines. Any given event of inflammation, such as vasodilation, may be induced by multiple mediators. Moreover, any given mediator may induce more than one event. Based on their origins, the mediators fall into two general categories: (1) polypeptides (for example, a group known as **kinins**; see Chapter 12) generated in the infected area by enzymatic actions on proteins that circulate in the plasma and (2) substances secreted into the extracellular fluid from cells that either already exist in the infected area (injured cells or mast cells, for example) or enter it during inflammation (neutrophils, for example).

Let us now go step by step through the process summarized in Figure 18.2, assuming that the bacterial infection in our example is localized to the tissue just beneath the skin. If the invading bacteria enter the blood or lymph, then similar inflammatory responses would take place in any other tissue or organ reached by the blood-borne or lymph-borne microorganisms.

Vasodilation and Increased Permeability to Protein A variety of chemical mediators dilate most of the microcirculation vessels in an infected and/or damaged area.



AP|R **Figure 18.2** The local inflammatory events occurring in response to a wound.

TABLE 18.3 Some Important Local Inflammatory Mediators

Mediator	Source	Selected Functions
Kinins	Generated from enzymatic action on plasma proteins	Dilate vessels; increase vascular permeability
Complement	Generated from enzymatic action on plasma proteins	Opsonizes or directly kills pathogens
Products of blood clotting	Generated from enzymatic action on plasma proteins	Tissue repair
Histamine	Secreted by mast cells and injured cells	Increases vascular permeability
Eicosanoids	Secreted by many cell types including myeloid cells	Vasodilation; trigger sensation of pain; induce fever
Platelet-activating factor	Secreted by many cell types including myeloid cells, endothelial cells, platelets, damaged tissue cells	Amplifies many aspects of inflammation; helps in platelet aggregation
Cytokines, including chemokines	Secreted by activated immune cells, monocytes, macrophages, neutrophils, lymphocytes, and several nonimmune cell types, including endothelial cells and fibroblasts	Chemoattraction for leukocytes
Lysosomal enzymes, nitric oxide, and other oxygen-derived substances	Secreted by injured cells, neutrophils, and macrophages	Destroy pathogen macromolecules

The mediators also cause the local capillaries and venules to become permeable to proteins by inducing their endothelial cells to contract, opening spaces between them through which the proteins can move.

The adaptive value of these vascular changes is twofold: (1) The increased blood flow to the inflamed area (which accounts for the redness and warmth) increases the delivery of proteins and leukocytes; and (2) the increased permeability to protein ensures that the plasma proteins that participate in inflammation—many of which are normally restrained by the intact endothelium—can gain entry to the interstitial fluid.

By mechanisms described in Chapter 12 (see Figure 12.45), the vasodilation and increased permeability to protein, however, cause net filtration of plasma into the interstitial fluid and the development of edema. This accounts for the swelling in an inflamed area, which is simply a consequence of the changes in the microcirculation and has no known adaptive value of its own.

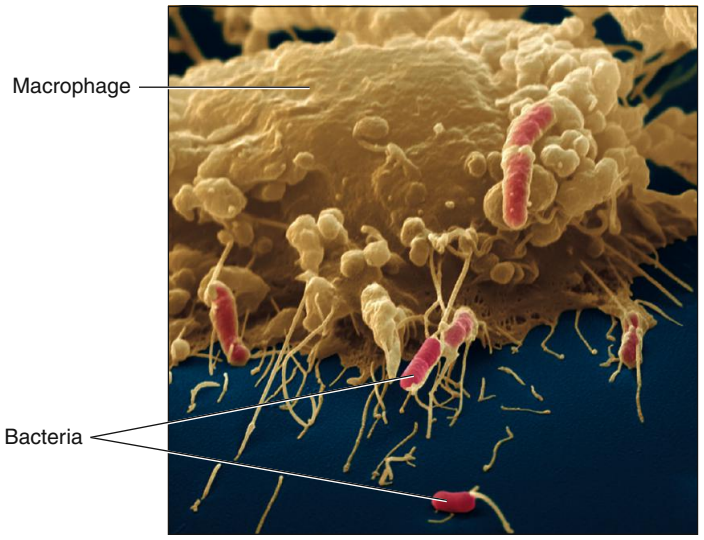
Chemotaxis With the onset of inflammation, circulating neutrophils begin to move out of the blood across the endothelium of capillaries and venules to enter the inflamed area (see Figure 18.2). This multistage process is known as **chemotaxis.** It involves a variety of protein and carbohydrate adhesion molecules on both the endothelial cell and the neutrophil. It is regulated by messenger molecules released by cells in the injured area, including the endothelial cells. These messengers are collectively called **chemoattractants** (also called **chemotaxins** or chemotactic factors).

In the first stage, the neutrophil is loosely tethered to the endothelial cells by certain adhesion molecules. This event, known as **margination,** occurs as the neutrophil rolls along the vessel surface. In essence, this initial reversible event exposes the neutrophil to chemoattractants being released in the injured area. These chemoattractants act on the neutrophil to induce the rapid appearance of another class of adhesion molecules in its plasma membrane—molecules that bind tightly to their matching molecules on the surface of endothelial cells. As a result, the neutrophils collect along the site of injury rather than being washed away with the flowing blood.

In the next stage, known as **diapedesis,** a narrow projection of the neutrophil is inserted into the space between two endothelial cells, and the entire neutrophil squeezes through the endothelial wall and into the interstitial fluid. In this way, huge numbers of neutrophils migrate into the inflamed area. Once in the interstitial fluid, neutrophils follow a chemotactic gradient and migrate toward the site of tissue damage (chemotaxis). This occurs because pathogen-stimulated innate immune cells release chemoattractants. As a result, neutrophils tend to move toward the pathogens that entered into an injured area.

Movement of leukocytes from the blood into the damaged area is not limited to neutrophils. Monocytes follow later; once in the tissue, they undergo anatomical and functional changes that transform them to macrophages. As we will see later, lymphocytes undergo chemotaxis in adaptive immune responses, as do basophils and eosinophils under certain conditions.

An important aspect of the multistep chemotaxis process is that it provides selectivity and flexibility for the migration of the various leukocyte types. Multiple adhesion molecules that are relatively distinct for the different leukocytes are controlled by different sets of chemoattractants. Particularly important in this regard are those cytokines that function as chemoattractants for distinct subsets of leukocytes. For example, one type of cytokine stimulates the chemotaxis of neutrophils, whereas another stimulates that of eosinophils. Consequently, subsets of leukocytes can be stimulated to enter particular tissues at designated times during an inflammatory response, depending on the type of invader and the cytokine response it induces. The various cytokines that have chemoattractant actions are collectively referred to as **chemokines.**



AP|R **Figure 18.3** Macrophage contacting bacteria and preparing to engulf them.

Killing by Phagocytes Once neutrophils and other leukocytes arrive at the site of an infection, they begin the process of destroying invading pathogens by phagocytosis (**Figure 18.3**). The initial step in phagocytosis is contact between the surfaces of the phagocyte and pathogen. One of the major triggers for phagocytosis during this contact is the interaction of phagocyte surface receptors with certain carbohydrates or lipids in the pathogen or microbial cell walls. Contact is not always sufficient to trigger engulfment, however, particularly with bacteria that are surrounded by a thick, gelatinous capsule. Instead, chemical factors produced by the body can bind the phagocyte tightly to the pathogen and thereby enhance phagocytosis. Any substance that does this is known as an **opsonin,** from the Greek word that means "to prepare for eating."

As a phagocyte engulfs a bacterium, for example (**Figure 18.4**), the internal, microbe-containing sac formed in this step is called a **phagosome.** A layer of plasma membrane separates the microbe from the cytosol of the phagocyte. The phagosome membrane then makes contact with one of the phagocyte's lysosomes, which is filled with a variety of hydrolytic enzymes. The membranes of the phagosome and lysosome fuse, and the combined vesicles are now called a **phagolysosome.** Inside the phagolysosome, the lysosomal enzymes break down the microbe's macromolecules. In addition, other enzymes in the phagolysosome membrane produce **nitric oxide** as well as **hydrogen peroxide** and other oxygen derivatives, all of which are extremely destructive to the microbe's macromolecules.

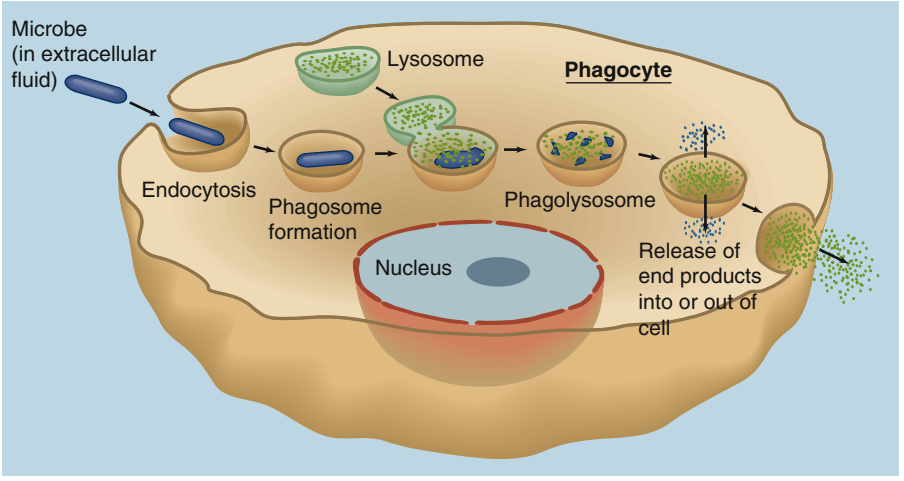
Such intracellular destruction is not the only way phagocytes can kill pathogens (**Figure 18.5**). The phagocytes also release antimicrobial substances into the extracellular fluid, where these chemicals can destroy the pathogens without prior phagocytosis. Some of these substances (for example, nitric oxide) secreted into the extracellular fluid also function as inflammatory mediators. Thus, when phagocytes enter the area and encounter pathogens, positive feedback mechanisms cause inflammatory mediators, including chemokines, to be released that bring in more phagocytes.

Complement The family of plasma proteins known as **complement** provides another means for extracellular killing of pathogens without prior phagocytosis. Certain complement proteins are always circulating in the blood in an inactive state. Upon activation of a complement protein in response to infection or cell damage, a cascade occurs so that this active protein activates a second complement protein, which activates a third, and so on. In this way, multiple active complement proteins are generated in the extracellular fluid of the infected area from inactive complement molecules that have entered from the blood. Because this system consists of at least 30 distinct proteins, it is extremely complex, and we will identify the functions of only a few of the individual complement proteins.

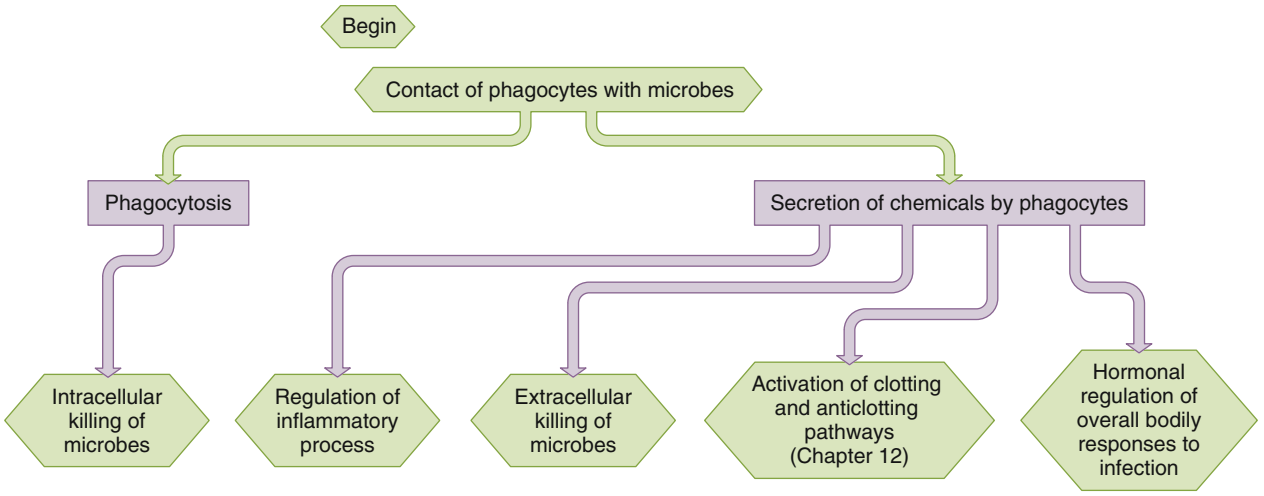
The central protein in the complement cascade is C3. Activation of C3 initiates a series of events. The first is the deposition of **C3b,** a component of C3, on the microbial surface. C3b acts as an opsonin that is recognized by receptors on phagocytes targeting the pathogen for destruction, as shown for a bacterium in **Figure 18.6**. C3b is also part of a proteolytic enzyme that amplifies the complement cascade and leads to the downstream development of a multiunit protein called the **membrane attack complex** (**MAC**)**.** The MAC embeds itself in the bacterial plasma membrane (or virus protein coat) and forms porelike channels in the membrane, making it leaky. Water, ions, and small molecules enter the microbe, which disrupts the intracellular environment and kills the microbe.

In addition to supplying a means for direct killing of pathogens, the complement system serves other important functions in inflammation (**Figure 18.7**). Some of the activated complement molecules along the cascade cause, either directly or indirectly (by stimulating the release of other inflammatory mediators), vasodilation, increased microvessel permeability to protein, and chemotaxis.

As we will see later, antibodies, a class of proteins secreted by certain lymphocytes, are required to activate the very first complement protein, **C1,**



AP|R **Figure 18.4** Phagocytosis and intracellular destruction of a microbe. After destruction has taken place in the phagolysosome, the end products are released to the outside of the cell by exocytosis or used by the cell for its own metabolism.



AP|R **Figure 18.5** Functions of phagocytes in innate immune responses. Hormonal regulation of overall bodily responses to infection, partly addressed in Chapter 11, will also be discussed later in this chapter.

in the full sequence known as the **classical complement pathway.** However, lymphocytes are not involved in *nonspecific* inflammation, our present topic. How, then, is the complement sequence initiated during nonspecific inflammation? The answer is that there are at least two other means of activating complement, including one called the **alternative complement pathway,** one that is not antibody dependent and that bypasses C1. The alternative pathway is initiated as the result of interactions between carbohydrates on the surface of the microbes and inactive complement molecules beyond C1. These interactions lead to the formation of active C3b, the opsonin described in the previous paragraph, and the activation of the subsequent complement molecules in the pathway.

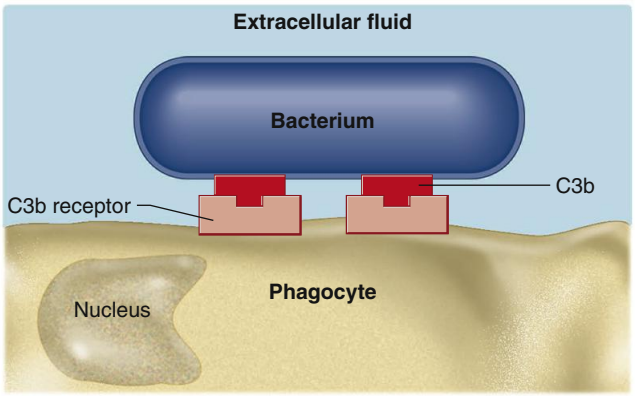


Figure 18.6 Function of complement C3b as an opsonin. One portion of C3b binds nonspecifically to carbohydrates on the surface of the bacterium, whereas another portion binds to specific receptor sites for C3b on the plasma membrane of the phagocyte. The structures are not drawn to scale.

PHYSIOLOGICAL INQUIRY

- In earlier chapters, you learned some of the characteristics of ligand-receptor interactions (e.g., see Figures 3.26 through 3.31). After reviewing Figures 3.26-3.31, hypothesize what general features may make the C3b receptor suitable for binding C3b but not other ligands.

Answer can be found at end of chapter.

However, not all microbes have a surface conducive to initiating the alternative pathway.

Other Opsonins in Innate Responses

In addition to complement C3b, other plasma proteins can bind nonspecifically to carbohydrates or lipids in the cell wall of microbes and facilitate opsonization. Many of these—for example, **C-reactive protein**—are produced by the liver and are always found at some concentration in the plasma. Their production and plasma concentrations, however, are greatly increased during inflammation.

Tissue Repair

The final stage of inflammation is tissue repair. Depending upon the tissue involved, multiplication of organ-specific cells by cell division may or may not occur during this stage. For example, liver cells multiply but skeletal muscle cells do not. In any case, fibroblasts (a type of connective-tissue cell) that reside in the area divide rapidly and begin to secrete large quantities of collagen, and blood vessel cells proliferate in a process called angiogenesis. All of these events are brought about by chemical mediators, particularly a group of locally produced growth factors. Finally, remodeling occurs as the healing process winds down. The final repair may be imperfect, leaving a scar.

Interferons

Interferons are cytokines and are grouped into two families called type I and type II interferons. The **type I interferons** include several proteins that nonspecifically inhibit viral replication inside host cells. In response to infection by a virus, most cell types produce these interferons and secrete them into the extracellular fluid. The type I interferons then bind to plasma membrane receptors on the secreting cell and on other cells, whether they are infected or not (**Figure 18.8**). This binding triggers the synthesis of dozens of different antiviral proteins by the cell. If the cell is already infected or eventually becomes infected, these proteins interfere with the ability of the viruses to replicate. Type I interferons also function in the killing of tumor cells and in generating fever during an infection.

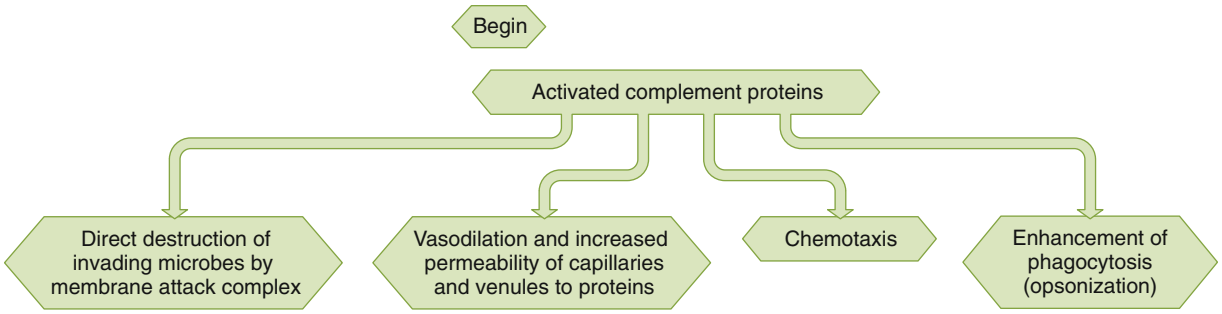


Figure 18.7 Functions of complement proteins. The effects on blood vessels and chemotaxis are exerted both directly by complement molecules and indirectly via other inflammatory mediators (for example, histamine) that are released by the complement molecules.

The actions of type I interferons just described are not specific. Many kinds of viruses induce interferon synthesis, and interferons in turn can inhibit the multiplication of many kinds of viruses. (Recent research, however, has revealed that type I interferons also influence the nature of certain aspects of the adaptive immune response.)

The one member of the **type II interferons**—called **interferon-gamma**—is produced by immune cells. This interferon potentiates some of the actions of type I interferons, enhances the bacteria-killing activity of macrophages, and acts as a chemokine in the inflammatory process.

Toll-Like Receptors

At the beginning of this section, we mentioned that innate immunity often depends upon an immune cell recognizing some general molecular feature common to many types of pathogens. These features are called **pathogen-associated molecular patterns** (**PAMPs**). We now ask, How is that recognition accomplished? In 1985, researchers interested in how embryonic animals differentiate into mature organisms discovered a protein they named Toll (now called Toll-1) that was required for the proper dorsoventral orientation of developing fruit flies. In 1996, however, it was discovered that Toll-1 also conferred upon *adult* fruit flies the ability to fight off fungal infections, a discovery that was recognized in 2011 with the awarding of the Nobel Prize in Physiology or Medicine. Since that time, a family of Toll proteins has been discovered in animals from nematodes to mammals, including humans, expressed in the plasma and endosomal membranes of macrophages and dendritic cells, among others. One function of these proteins is to recognize and bind to highly conserved molecular features associated with pathogens (that is, PAMPs); these include lipopolysaccharide and other lipids and carbohydrates, viral and bacteria nucleic acids, and a protein found in the flagellum common to many bacteria. When binding of one of these ligands occurs on the plasma membrane, second messengers are generated within the immune cell, which leads to secretion of several cytokines that act as inflammatory mediators, described in Table 18.3, such as IL-1, IL-12, and TNF-α. These in turn stimulate the activity of immune cells involved in the innate immune response. Some of these signals also activate cells involved in the adaptive immune response. Because many of the Toll proteins are plasma-membrane-bound, bind to extracellular ligands, and induce second-messenger formation, they are referred to as *receptors;* the family of proteins is known as **Toll-like receptors** (**TLRs**). Despite this, not all TLRs generate intracellular signals when bound to a ligand; some TLRs induce attachment of a microbe to a macrophage, for example, and thereby its phagocytosis and subsequent destruction.

TLRs belong to a family of proteins called **pattern-recognition receptors** (**PRRs**), all of which recognize and bind to a wide variety of ligands found in many pathogens. These ligands have conserved molecular features that are generally considered to be vital to the survival or function of that pathogen. It is

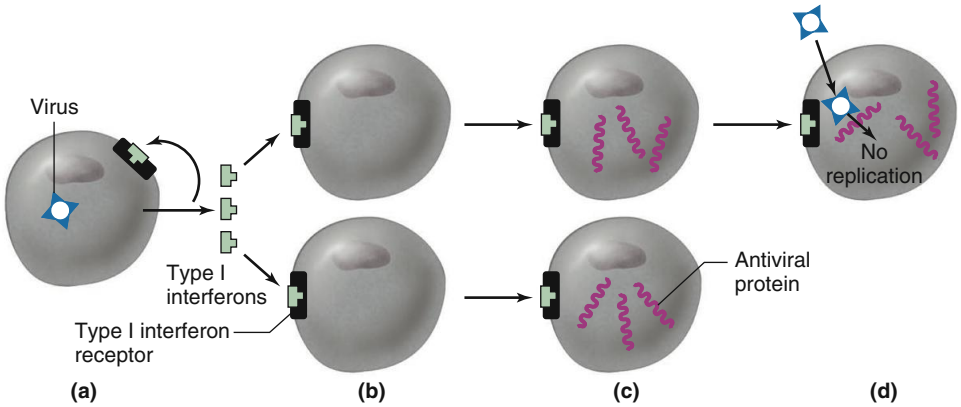


Figure 18.8 Function of type I interferon in preventing viral replication. (a) Most cell types, when infected with viruses, secrete type I interferons, which enter the interstitial fluid and (b) bind to type I interferon receptors on the secreting cells themselves (autocrine function) and adjacent cells (paracrine function). In addition, some type I interferons enter the blood and bind to type I interferon receptors on far-removed cells (endocrine function). (c) The binding of type I interferons to their receptors induces the synthesis of proteins that (d) inhibit viral replication should viruses enter the cell.

PHYSIOLOGICAL INQUIRY

- Are there other examples besides immune secretions in which a single substance may act as both an endocrine and paracrine substance? (*Hint:* Refer back to Chapters 11, 15, and 17 for help if necessary.)

Answer can be found at end of chapter.

estimated that as many as a thousand such molecular features are recognized by PRRs.

The importance of TLRs in mammals has been demonstrated in mice with a mutated form of one member of the family called Toll-4. These mice are hypersensitive to the effects of injections with the cell wall molecule lipopolysaccharide (to mimic a bacterial infection) and are less able to ward off bacterial infection. In humans, recent studies suggest that certain naturally occurring variants in a specific TLR are associated with increased risk of certain diseases.

TLRs are currently an active area of investigation among biologists because of their importance as developmental factors in invertebrates and their immune significance in some adult invertebrates and possibly all vertebrates. Certain domains of these receptors have even been identified in plants, where they seem also to be involved in disease resistance. Therefore, TLRs may be among the first mechanisms to ever evolve in living organisms to protect against pathogen infection.

18.3 Adaptive Immune Responses

Because of the complexity of adaptive immune responses, the following overview is presented as a brief orientation before more detail is given regarding the various components of the response.

Overview

Lymphocytes are the essential cells in adaptive immune responses. Unlike innate response mechanisms, lymphocytes must recognize the specific foreign material to be attacked. Any molecule that can trigger an adaptive immune response against itself or the cell bearing it is called an **antigen.** Technically speaking, an antigen is any molecule, regardless of its structure, location or function, that binds to an antibody or lymphocyte receptor; if the binding induces a specific immune response against the substance, it is also called an *immunogen*. Since most antigens do induce an immune response, we will ignore this distinction and use only the term "antigen" throughout this chapter. Therefore, an antigen is any molecule that the host does not recognize as self. Most antigens are either proteins or very large polysaccharides. Antigens include the protein coats of viruses, specific proteins on bacteria and other foreign cells, some cancer cells, transplanted cells, and toxins. The ability of lymphocytes to distinguish one antigen from another confers specificity upon the immune responses in which they participate.

A typical adaptive immune response can be divided into three stages:

1. *The encounter and recognition of an antigen by lymphocytes.* During its development, each lymphocyte synthesizes and inserts into its plasma membrane multiple copies of a single type of receptor that can bind to a specific antigen. If, at a later time, the lymphocyte ever encounters that antigen, the antigen becomes bound to the receptors. This binding is the physicochemical meaning of the word *recognize* in immunology. As a result, the ability of lymphocytes to distinguish one antigen from another is determined by the nature of their plasma membrane receptors. *Each lymphocyte is specific for just one type of antigen.*
2. *Lymphocyte activation*. The binding of an antigen to a receptor must occur for **lymphocyte activation.** Upon binding to an antigen, the lymphocyte becomes activated and undergoes multiple rounds of cell division. As a result, many daughter lymphocytes develop from a single progenitor that are identical in their ability to recognize a specific antigen; this is called **clonal expansion.** It is estimated that in a typical person the lymphocyte population expresses more than 100 million distinct antigen receptors. After activation, some lymphocytes will function as effector lymphocytes to carry out the attack response. Others will be set aside as **memory cells,** poised to recognize the antigen if it returns in the future.
3. *The attack launched by the activated lymphocytes and their secretions.* The activated effector lymphocytes launch an attack against the antigens that are recognized by the antigen-specific receptor. Activated B cells, which comprise one group of lymphocytes, differentiate into plasma cells that secrete antibodies into the blood. These antibodies opsonize pathogens or foreign substances and target them for attack by innate immune cells. Activated cytotoxic T cells, another type of lymphocyte, directly attack and kill the cells bearing the antigens. Once the attack is successfully completed, the great majority of the B cells, plasma cells, and T cells that participated in it die by apoptosis. The timely death of these effector cells is a homeostatic response that prevents the immune response from becoming excessive and possibly destroying its own tissues. However, memory cells persist even after the immune response has been successfully completed.

Lymphoid Organs and Lymphocyte Origins

Our first task is to describe the organs and tissues in which lymphocytes originate and come to reside. Then the various types of lymphocytes alluded to in the overview and summarized in Table 18.1 will be described.

Lymphoid Organs Like all leukocytes, lymphocytes circulate in the blood. At any moment, the great majority of lymphocytes are not actually in the blood, however, but in a group of organs and tissues collectively called the **lymphoid organs.** These are subdivided into primary and secondary lymphoid organs.

The **primary lymphoid organs** are the bone marrow and thymus. These organs are the initial sites of lymphocyte development. They supply the body with mature but naive lymphocytes—that is, lymphocytes that have not yet been activated by specific antigen. The bone marrow and thymus are not normally sites in which naive lymphocytes undergo activation during an immune response.

The **secondary lymphoid organs** include the lymph nodes, spleen, tonsils, and lymphocyte accumulations in the linings of the intestinal, respiratory, genital, and urinary tracts. It is in the secondary lymphoid organs that naive lymphocytes are activated to participate in adaptive immune responses.

We have stated that the bone marrow and thymus supply mature lymphocytes to the secondary lymphoid organs. Most of the lymphocytes in the secondary organs are not, however, the same cells that originated in the primary lymphoid organs. The explanation of this seeming paradox is that, once in the secondary organ, a mature lymphocyte coming from the bone marrow or thymus can undergo cell division to produce additional identical lymphocytes, which in turn undergo cell division, and so on. In other words, all lymphocytes are *descended* from

ancestors that matured in the bone marrow or thymus but may not themselves have arisen in those organs. All the progeny cells derived by cell division from a single lymphocyte constitute a lymphocyte **clone.**

There are no anatomical links, other than via the circulatory system, between the various lymphoid organs. Let us look briefly at these organs—with the exception of the bone marrow, which was described in Section A of Chapter 12.

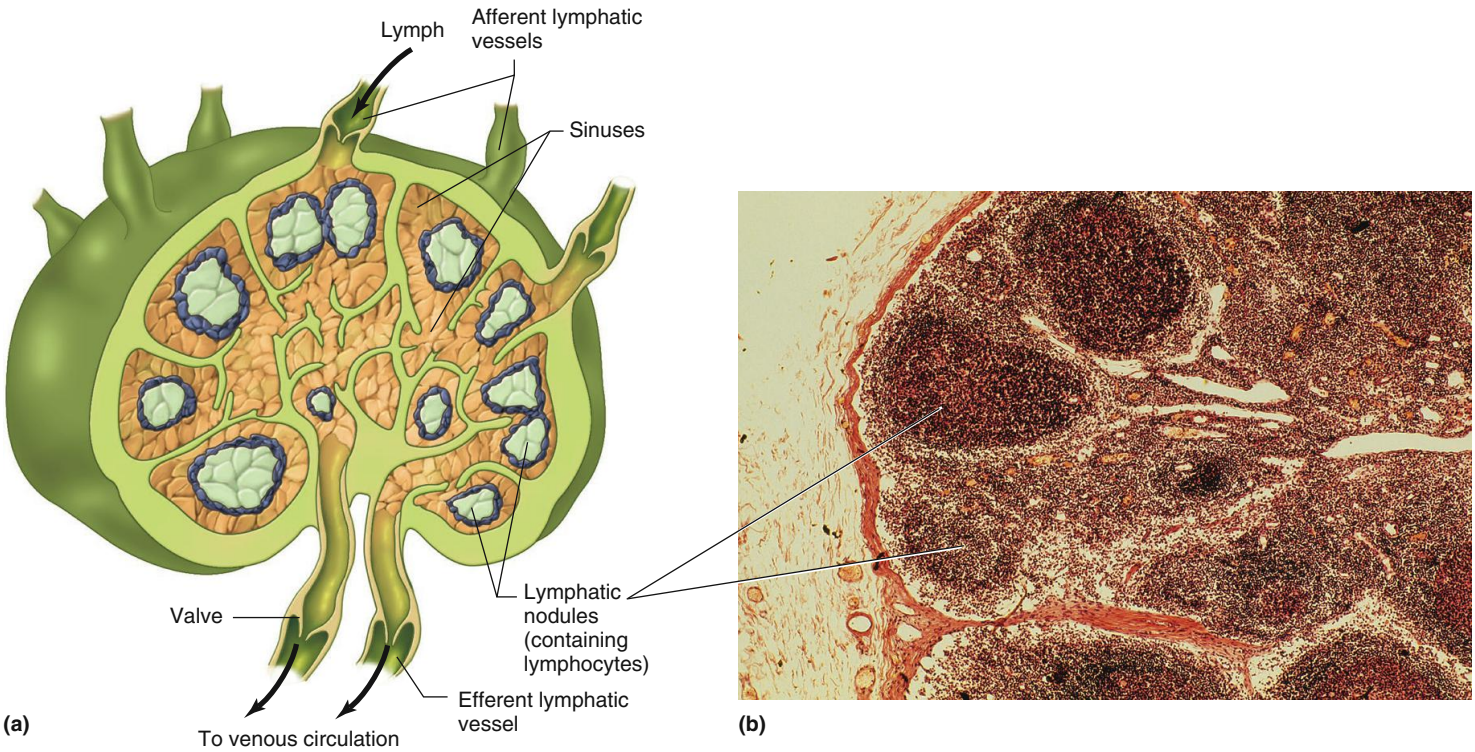
The **thymus** lies in the upper part of the chest. Its size varies with age, being relatively large at birth and continuing to grow until puberty, when it gradually atrophies and is replaced by fatty tissue. Before its atrophy, the thymus consists mainly of immature lymphocytes that will develop into mature T cells that will eventually migrate via the blood to the secondary lymphoid organs.

Recall from Chapter 12 that the fluid flowing in the lymphatic vessels is called *lymph,* which is interstitial fluid that has entered the lymphatic capillaries and is routed to the large lymphatic vessels that drain into systemic veins. During this trip, the lymph flows through **lymph nodes** scattered along the vessels. Lymph, therefore, is the route by which lymphocytes in the lymph nodes encounter the antigens that activate them. Each node is a honeycomb of lymph-filled sinuses (**Figure 18.9**) with large clusters of lymphocytes (the lymphatic nodules) between the sinuses. The lymph nodes also contain many macrophages and dendritic cells.

The **spleen** is the largest of the secondary lymphoid organs and lies in the left part of the abdominal cavity between the stomach and the diaphragm. The spleen is to the circulating blood what the lymph nodes are to the lymph. Blood percolates through the vascular meshwork of the spleen's interior, where large collections of lymphocytes, macrophages, and dendritic cells are found. The macrophages of the spleen, in addition to interacting with lymphocytes, also phagocytose aging or dead erythrocytes.

The **tonsils** and **adenoids** are a group of small, rounded lymphoid organs in the pharynx. They are filled with lymphocytes, macrophages, and dendritic cells; and they have openings called crypts to the surface of the pharynx. Their lymphocytes respond to microbes that arrive by way of ingested food as well as through inspired air.

At any moment in time, some lymphocytes are on their way from the bone marrow or thymus to the secondary lymphoid organs. The vast majority, though, are cells that are participating in lymphocyte traffic *between* the secondary lymphoid organs, blood, lymph, and all the tissues of the body. Lymphocytes from all the secondary lymphoid organs constantly enter the lymphatic vessels that drain them (all lymphoid organs, not just lymph nodes, are drained by lymphatic vessels). From there, they are carried to the blood. Simultaneously, some blood lymphocytes are pushing through the endothelium of venules all over the body to enter the interstitial



AP|R **Figure 18.9** Anatomy of a lymph node as seen in (a) a sketch and in (b) a section viewed by light microscopy.

PHYSIOLOGICAL INQUIRY

- The innate immune response includes vasodilation of the microcirculation and an increase in protein permeability of the capillaries (see Figure 18.2). How might these changes enhance the adaptive immune response during an infection? (*Hint:* What effect would these circulatory changes have on the volume of fluid in the interstitial space and, therefore, lymph flow?)

Answer can be found at end of chapter.

fluid. From there, they move into lymphatic capillaries and along the lymphatic vessels to lymph nodes. They may then leave the lymphatic vessels to take up residence in the node.

This recirculation is going on all the time, not just during an infection, although the migration of lymphocytes into an inflamed area is greatly increased by the chemotaxis process (see Figure 18.2). Lymphocyte trafficking greatly increases the likelihood that any given lymphocyte will encounter the antigen it is specifically programmed to recognize.

Lymphocyte Origins The multiple populations and subpopulations of lymphocytes are summarized in Table 18.1. *B lymphocytes* (*B cells*) mature in the bone marrow and then are carried by the blood to the secondary lymphoid organs (**Figure 18.10**). This process of maturation and migration continues throughout a person's life. All generations of lymphocytes that subsequently arise from these cells by cell division in the secondary lymphoid organs will be identical to the parent cells; that is, they will be B-cell clones.

In contrast to the B cells, other lymphocytes leave the bone marrow in an immature state during fetal and early neonatal life. They are carried to the thymus and mature there before moving to the secondary lymphoid organs. These cells are called *T lymphocytes* (*T cells*). Like B cells, T cells also undergo cell division in secondary lymphoid organs, the progeny being identical to the original T cells and thereby part of that T-cell clone.

In addition to the B and T cells, there is another distinct population of lymphocytes called *natural killer* (*NK*) *cells*. These cells arise in the bone marrow, but their precursors and life history are still unclear. As we will see, NK cells, unlike B and T cells, are not specific to a given antigen.

Humoral and Cell-Mediated Responses: Functions of B Cells and T Cells

Upon activation, B cells differentiate into plasma cells, which secrete **antibodies,** proteins that travel all over the body to reach antigens identical to those that stimulated their production. In the body fluids outside of cells, the antibodies combine with these antigens and guide an attack that eliminates the antigens or the cells bearing them.

Antibody-mediated responses are also called *humoral* responses, the adjective *humoral* denoting communication "by way of soluble chemical messengers" (in this case, antibodies in the blood). Antibody-mediated responses have an extremely wide diversity of targets and are the major defense against bacteria, viruses, and other pathogens in the extracellular fluid and against toxic molecules (toxins).

In contrast to humoral responses, T-cell responses are *cell-mediated* responses. T cells constitute a family that has at least two major functional subsets, **cytotoxic T cells** and **helper T cells.** Recently, it has become clear that a third subset—called suppressor or **regulatory T cells**—inhibits the function of both B cells and cytotoxic T cells.

Another way to categorize T cells is not by function but, rather, by the presence of certain proteins, called CD4 and CD8, in their plasma membranes. Cytotoxic T cells have CD8 and so are also commonly called CD8+ (pronounced "CD8-positive") cells; helper T cells and regulatory T cells express CD4 and so are also commonly called CD4+ cells.

Cytotoxic T cells are "attack" cells. Following activation, they travel to the location of their target, bind to them via antigen on these targets, and directly kill their targets via secreted chemicals. Responses mediated by cytotoxic T cells are directed against the body's own cells that have become cancerous or infected with viruses (or certain bacteria and parasites that, like viruses, take up residence inside host cells).

It is worth emphasizing the important geographic difference in antibody-mediated responses and responses mediated by cytotoxic T cells. The B cells (and plasma cells derived from them) remain in whatever location the recognition and activation steps occurred. The plasma cells send their antibodies forth via the blood to seek out antigens identical to those that triggered the response. Cytotoxic T cells must enter the blood and seek out the targets.

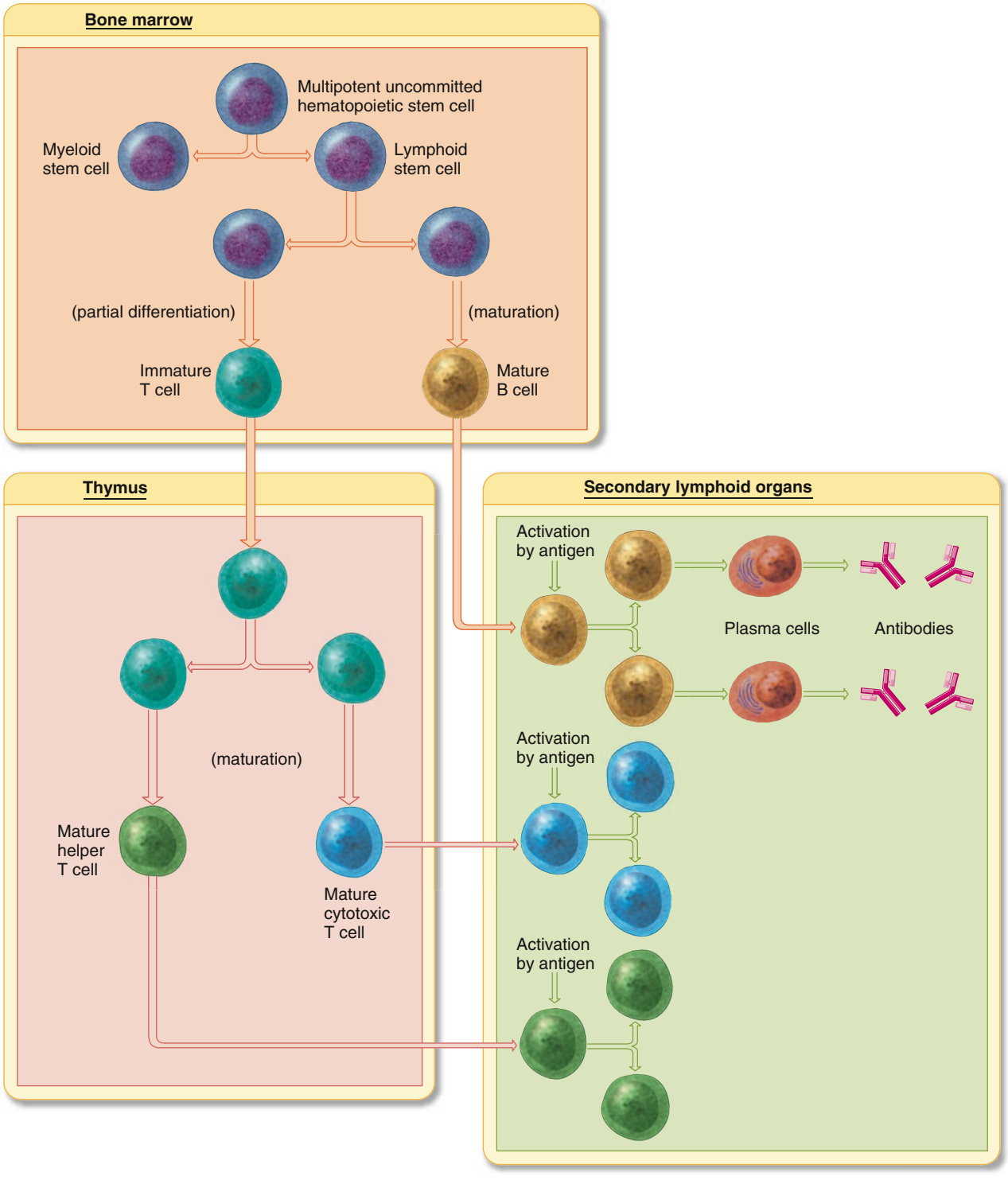
We have now assigned general roles to the B cells and cytotoxic T cells. What role is performed by the helper T cells? As their name implies, these cells do not themselves function as attack cells but, rather, assist in the activation and function of B cells, macrophages, and cytotoxic T cells. Helper T cells go through the usual first two stages of the immune response. First, they combine with antigen and second, they undergo activation. Once activated, however, they migrate to the site of B-cell activation. B cells that have bound antigen present it to activated helper cells. Antigen-specific helper T cells make direct contact with the B cell, and the communication given by surface receptors—along with the secretion of cytokines—induces B-cell activation. The function of helper T cells in cytotoxic T-cell activation is more complex. To activate cytotoxic T cells, activated helper T cells help other cells, most likely dendritic cells, to activate cytotoxic T cells. Unlike the B cell, which directly interacts with the helper T cell, the helper T cell assists cytotoxic T-cell activation indirectly through other cells. With only a few exceptions, B cells and cytotoxic T cells cannot function adequately unless they are stimulated by cytokines from helper T cells.

Helper T cells will be considered as though they were a homogeneous cell population, but in fact, there are different subtypes of helper T cells, distinguished by the different cytokines they secrete when activated. By means of these different cytokines, they help different sets of lymphocytes, macrophages, and NK cells. Some of the cytokines secreted by helper T cells also act as inflammatory mediators. **Figure 18.11** summarizes the basic interactions among B cells, cytotoxic T cells, and helper T cells.

Regulatory T cells are believed to suppress the ability of certain B and cytotoxic T cells to attack a person's own proteins, which can occur in diseases known as autoimmune diseases (described later). As such, investigators are actively pursuing the possibility that regulatory T cells could someday prove effective in the treatment or prevention of certain autoimmune diseases. Also, the *suppression* of regulatory T cells has been proposed as a possible means of increasing cytotoxic T-cell activity in, for example, someone with cancer.

Lymphocyte Receptors

As described earlier, the ability of lymphocytes to distinguish one antigen from another is determined by the lymphocytes' receptors. Both B cells and T cells express receptors on their plasma membrane.

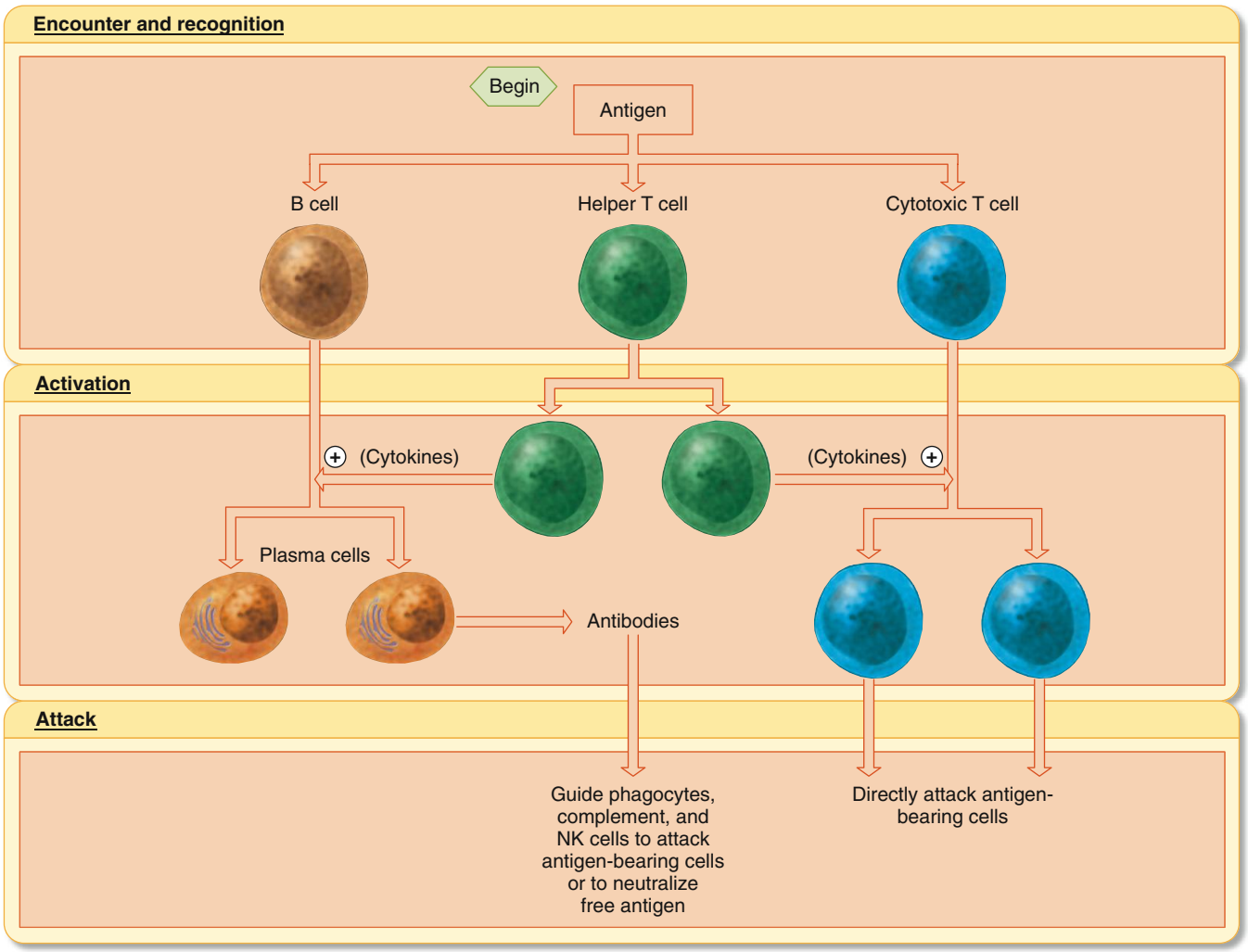


AP|R **Figure 18.10** Derivation of B cells and T cells. NK cells are not shown because their transformations, if any, after leaving the bone marrow are still not clear. (Refer back to Figure 12.2 for additional detail.)

PHYSIOLOGICAL INQUIRY

■ Into which types of cells do myeloid stem cells differentiate?

Answer can be found at end of chapter.



AP|R **Figure 18.11** Summary of the functions of B, cytotoxic T, and helper T cells in immune responses. Events of the attack phase are described in later sections. The ⊕ symbol denotes a stimulatory effect (activation) of cytokines.

B-Cell Receptors

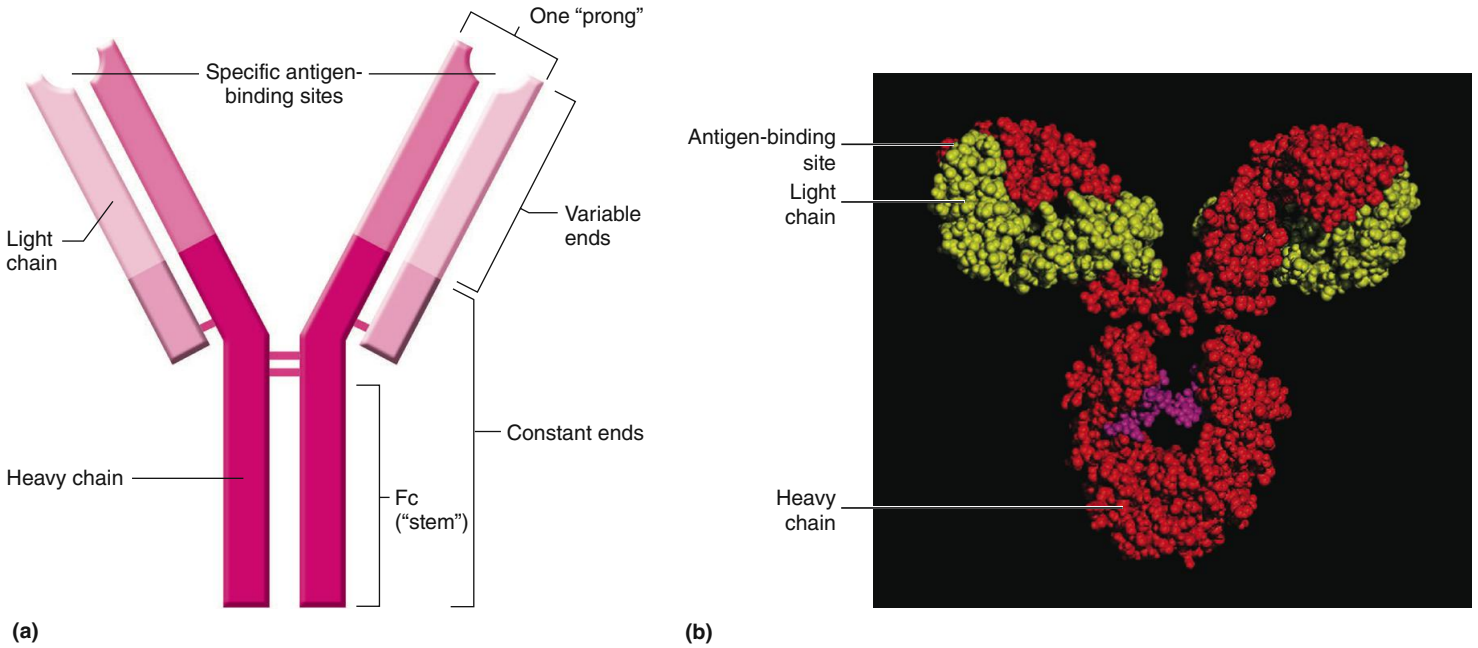
Recall that once B cells are activated by antigen and helper T-cell cytokines, they proliferate and differentiate into plasma cells, which secrete antibodies. The plasma cells derived from a particular B cell can secrete only one particular antibody. Each B cell always displays on its plasma membrane copies of the particular antibody its plasma cell progeny can produce. This surface protein (glycoprotein, to be more accurate) acts as the receptor for the antigen specific to it.

B-cell receptors and plasma cell antibodies constitute the family of proteins known as **immunoglobulins.** The receptors themselves, even though they are identical to the antibodies to be secreted by the plasma cell derived from the activated B cell, are technically not antibodies because only *secreted* immunoglobulins are called antibodies. Each immunoglobulin molecule is composed of four interlinked polypeptide chains (**Figure 18.12**). The two long chains are called heavy chains, and the two short ones, light chains. There are five major classes of immunoglobulins, determined by the amino acid sequences in the heavy chains and a portion of the light chains. The classes are designated by the letters A, D, E, G, and M following the symbol Ig for immunoglobulin; thus, we have IgA, IgD, and so on.

As illustrated in Figure 18.12, immunoglobulins have a "stem" called the **Fc** portion and comprising the lower half of the two heavy chains. The amino acid sequences of the Fc portion plus an additional portion of the heavy chains and part of the light chains are identical for all immunoglobulins of a single class (IgA, IgD, and so on). This portion of an immunoglobulin is important for the interaction of the molecule with phagocytes and the complement system, as we will see later.

The upper part of each heavy chain and its associated light chain form an **antigen-binding site**—the amino acid sequences that bind antigen. In contrast to the identical (or "constant") regions of the heavy and light chains, the amino acid sequences of the antigen-binding sites vary from immunoglobulin to immunoglobulin in a given class and are therefore known as variable ends. Each of the five classes of antibodies, therefore, could contain millions of unique immunoglobulins, each capable of combining with only one specific antigen (or, in some cases, several antigens whose structures are very similar). The interaction between an antigen-binding site of an immunoglobulin and an antigen is analogous to the lock-and-key interactions that apply generally to the binding of ligands by proteins.

One more point should be mentioned: B-cell receptors can bind antigen whether the antigen is a molecule dissolved in the extracellular fluid or is present on the surface of a foreign cell, such as a microbe, floating free in the fluids. In the latter case, the



AP R Figure 18.12 Immunoglobulin structure. (a) The amino acid sequence of the Fc portions and an extended region of the heavy chains are the same for all immunoglobulins of a particular class. A small portion of the light chains are also the same for a given immunoglobulin class. Collectively, these portions of the heavy and light chains are called "constant ends." Each "prong" contains a variable amino acid sequence, which represents the single antigen-binding site. The links between chains represent disulfide bonds. (b) Three-dimensional simulation of an immunoglobulin showing antigen-binding sites and the light and heavy chains. The purple region represents associated carbohydrate, the function of which is uncertain but may be related to binding of immunoglobulins to substrates.

PHYSIOLOGICAL INQUIRY

- You have learned many examples of the general principle of physiology that structure is a determinant of—and has coevolved with—function. How does this principle apply at the molecular level in the case of immunoglobulins?

Answer can be found at end of chapter.

B cell becomes linked to the foreign cell via the bonds between the B-cell receptor and the surface antigen.

To summarize so far, any given B cell or clone of identical B cells possesses unique immunoglobulin receptors—that is, receptors with unique antigen-binding sites. Consequently, the body arms itself with millions of clones of different B cells to ensure that specific receptors exist for the vast number of different antigens the organism *might* encounter during its lifetime. The particular immunoglobulin that any given B cell displays as a receptor on its plasma membrane (and that its plasma cell progeny will secrete as antibodies) is determined during the cell's maturation in the bone marrow.

This raises a very interesting question. In the human genome, there are only about 200 genes that code for immunoglobulins. How, then, can the body produce immunoglobulins having millions of different antigen-binding sites, given that each immunoglobulin requires coding by a distinct gene? This diversity arises as the result of a genetic process unique to developing lymphocytes because only these cells express the enzymes required to catalyze the process. The DNA in each of the genes that code for immunoglobulin antigen-binding sites is cut into small segments, randomly rearranged along the gene, and then rejoined to form new DNA molecules. This cutting and rejoining varies from B cell to B cell, thereby resulting in great diversity of the genes coding for the immunoglobulins of all the B cells taken together.

T-Cell Receptors T-cell receptors for antigens are two-chained proteins that, like immunoglobulins, have variable regions that differ from one T-cell clone to another. However, T-cell receptors remain embedded in the T-cell membrane and are not secreted like antibodies. As in B-cell development, multiple DNA rearrangements occur during T-cell maturation, leading to millions of distinct T-cell clones—distinct in that the cells of any given clone possess receptors of a single specificity. For T cells, this maturation occurs during their residence in the thymus.

In addition to their general structural differences, the B-cell and T-cell receptors differ in a much more important way: *The T-cell receptor cannot combine with antigen unless the antigen is first complexed with certain of the body's own plasma membrane proteins.* The T-cell receptor then combines with the entire complex of antigen and body (self) protein.

The self plasma membrane proteins that must be complexed with the antigen in order for T-cell recognition to occur constitute a group of proteins coded for by genes found on a single chromosome (chromosome 6) and known collectively as the **major histocompatibility complex** (**MHC**). The proteins are therefore called **MHC proteins** (in humans, also known as the human

TABLE 18.4	MHC Restriction of the Lymphocyte Receptors
Cell Type	**MHC Restriction**
B	Do not interact with MHC proteins
Helper T	Class II, found only on macrophages, dendritic cells, and B cells
Cytotoxic T	Class I, found on all nucleated cells of the body
NK	Interaction with MHC proteins not required for activation

leukocyte antigens, or HLAs). Because no two persons other than identical twins have the same sets of MHC genes, no two individuals have the same MHC proteins on the plasma membranes of their cells. MHC proteins are, in essence, cellular "identity tags"—that is, genetic markers of biological self.

The MHC proteins are often called "restriction elements" because the ability of a T cell's receptor to recognize an antigen is restricted to situations in which the antigen is first complexed with an MHC protein. There are two classes of MHC proteins: I and II. **Class I MHC proteins** are found on the surface of virtually all cells of the body except erythrocytes. **Class II MHC proteins** are found mainly on the surface of macrophages, B cells, and dendritic cells. Under certain conditions, other cell types are induced to express class II MHC.

Another important point is that the different subsets of T cells do not all have the same MHC requirements (Table 18.4). Cytotoxic T cells require antigen to be associated with class I MHC proteins, whereas helper T cells require class II MHC proteins. One reason for this difference in requirements stems from the presence, as described earlier, of CD4 proteins on the helper T cells and CD8 proteins on the cytotoxic T cells; CD4 binds to class II MHC proteins, whereas CD8 binds to class I MHC proteins.

How do antigens, which are foreign, end up on the surface of the body's own cells complexed with MHC proteins? The answer is provided by the process known as **antigen presentation,** to which we now turn.

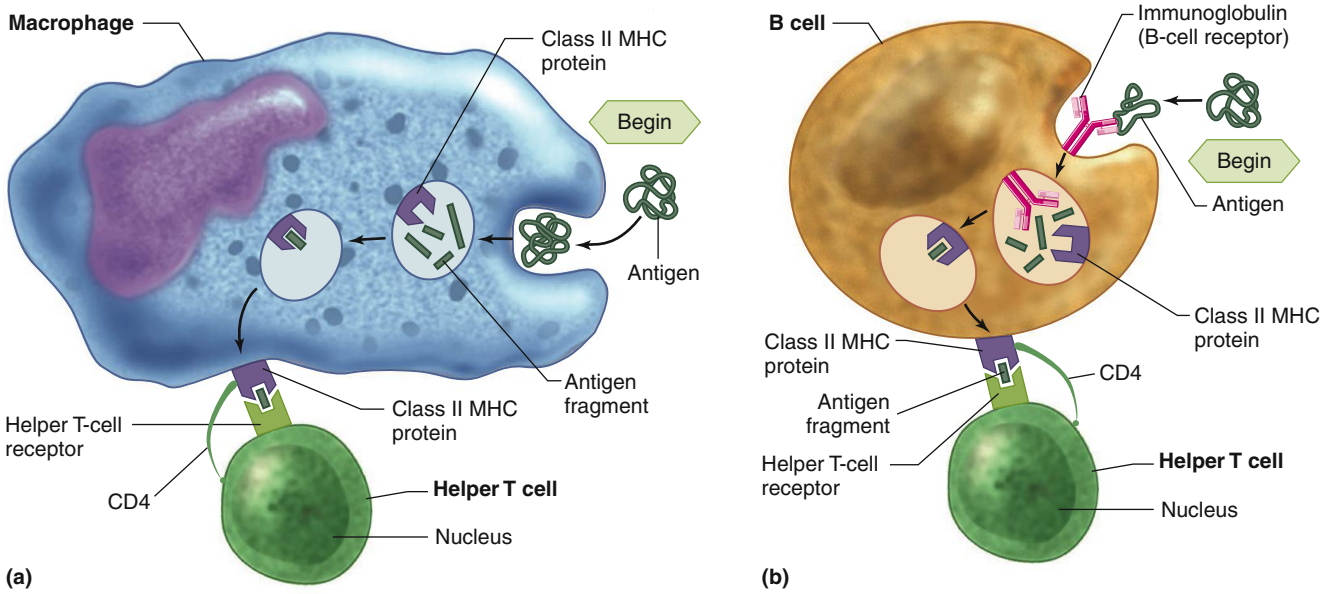
Antigen Presentation to T Cells

T cells can bind antigen only when the antigen appears on the plasma membrane of a host cell complexed with the cell's MHC proteins. Cells bearing these complexes, therefore, function as **antigen-presenting cells** (**APCs**).

Presentation to Helper T Cells Helper T cells require class II MHC proteins to function. Only macrophages, B cells, and dendritic cells express class II MHC proteins and therefore can function as APCs for helper T cells.

The function of the macrophage or dendritic cell as an APC for helper T cells is depicted in Figure 18.13, which shows that the cells form a link between innate and adaptive immune responses. After a microbe or noncellular antigen has been phagocytosed by a macrophage or dendritic cell in a *nonspecific* response, it is partially broken down into smaller polypeptide fragments by the cell's proteolytic enzymes. The resulting digested fragments then bind (within endosomes) to class II MHC proteins synthesized by the cell. This entire complex is then transported to the cell surface, where it is displayed in the plasma membrane. It is to this complex on the cell surface of the macrophage or dendritic cell that a specific helper T cell binds.

Note that it is not the intact antigen but rather the polypeptide fragments, called antigenic determinants or **epitopes,** of the antigen that are complexed to the MHC proteins and presented to the T cell. Despite this, it is customary to refer to "antigen" presentation rather than "epitope" presentation.



AP|R **Figure 18.13** Sequence of events by which antigen is processed and presented to a helper T cell by (a) a macrophage or (b) a B cell. In both cases, begin the figure with the antigen in the extracellular fluid.

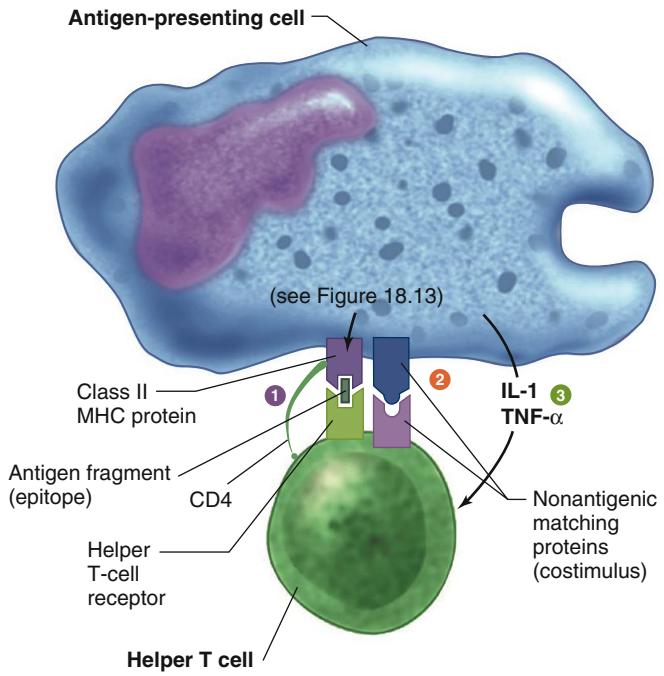
How B cells process antigen and present it to helper T cells is essentially the same as just described for dendritic cells and macrophages (**Figure 18.13b**). The ability of B cells to present antigen to helper T cells is a *second* function of B cells in response to antigenic stimulation, the other being the differentiation of the B cells into antibody-secreting plasma cells.

The binding between a helper T-cell receptor and an antigen bound to class II MHC proteins on an APC is the essential *antigen-specific* event in helper T-cell activation. However, this binding by itself will not result in T-cell activation. In addition, interactions occur between other (nonantigenic) pairs of proteins on the surfaces of the attached helper T cell and APC, and these provide a necessary **costimulus** for T-cell activation (**Figure 18.14**).

Finally, the antigenic binding of the APC to the T cell—along with the costimulus—causes the APC to secrete large amounts of the cytokines **interleukin 1** (**IL-1**) and **tumor necrosis factor-alpha** (**TNF-α**), which act as paracrine substances on the attached helper T cell to provide yet another important stimulus for activation.

Thus, the APC participates in the activation of a helper T cell in three ways: (1) antigen presentation; (2) provision of a costimulus in the form of a matching nonantigenic plasma membrane protein; and (3) secretion of IL-1, TNF-α, and other cytokines (see Figure 18.14).

The activated helper T cell itself now secretes various cytokines that have both autocrine effects on the helper T cell and paracrine effects on adjacent B cells and any nearby cytotoxic T cells, NK cells, and still other cell types. Recent evidence suggests that helper T cells may program dendritic cells to activate CD8+ T cells. These processes will be described in later sections.



AP|R **Figure 18.14** Three events are required for the activation of helper T cells: (1) presentation of the antigen bound to a class II MHC protein on an antigen-presenting cell (APC); (2) the binding of matching nonantigenic proteins in the plasma membranes of the APC and the helper T cell (costimulus); and (3) secretion by the APC of the cytokines interleukin 1 (IL-1), tumor necrosis factor-alpha (TNF-α), and other cytokines, which act on the helper T cell.

Presentation to Cytotoxic T Cells

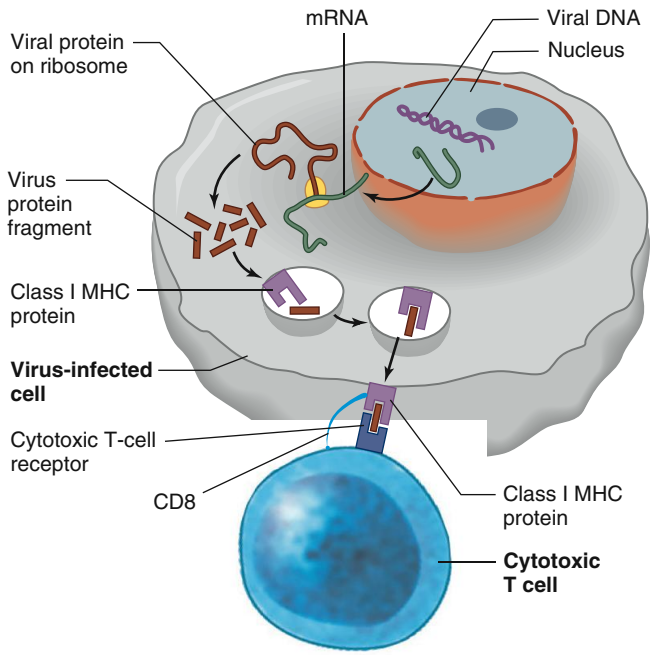
Because class I MHC proteins are synthesized by virtually all nucleated cells, any such cell can act as an APC for a cytotoxic T cell. This distinction helps explain the major function of cytotoxic T cells—destruction of *any* of the body's own cells that have become cancerous or infected with viruses. The key point is that the antigens that complex with class I MHC proteins arise *within* body cells. They are endogenous antigens, synthesized by the body's own cells.

How do such antigens arise? In the case of viruses, once a virus has taken up residence inside a host cell, the viral nucleic acid causes the host cell to manufacture viral proteins that are foreign to the cell. A cancerous cell has had one or more of its genes altered by chemicals, radiation, or other factors. The altered genes, called ***oncogenes,*** code for proteins that are not normally found in the body. Such proteins act as antigens.

In both virus-infected cells and cancerous cells, some of the endogenously produced antigenic proteins are hydrolyzed by cytosolic enzymes (in proteasomes) into polypeptide fragments, which are transported into the endoplasmic reticulum. There, they are complexed with the host cell's class I MHC proteins and then shuttled by exocytosis to the plasma membrane surface, where a cytotoxic T cell specific for the complex can bind to it (**Figure 18.15**).

NK Cells

As noted earlier, NK (natural killer) cells constitute a distinct class of lymphocytes. They have several functional similarities to those of cytotoxic T cells. For example, their major targets are virus-infected cells and cancer cells, and they attack and kill these target cells directly after binding to them. However, unlike cytotoxic



AP|R **Figure 18.15** Processing and presentation of viral antigen to a cytotoxic T cell by an infected cell. Begin this figure with the viral DNA in the cell's nucleus. The viral DNA induces the infected cell to produce viral protein, which is then hydrolyzed (by proteasomes). The fragments are complexed to the cell's class I MHC proteins in the endoplasmic reticulum, and these complexes are then shuttled to the plasma membrane.

T cells, NK cells are not antigen-specific; that is, each NK cell can attack virus-infected cells or cancer cells without recognizing a specific antigen. They have neither T-cell receptors nor the immunoglobulin receptors of B cells, and the exact nature of the NK-cell surface receptors that permits the cells to identify their targets is unknown (except in one case presented later). MHC proteins are not involved in the activation of NK cells.

Why, then, do we deal with them in the context of *specific* (adaptive) immune responses? The reason is that, as will be described subsequently, their participation in an immune response is greatly enhanced either by certain antibodies or by cytokines secreted by helper T cells activated during adaptive immune responses.

Development of Immune Tolerance

Our basic framework for understanding adaptive immune responses requires consideration of one more crucial question. How does the body develop what is called **immune tolerance**—lack of immune responsiveness to self? This may seem a strange question given the definition of an antigen as a foreign molecule that can generate an immune response. How is it, though, that the body "knows" that its own molecules, particularly proteins, are not foreign but are self molecules?

Recall that the huge diversity of lymphocyte receptors is ultimately the result of multiple, random DNA cutting and recombination processes. It is virtually certain, therefore, that in each person, clones of lymphocytes would have emerged with receptors that could bind to that person's own proteins. The existence and functioning of such lymphocytes would be disastrous because such binding would launch an immune attack against the cells expressing these proteins. There are at least two mechanisms—*clonal deletion* and *clonal inactivation*—that explain why normally there are no active lymphocytes that respond to self components.

First, during fetal and early postnatal life, T cells are exposed to a wide mix of self proteins in the thymus. Those T cells with receptors capable of binding self proteins are destroyed by apoptosis (programmed cell death). This process is called **clonal deletion.** The second process, **clonal inactivation,** occurs not in the thymus but in the periphery and causes potentially self-reacting T cells to become nonresponsive.

What are the mechanisms of clonal deletion and inactivation during fetal and early postnatal life? Recall that full activation of a helper T cell requires not only an antigen-specific stimulus but a nonspecific costimulus (interaction between complementary non-antigenic proteins on the APC and the T cell). If this costimulus is *not* provided, the helper T cell not only fails to become activated by antigen but dies or becomes inactivated forever. This is the case during early life. The induction of costimulatory molecules requires activated, antigen-presenting cells. Signaling through TLRs and secretion of inflammatory cytokines are two mechanisms of activating antigen-presenting cells to express costimulatory molecules that provide costimulus for T-cell activation.

This completes the framework for understanding adaptive immune responses. The next two sections utilize this framework in presenting typical responses from beginning to end, highlighting the interactions between lymphocytes, and describing the attack mechanisms used by the various pathways.

Antibody-Mediated Immune Responses: Defenses Against Bacteria, Extracellular Viruses, and Toxins

One classical antibody-mediated response is that which results in the destruction of bacteria. The sequence of events, which is quite similar to the response to a virus in the extracellular fluid, is summarized in **Table 18.5** and **Figure 18.16**.

Antigen Recognition and B-Cell Activation

This process starts the same way as for nonspecific responses, with the bacteria penetrating one of the body's linings and entering the interstitial fluid. The bacteria then enter the lymphatic system and/or the bloodstream and are taken up by the lymph nodes and/or the spleen, respectively. There, a B cell, using its immunoglobulin receptor, recognizes the bacterial surface antigen and binds the bacterium.

In a few cases (notably, bacteria with cell-wall polysaccharide capsules), this binding is all that is needed to trigger B-cell activation. For the great majority of antigens, however, antigen binding is not enough, and signals in the form of cytokines released into the interstitial fluid by helper T cells near the antigen-bound B cells are also required.

TABLE 18.5 Summary of Events in Antibody-Mediated Immunity Against Bacteria

I.	In secondary lymphoid organs, bacterial antigen binds to specific receptors on the plasma membranes of B cells.
II.	Antigen-presenting cells (APCs)—most likely the dendritic cells but macrophages and B cells— A. Present to helper T cells' processed antigen complexed to class II MHC proteins on the APCs; B. Provide a costimulus in the form of another membrane protein; and C. Secrete IL-1, TNF-α, and other cytokines, which act on the helper T cells.
III.	In response, the helper T cells secrete IL-2, which stimulates the helper T cells themselves to proliferate and secrete IL-2 and other cytokines. These activate antigen-bound B cells to proliferate and differentiate into plasma cells. Some of the B cells differentiate into memory cells rather than plasma cells.
IV.	The plasma cells secrete antibodies specific for the antigen that initiated the response, and the antibodies circulate all over the body via the blood.
V.	These antibodies combine with antigen on the surface of the bacteria anywhere in the body.
VI.	Presence of antibody bound to antigen facilitates phagocytosis of the bacteria by neutrophils and macrophages. It also activates the complement system, which further enhances phagocytosis and can directly kill the bacteria by the membrane attack complex. It may also induce antibody-dependent cellular cytotoxicity mediated by NK cells that bind to the antibody's Fc portion.

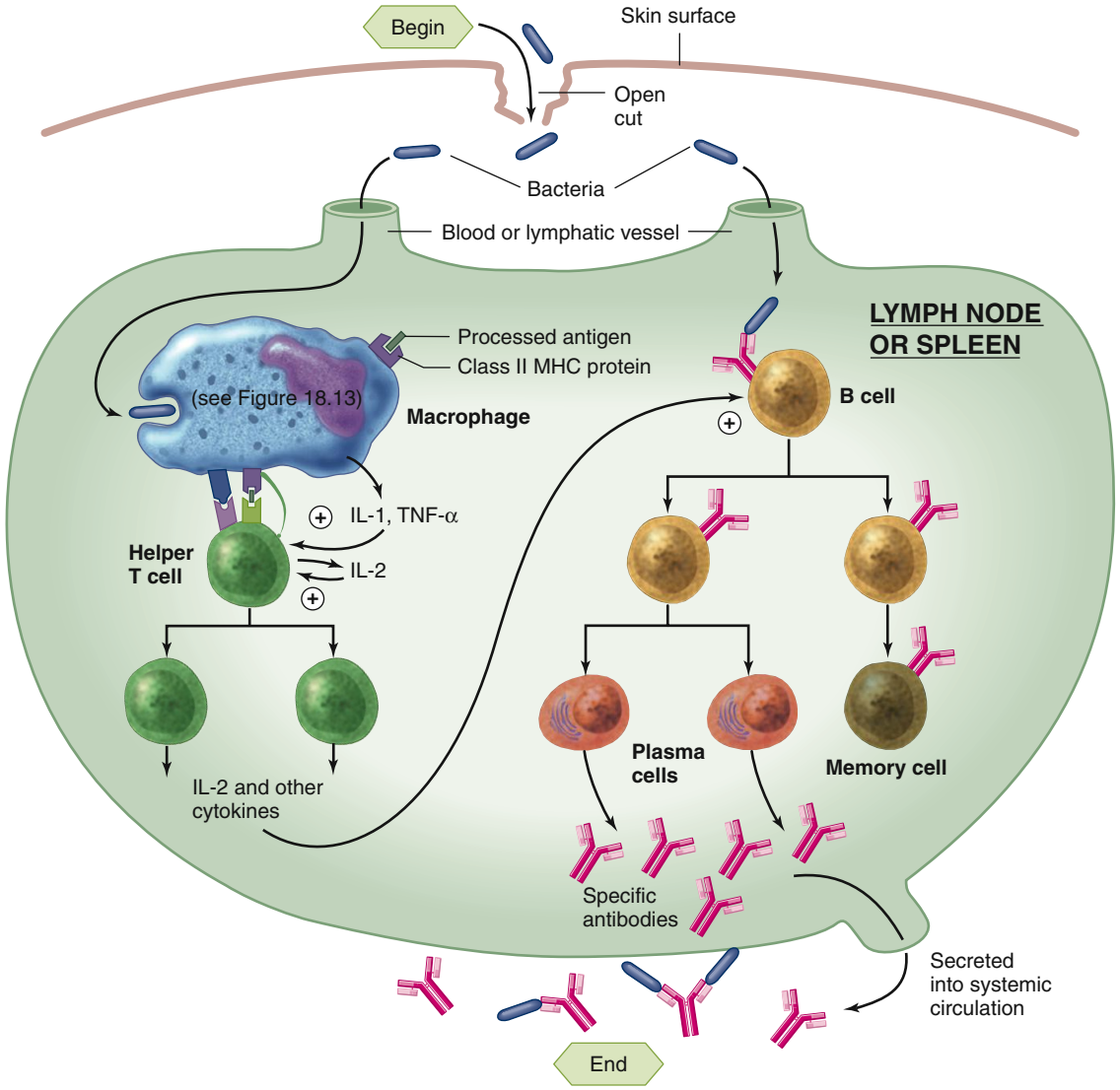


Figure 18.16 Summary of events by which a bacterial infection leads to antibody synthesis in secondary lymphoid organs. Refer back to Figure 18.13 for additional details about intracellular processing of antigen. The secreted antibodies travel by the blood to the site of infection, where they bind to bacteria of the type that induced the response. The attack triggered by antibodies' binding to bacteria is described in the text.

PHYSIOLOGICAL INQUIRY

- What is the advantage of having some B cells differentiate into memory cells?

Answer can be found at end of chapter.

For helper T cells to react against bacteria by secreting cytokines, they must bind to a complex of antigen and class II MHC protein on an APC. Let us assume that in this case the APC is a macrophage that has phagocytosed one of the bacteria, hydrolyzed its proteins into polypeptide fragments, complexed them with class II MHC proteins, and displayed the complexes on its surface. A helper T cell specific for the complex then binds to it, beginning the activation of the helper T cell. Moreover, the macrophage helps this activation process in two other ways: (1) It provides a costimulus via nonantigenic plasma membrane proteins, and (2) it secretes IL-1 and TNF-α.

The costimulus activates the helper T cell to secrete another cytokine named **interleukin 2** (**IL-2**). Among other functions, IL-1 and TNF-α stimulate the helper T cell to express more receptors for IL-2. Interleukin 2, acting in an autocrine manner, then provides a proliferative stimulus to the activated helper T cell (see Figure 18.16). The cell divides, beginning the mitotic cycles that lead to the formation of a clone of activated helper T cells; these cells then release not only IL-2 but other cytokines as well.

Once activated, helper T cells migrate to lymph nodes where they interact with antigen-presenting B cells. The helper T cell stimulates B-cell activation by direct contact and cytokine release. Other cytokines—notably, IL-4 possibly produced by basophils—are also important in this step. Once activated, the B cell differentiates into a plasma cell that secretes antibodies that recognize the specific antigen. Thus, as shown in Figure 18.16, a series of protein messengers interconnects the various cell types, the helper T cells serving as the central coordinators.

As stated earlier, however, some of the B-cell progeny differentiate not into plasma cells but instead into long-lived memory cells, whose characteristics permit them to respond more rapidly and vigorously should the antigen reappear at a future time (see Figure 18.16).

The example we have been using employed a macrophage as the APC to helper T cells, but B cells can also serve in this capacity (see Figure 18.13). The binding of the helper T cell to the antigen-bound B cell ensures maximal stimulation of the B cell by the cytokines secreted by that helper T cell and any of its progeny that remain nearby.

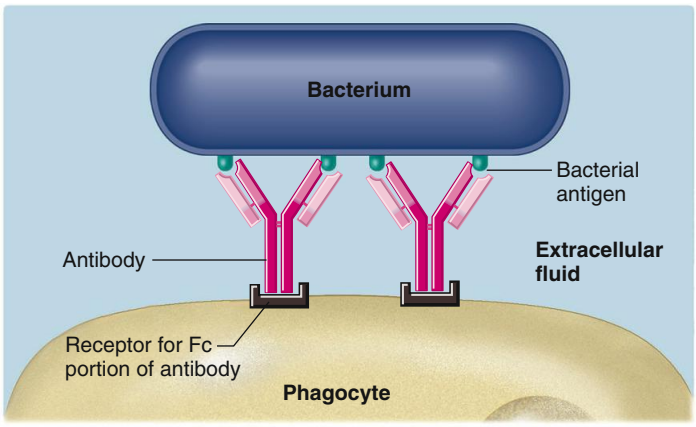
Antibody Secretion After their differentiation from B cells, plasma cells produce thousands of antibody molecules per second before they die in a day or so. We mentioned earlier that there are five major classes of antibodies. The most abundant are the **IgG** antibodies, commonly called **gamma globulin,** and **IgM** antibodies. These two groups together provide the bulk of specific immunity against bacteria and viruses in the extracellular fluid. **IgE** antibodies participate in defenses against multicellular parasites and also mediate allergic responses. **IgA** antibodies are secreted by plasma cells in the linings of the gastrointestinal, respiratory, and genitourinary tracts; these antibodies generally act locally in the linings or on their surfaces. They are also secreted by the mammary glands and, therefore, are the major antibodies in milk. The functions of **IgD** are still unclear.

In the kind of infection described in this chapter, the B cells and plasma cells, residing in the nodes near the infected tissues, recognize antigen and are activated to make antibodies. The antibodies (mostly IgG and IgM) circulate through the lymph and blood to return to the infected site. At sites of infection, the antibodies leave the blood (recall that nonspecific inflammation has already made capillaries and venules leaky at these sites) and combine with the type of bacterial surface antigen that initiated the immune response (see Figure 18.16). These antibodies then direct the attack (see following discussion) against the bacteria to which they are now bound.

Consequently, immunoglobulins have two distinct functions in immune responses during the initial recognition step: (1) Those on the surface of B cells bind to antigen brought to them; and (2) those secreted by the plasma cells (antibodies) bind to bacteria bearing the same antigens, "marking" them as the targets to be attacked.

The Attack: Effects of Antibodies The antibodies bound to antigen on the microbial surface do not directly kill the microbe but instead link up the microbe physically to the actual killing mechanisms—phagocytes (neutrophils and macrophages), complement, or NK cells. This linkage not only triggers the attack mechanism but ensures that the killing effects are restricted to the microbe. Linkage to specific antibodies helps protect adjacent normal structures from the toxic effects of the chemicals employed by the killing mechanisms.

Direct Enhancement of Phagocytosis Antibodies can act directly as opsonins. The mechanism is analogous to that for complement C3b (see Figure 18.6) in that the antibody links the phagocyte to the antigen. As shown in **Figure 18.17**, the phagocyte has membrane receptors that bind to the Fc portion of an antibody.



AP|R **Figure 18.17** Direct enhancement of phagocytosis by antibody. The antibody links the phagocyte to the bacterium. Compare this mechanism of opsonization to that mediated by complement C3b (see Figure 18.6).

This linkage promotes attachment of the antigen to the phagocyte and the triggering of phagocytosis of the bacterium.

Activation of the Complement System As described earlier in this chapter, the plasma complement system is activated in *nonspecific* (innate) inflammatory responses via the alternative complement pathway. In contrast, in *adaptive* immune responses, the presence of antibody of the IgG or IgM class bound to antigen activates the *classical complement pathway.* The first molecule in this pathway, C1, binds to the Fc portion of an antibody that has combined with antigen (**Figure 18.18**). This results in activation of the enzymatic portions of C1, thereby initiating the entire classical pathway. The end product of this cascade, the membrane attack complex (MAC), can kill the cells the antibody is bound to by making their membranes leaky. In addition, as we saw in Figure 18.6, another activated complement molecule (C3b) functions as an opsonin to enhance phagocytosis of the microbe by neutrophils and macrophages (see Figure 18.18). As a result, antibodies enhance phagocytosis both directly (see Figure 18.17) and via activation of complement C3b.

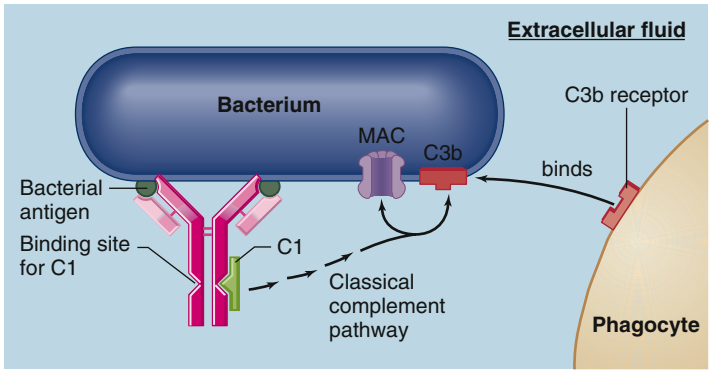


Figure 18.18 Activation of classical complement pathway by binding of antibody to bacterial antigen. C1 is activated by its binding to the Fc portion of the antibody. The membrane attack complex (MAC) is then generated, along with C3b, which acts as an opsonin by binding the bacteria to a phagocyte. C3b also participates in initiating the MAC (not shown here).

It is important to note that C1 binds not to the unique antigen-binding sites in the antibody's prongs but rather to complement-binding sites in the Fc portion. Because the latter are the same in virtually all antibodies of the IgG and IgM classes, the complement molecule will bind to *any* antigen-bound antibodies belonging to these classes. In other words, there is only one set of complement molecules and, once activated, they do essentially the same thing regardless of the specific identity of the invader.

Antibody-Dependent Cellular Cytotoxicity We have seen that both a particular complement molecule (C1) and a phagocyte can bind nonspecifically to the Fc portion of an antibody bound to antigen. NK cells can also do this (just substitute an NK cell for the phagocyte in Figure 18.17). Thus, antibodies can link target cells to NK cells, which then kill the targets directly by secreting toxic chemicals. This is called **antibody-dependent cellular cytotoxicity** (**ADCC**), because killing (cytotoxicity) is carried out by cells (NK cells) but the process depends upon the presence of antibody. Note that the antibodies confer specificity upon ADCC, just as they do on antibody-dependent phagocytosis and complement activation. This mechanism for bringing NK cells into play is the one exception, mentioned earlier, to the generalization that the mechanism by which NK cells identify their targets is unclear.

Direct Neutralization of Bacterial Toxins and Viruses Toxins secreted by bacteria into the extracellular fluid can act as antigens to induce antibody production. The antibodies then combine with the free toxins, thereby preventing interaction of the toxins with susceptible cells. Because each antibody has two binding sites for antigen, clumplike chains of antibody–antigen complexes form, and these clumps are then phagocytosed.

A similar binding process occurs as part of the major antibody-mediated mechanism for eliminating viruses in the extracellular fluid. Certain of the viral surface proteins serve as antigens, and the antibodies produced against them combine with them, preventing attachment of the virus to plasma membranes of potential host cells. This prevents the virus from entering a cell. As with bacterial toxins, chains of antibody–virus complexes are formed and can be phagocytosed.

Active and Passive Humoral Immunity

The response of the antibody-producing machinery to invasion by a foreign antigen varies enormously, depending upon whether the machinery has previously been exposed to that antigen. Antibody production occurs slowly over several weeks following the first contact with an antigen, but any subsequent infection by the same invader elicits an immediate and considerable outpouring of additional specific antibodies (**Figure 18.19**). This response, which is mediated by the memory B cells described earlier, is one of the key features that distinguishes innate and adaptive immunity. It confers a greatly enhanced resistance toward subsequent infection with that particular microorganism. Resistance built up as a result of the body's contact with microorganisms and their toxins or other antigenic components is known as **active immunity.**

Until the twentieth century, the only way to develop active immunity was to suffer an infection, but now the administration of microbial derivatives in vaccines is used. A ***vaccine*** may consist of small quantities of living or dead pathogens, small quantities of

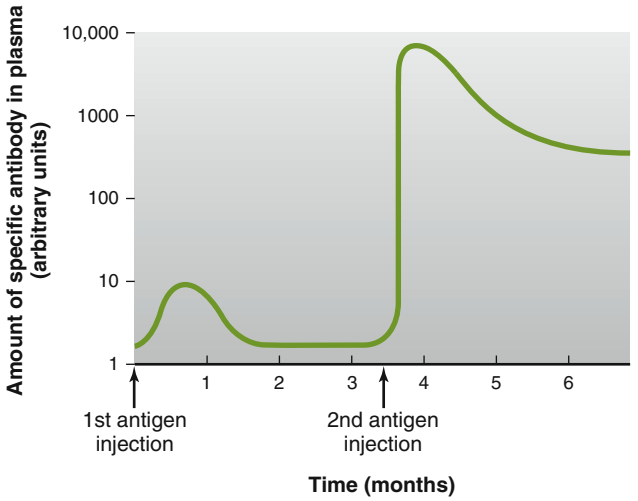


Figure 18.19 Rate of antibody production following initial exposure to an antigen and subsequent exposure to the same antigen. Note that the *y*-axis is a log scale.

PHYSIOLOGICAL INQUIRY

- Roughly how manyfold greater is the second response to antigen in this example?

Answer can be found at end of chapter.

toxins, or harmless antigenic molecules derived from the microorganism or its toxin. The general principle is always the same: Exposure of the body to the antigenic substance results in an active immune response along with the induction of the memory cells required for rapid, effective response to possible future infection by that particular organism.

A second kind of immunity, known as **passive immunity,** is simply the direct transfer of antibodies from one person to another, the recipient thereby receiving preformed antibodies. Such transfers occur between mother and fetus because IgG can move across the placenta. Also, a breast-fed child receives IgA antibodies in the mother's milk; the intestinal mucosa is permeable to IgA antibodies during early life. These are important sources of protection for the infant during the first months of life, when the antibody-synthesizing capacity is relatively poor.

The same principle is used clinically when specific antibodies (produced by genetic engineering) or pooled gamma globulin injections are given to patients exposed to or suffering from certain infections such as hepatitis. Because antibodies are proteins with a limited life span, the protection afforded by this transfer of antibodies is relatively short-lived, usually lasting only a few weeks or months.

Summary

It is now possible to summarize the interplay between innate and adaptive immune responses in resisting a bacterial infection. When a particular bacterium is encountered for the first time, *innate* defense mechanisms resist its entry and, if entry is gained, attempt to eliminate it by phagocytosis and nonphagocytic killing in the inflammatory process. Simultaneously, bacterial antigens induce the relevant specific B-cell clones to differentiate into plasma cells capable of antibody production. If the innate defenses are rapidly successful, these

slowly developing *specific* immune responses may never have an important function. If the innate responses are only partly successful, the infection may persist long enough for significant amounts of antibody to be produced. The presence of antibody leads to both enhanced phagocytosis and direct destruction of the foreign cells, as well as to neutralization of any toxins the bacteria secrete. All subsequent encounters with that type of bacterium will activate the specific responses much sooner and with greater intensity. That is, the person may have active immunity against those bacteria.

The defenses against viruses in the extracellular fluid are similar, resulting in destruction or neutralization of the virus.

Defenses Against Virus-Infected Cells and Cancer Cells

The previous section described how antibody-mediated immune responses constitute the major long-term defense against exogenous antigens—those on bacteria and viruses, and also individual foreign molecules that enter the body and are encountered by the immune system in the extracellular fluid. This section now details how the body's own cells that have become infected by viruses (or other intracellular pathogens) or transformed into cancer cells are destroyed.

What is the value of destroying virus-infected host cells? Such destruction results in release of the viruses into the extracellular fluid, where they can be directly neutralized by circulating antibody, as just described. Generally, only a few host cells are sacrificed in this way, but once viruses have had a chance to replicate and spread from cell to cell, so many virus-infected host cells may be killed by the body's own defenses that organ malfunction may occur.

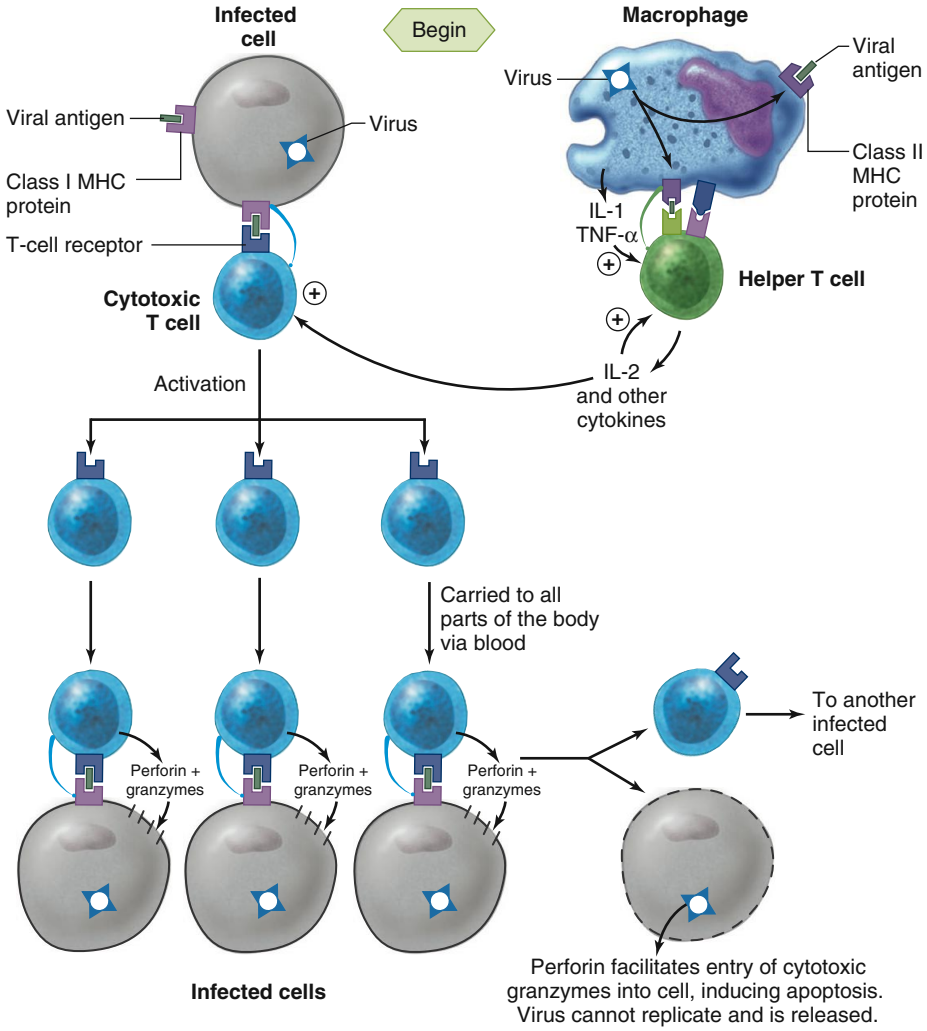
Role of Cytotoxic T Cells Figure 18.20

summarizes a typical cytotoxic T-cell response triggered by viral infection of body cells. The response triggered by a cancer cell would be similar. As described earlier, a virus-infected or cancer cell produces foreign proteins, "endogenous antigens," which are processed and presented on the plasma membrane of the cell complexed with class I MHC proteins. Cytotoxic T cells specific for the particular antigen can bind to the complex; just as with B cells, however, binding to antigen alone does not cause activation of the cytotoxic T cell. Cytokines from adjacent activated helper T cells are also required.

What function do the helper T cells have in these cases? Figure 18.20 illustrates the most likely mechanism. Macrophages phagocytose free extracellular viruses (or, in the case of cancer, antigens released from the surface of the cancerous cells) and then process and present antigen, in association with class II MHC proteins, to the helper T cells. In addition, the macrophages provide a costimulus and also secrete IL-1 and TNF-α. The activated helper T cell releases IL-2 and other cytokines. IL-2 then acts as an autocrine substance to stimulate proliferation of the helper T cell.

The IL-2 also acts as a paracrine substance on the cytotoxic T cell bound to the surface of the virus-infected or cancer cell, stimulating this attack cell to proliferate. Other cytokines secreted by the activated helper T cell perform the same functions. Why is proliferation important if a cytotoxic T cell has already found and bound to its target? The answer is that there is rarely just one virus-infected cell or one cancer cell. By expanding the clone of cytotoxic T cells capable of recognizing the particular antigen, proliferating attack cells increase the likelihood that other virus-infected or cancer cells will be encountered by the specific type of cytotoxic T cell.

There are several mechanisms of target-cell killing by activated cytotoxic T cells, but one of the most important is as follows (see Figure 18.20). The cytotoxic T cell releases, by



AP|R **Figure 18.20** Summary of events in the killing of virus-infected cells by cytotoxic T cells. The released viruses can then be phagocytosed. The precise mechanism of action of perforin is uncertain. The sequence would be similar if the inducing cell were a cancer cell rather than a virus-infected cell.

exocytosis, the contents of its secretory vesicles into the extracellular space between itself and the target cell to which it is bound. These vesicles contain a protein, **perforin,** which is similar in structure to the proteins of the complement system's membrane attack complex. Exactly how perforin acts is currently uncertain. However, it is believed that at least one mechanism by which perforin acts is to facilitate the transport of cytotoxic enzymes called granzymes, released by the cytotoxic T cells, into the infected cell. These enzymes then activate intracellular enzymes that induce apoptosis, killing the cell. The fact that perforin is released directly into the extracellular fluid between the tightly attached cytotoxic T cell and the target ensures that uninfected host bystander cells will not be killed, because perforin is not specific.

Some cytotoxic T cells generated during proliferation following an initial antigenic stimulation do not complete their full activation at this time but remain as memory cells. Thus, active immunity exists for cytotoxic T cells just as for B cells.

Role of NK Cells and Activated Macrophages

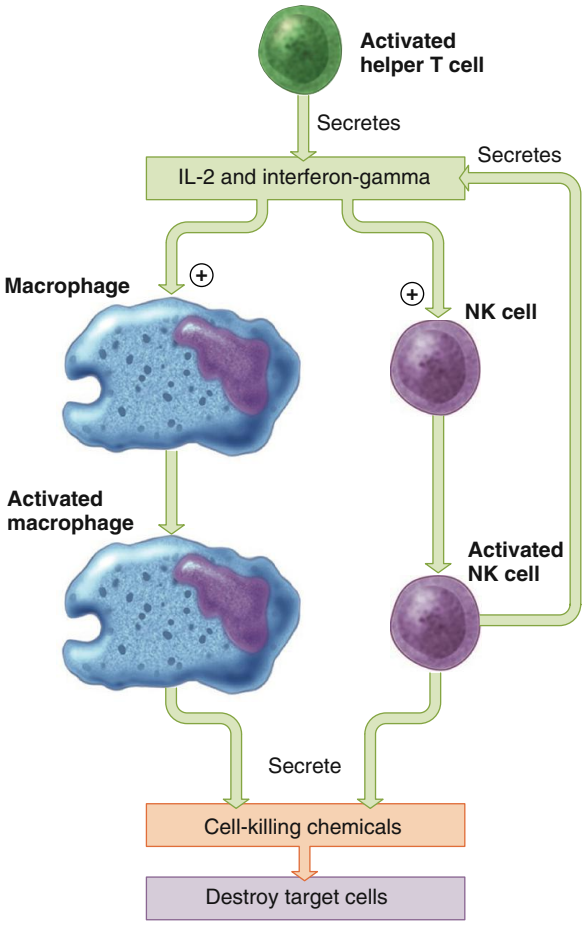
Although cytotoxic T cells are very important attack cells against virus-infected and cancer cells, they are not the only ones. NK cells and activated macrophages also destroy such cells by secreting toxic chemicals.

In the section on antibody-dependent cellular cytotoxicity (ADCC), we pointed out that NK cells can be linked to target cells by antibodies; this constitutes one potential method of bringing them into play against virus-infected or cancer cells. In most cases, however, strong antibody responses are not triggered by virus-infected or cancer cells, and the NK cell must bind *directly* to its target, without the help of antibodies. As noted earlier, NK cells do not have antigen specificity; rather, they nonspecifically bind to any virus-infected or cancer cell.

The major signals for NK cells to proliferate and secrete their toxic chemicals are IL-2 and interferon-gamma, secreted by the helper T cells that have been activated specifically by the targets (**Figure 18.21**). (Whereas essentially all body cells can produce the type I interferons, as described earlier, only activated helper T cells and NK cells can produce interferon-gamma.)

Thus, the attack by the NK cells is nonspecific, but a specific immune response on the part of the helper T cells is required to bring the NK cells into play. Moreover, there is a positive feedback mechanism at work here because activated NK cells can themselves secrete interferon-gamma (see Figure 18.21).

IL-2 and interferon-gamma act not only on NK cells but on macrophages in the vicinity to enhance their ability to kill cancer cells and cells infected with viruses and other pathogens. Macrophages stimulated by IL-2 and interferon-gamma are called **activated macrophages** (see Figure 18.21). In addition to phagocytosis, they secrete large amounts of many chemicals that are capable of killing cells by a variety of mechanisms. As long as there is a pathogen at the site of infection, activated macrophages will continue to present antigens to T cells that will maintain the ensuing immune response. Once cleared of infection, tissue repair will continue and the immune response will wane as T cells are no longer being activated against the pathogen.



AP|R **Figure 18.21** Role of IL-2 and interferon-gamma, secreted by activated helper T cells, in stimulating the killing ability of NK cells and macrophages.

PHYSIOLOGICAL INQUIRY

- What type of feedback is exemplified by the secretion of interferon-gamma by NK cells?

Answer can be found at end of chapter.

Table 18.6 summarizes the multiple defenses against viruses described in this chapter.

18.4 Systemic Manifestations of Infection

There are many *systemic* responses to infection, that is, responses of organs and tissues distant from the site of infection or immune response. These systemic responses are collectively known as the **acute phase response** (**Figure 18.22**). It is natural to think of these responses as part of the disease, but the fact is that most of them actually represent the body's own adaptive responses to the infection.

The single most common and striking systemic sign of infection is fever, the mechanism of which was described in

TABLE 18.6 Summary of Host Responses to Viruses

	Main Cells Involved	Comment on Action
Innate responses		
Anatomical barriers	Body surface linings	Provide physical barrier; antiviral chemicals
Inflammation	Tissue macrophages	Provide phagocytosis of extracellular virus
Interferon (type I)	Most cell types after viruses enter them	Type I interferon nonspecifically prevents viral replication inside host cells
Adaptive responses		
Antibody-mediated	Plasma cells (derived from B cells) that secrete antibodies	Antibodies neutralize virus and thus prevent viral entry into cell Antibodies activate complement, which leads to enhanced phagocytosis of extracellular virus Antibodies recruit NK cells via antibody-mediated cellular cytotoxicity
Helper	Helper T cells	Secrete interleukins; keep NK cells, macrophages, cytotoxic T cells, and helper T cells active; also help convert B cells to plasma cells
Direct cell killing	Cytotoxic T cells, NK cells, and activated macrophages	Destroy host cell via secreted chemicals and thus induce release of virus into extracellular fluid where it can be phagocytosed Activity stimulated by IL-2 and interferon-gamma

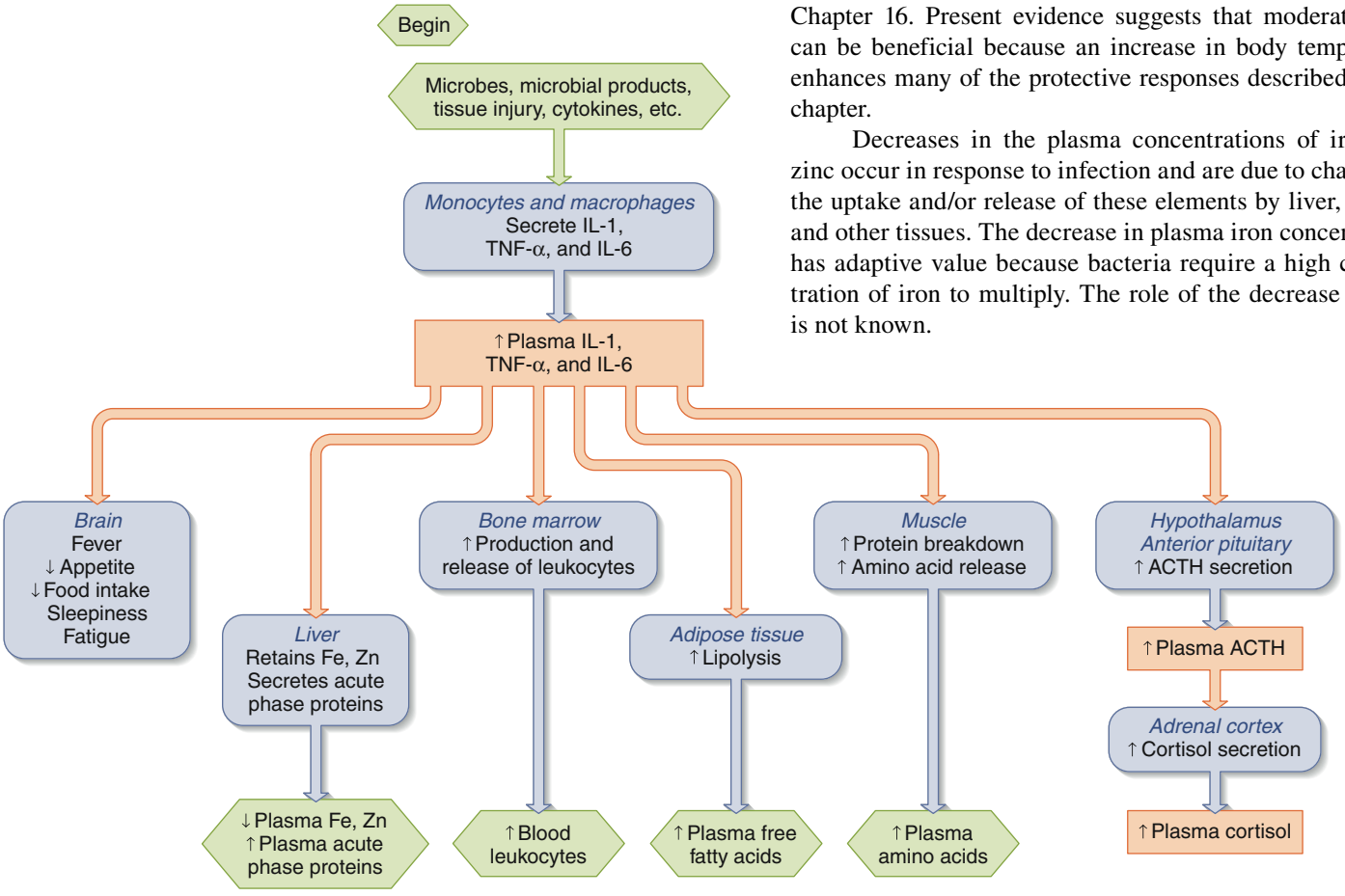


Figure 18.22 Systemic responses to infection or injury (the acute phase response). Other cytokines probably also participate. This figure does not include all the components of the acute phase response; for example, IL-1 and several other cytokines also stimulate the secretion of insulin and glucagon. The effect of cortisol on the immune response is inhibitory; cortisol provides a negative feedback action to prevent excessive immune activity (see Chapter 11 for the control mechanisms and basic functions of cortisol).

Chapter 16. Present evidence suggests that moderate fever can be beneficial because an increase in body temperature enhances many of the protective responses described in this chapter.

Decreases in the plasma concentrations of iron and zinc occur in response to infection and are due to changes in the uptake and/or release of these elements by liver, spleen, and other tissues. The decrease in plasma iron concentration has adaptive value because bacteria require a high concentration of iron to multiply. The role of the decrease in zinc is not known.

TABLE 18.7 Functions of Macrophages in Immune Responses

In innate inflammation, macrophages phagocytose particulate matter, including microbes. They also secrete antimicrobial chemicals and protein messengers (cytokines) that function as local inflammatory mediators. The inflammatory cytokines include IL-1 and TNF-α.
Macrophages process and present antigen to cytotoxic T cells and helper T cells.
The secreted IL-1 and TNF-α stimulate helper T cells to secrete IL-2 and to express the receptor for IL-2.
During adaptive immune responses, macrophages perform the same killing and inflammation-inducing functions as above but are more efficient because antibodies act as opsonins and because the cells are transformed into activated macrophages by IL-2 and interferon-gamma, both secreted by helper T cells.
The secreted IL-1, TNF-α, and IL-6 mediate many of the systemic responses to infection or injury.

Another adaptive response to infection is the secretion by the liver of a group of proteins known collectively as **acute phase proteins.** These proteins exert many effects on the inflammatory process that serve to minimize the extent of local tissue damage. In addition, they are important for tissue repair and for clearance of cell debris and the toxins released from microbes. An example of an acute phase protein is C-reactive protein, which functions as a nonspecific opsonin to enhance phagocytosis.

Another response to infection, increased production and release of neutrophils and monocytes by the bone marrow, is of obvious value. Also occurring is a release of amino acids from muscle; the amino acids provide the building blocks for the synthesis of proteins required to fight the infection and for tissue repair. Increased release of fatty acids from adipose tissue also occurs, providing a source of energy. The secretion of certain hormones—notably, cortisol—is increased in the acute phase response, exerting negative feedback actions on immune function.

All of these systemic responses to infection and many others are elicited by one or more of the cytokines released from activated macrophages and other cells (see Figure 18.22). In particular, IL-1, TNF-α, and another cytokine—**interleukin 6** (**IL-6**), all of which have local functions in immune responses, also serve as hormones to elicit distant responses such as fever.

The participation of macrophages in the acute phase response completes our discussion of these cells, the various functions of which are summarized in Table 18.7.

18.5 Factors That Alter the Resistance to Infection

Many factors determine the capacity to resist infection; a few important examples are presented here. Protein–calorie malnutrition is, worldwide, the single greatest contributor to decreased resistance to infection. Because inadequate amino acids are available to synthesize essential proteins, immune function is impaired. Deficits of specific nutrients other than protein can also lower resistance to infection.

A preexisting disease, infectious or noninfectious, can also predispose the body to infection. People with diabetes mellitus, for example, are more likely to develop infections, at least partially explainable on the basis of defective leukocyte function. Moreover, any injury to a tissue lowers its resistance, perhaps by altering the chemical environment or interfering with the blood supply.

Both stress and a person's state of mind can either enhance or reduce resistance to infection (and cancer). There are multiple mechanisms that constitute the links in these "mind–body" interactions. For example, lymphoid tissue is innervated, and the cells that mediate immune defenses have receptors for many neurotransmitters and hormones. Conversely, as we have seen, some of the cytokines the immune cells release have important effects on the brain and endocrine system. Moreover, lymphocytes secrete several of the same hormones produced by endocrine glands. Thus, the immune system can alter neural and endocrine function; in turn, neural and endocrine activity can modify immune function. For example, it has been shown in mice and rats that the production of antibodies can be altered by psychological conditioning. If this proves to be the case in humans, it could someday partially replace the requirement for medications to control the immune activity of persons with autoimmune disease.

The influence of physical exercise on the body's resistance to infection and cancer has been debated for decades. Present evidence indicates that the intensity, duration, chronicity, and psychological stress of the exercise all have important influences, both negative and positive, on a host of immune functions (for example, the number of circulating NK cells). Most experts in the field believe that, despite all these complexities, modest exercise and physical conditioning have net beneficial effects on the immune system and on host resistance.

Another factor associated with decreased immune function is sleep deprivation. For example, loss of a single night's sleep has been observed to reduce the activity of blood NK cells. The mechanism of this response is uncertain, but the results have been replicated by numerous investigators.

Resistance to infection will be impaired if one of the basic resistance mechanisms itself is deficient, as, for example, in people who have a genetic deficiency that impairs their ability to produce antibodies. These people experience frequent and sometimes life-threatening infections that can be prevented by regular replacement injections of gamma globulin. Another genetic defect is ***severe combined immunodeficiency*** (***SCID***), which is actually a group of related diseases that arise from an absence of both B and T cells and, in some cases, NK cells. If untreated, infants with this disorder usually die within their first year of life from overwhelming infections. SCID can sometimes be cured by bone marrow transplantation, which supplies both B cells and cells that will migrate to the thymus and become T cells, but these transplants are difficult and not always successful. Beginning in the 1990s, gene therapy to restore the defective gene using a viral vector targeted to hematopoietic stem cells has proven successful in a small number of SCID patients. Several defective genes have been identified, including one for an enzyme required for immunoglobulin production and one for an enzyme that protects immature lymphocytes against toxic by-products of purine metabolism.

An artificially induced decrease in the production of leukocytes is also an important cause of lowered resistance. This can occur, for example, in patients given drugs to inhibit the rejection of tissue or organ transplants (see the section on graft rejection that follows).

In terms of the numbers of people involved, a very important example of the lack of a basic resistance mechanism is the disease called acquired immune deficiency syndrome (AIDS).

Acquired Immune Deficiency Syndrome (AIDS)

Acquired immune deficiency syndrome (***AIDS***) is caused by the ***human immunodeficiency virus*** (***HIV***), which incapacitates the immune system (**Figure 18.23**). HIV belongs to the retrovirus family, whose nucleic acid core is RNA rather than DNA. Retroviruses possess an enzyme called reverse transcriptase, which, once the virus is inside a host cell, transcribes the virus's RNA into DNA, which is then integrated into the host cell's chromosomes. Replication of the virus inside the cell causes the death of the cell.

The cells that HIV preferentially (but not exclusively) enters are helper T cells. HIV infects these cells because the CD4 protein on the plasma membrane of helper T cells acts as a receptor for one of the HIV's surface proteins called gp120. As a result, the helper T cell binds the virus, making it possible for the virus to enter the cell. Very importantly, this binding of the HIV gp120 protein to CD4 is not sufficient to grant the HIV entry into the helper T cell. In addition, another surface protein on the helper T cell, one that serves normally as a receptor for certain chemokines, must serve as a coreceptor for the gp120. It has been found that persons who have a mutation in this chemokine receptor are highly resistant to infection with HIV. Much research is now focused on the possible therapeutic use of chemicals that can interact with and block this coreceptor.

Once in the helper T cell, the replicating HIV can directly kill the helper T cell but also indirectly causes its death via the body's usual immune attack. The attack is mediated in this case mainly by cytotoxic T cells attacking the virus-infected cells. In addition, by still poorly understood mechanisms, HIV causes the death of many *uninfected* helper T cells by apoptosis. Without adequate numbers of helper T cells, neither B cells nor cytotoxic T cells can function normally. As a result, the AIDS patient dies from infections and cancers that the immune system would ordinarily readily handle.

Figure 18.23 Human immunodeficiency viruses budding from a T cell.

AIDS was first described in 1981, and it has since reached epidemic proportions worldwide. The great majority of persons now infected with HIV have no symptoms of AIDS. It is important to distinguish between the presence of the symptomatic disease—AIDS—and asymptomatic infection with HIV. The latter is diagnosed by the presence of anti-HIV antibodies or HIV RNA in the blood. It is thought, however, that most infected persons will eventually develop AIDS, although at highly varying rates.

The path from HIV infection to AIDS commonly takes about 10 years in untreated persons. Typically, during the first 5 years, the rapidly replicating viruses continually kill large numbers of helper T cells in lymphoid tissues, but these are replaced by new cells. Therefore, the number of helper T cells stays relatively normal (about 1000 cells/mm^3 of blood) and the person is asymptomatic. During the next 5 years, this balance is lost; the number of helper T cells, as measured in blood, decreases to about half the normal level but many people still remain asymptomatic. As the helper T-cell count continues to decrease, however, the symptoms of AIDS begin—infections with bacteria, viruses, fungi, and parasites. These are accompanied by systemic symptoms of weight loss, lethargy, and fever—all caused by high concentrations of the cytokines that induce the acute phase response. Certain unusual cancers (such as ***Kaposi's sarcoma***) also occur with relatively high frequency. In untreated persons, death usually ensues within 2 years after the onset of AIDS symptoms.

The major routes of transmission of HIV are through (1) transfer of contaminated blood or blood products from one person to another, (2) unprotected sexual intercourse with an infected partner, (3) transmission from an infected mother to her fetus across the placenta during pregnancy and delivery, or (4) transfer via breast milk during nursing.

Two components to the therapeutic management of HIV-infected persons include one directed against the virus itself to delay progression of the disease and one to prevent or treat the opportunistic infections and cancers that ultimately cause death. The present recommended treatment for HIV infection itself is a simultaneous battery of at least four drugs. Two of these inhibit the action of the HIV enzyme (reverse transcriptase) that converts the viral RNA into the host cell's DNA; a third drug inhibits the HIV enzyme (α-protease) that cleaves a large protein into smaller units required for the assembly of new HIV; and a fourth drug blocks fusion of the virus with the T cell. The use of this complex and expensive regimen (called ***HAART,*** for *highly active anti-retroviral therapy*) greatly reduces the replication of HIV in the body and ideally should be introduced very early in the course of HIV infection, not just after the appearance of AIDS.

The ultimate hope for prevention of AIDS is the development of a vaccine. For a variety of reasons related to the nature of the virus (it generates large numbers of distinct subspecies) and the fact that it infects helper T cells, which are crucial for immune responses, vaccine development is not an easy task.

Antibiotics

The most important of the drugs employed in helping the body to resist microbes, mainly bacteria, are antibiotics. An ***antibiotic*** is any molecule or substance that kills bacteria. Antibiotics may be produced by one strain of bacteria to defend against other strains. Since the mid-twentieth century, commercial manufacture of antibiotics such as ***penicillin*** has revolutionized our ability to treat disease.

Antibiotics inhibit a wide variety of processes, including bacterial cell-wall synthesis, protein synthesis, and DNA replication. Fortunately, a number of the reactions involved in the synthesis of protein by bacteria and the proteins themselves are sufficiently different from those in human cells that certain antibiotics can inhibit them without interfering with the body's own protein synthesis. For example, the antibiotic ***erythromycin*** blocks the movement of ribosomes along bacterial messenger RNA.

Antibiotics, however, must not be used indiscriminately. They may exert allergic reactions, and they may exert toxic effects on the body's cells. Another reason for judicious use is the escalating and very serious problem of antibiotic resistance. Most large bacterial populations contain a few mutants that are resistant to the antibiotic, and these few may be capable of multiplying into large populations resistant to the effects of that particular antibiotic. Alternatively, the antibiotic can induce the expression of a latent gene that confers resistance. Finally, resistance can be transferred from one resistant microbe directly to another previously nonresistant microbe by means of DNA passed between them. (One example of how antibiotic resistance can spread by these phenomena is that many bacterial strains that were once highly susceptible to penicillin now produce an enzyme that cleaves the penicillin molecule.) Yet another reason for the judicious use of antibiotics is that these substances may actually contribute to a new infection by eliminating certain species of relatively harmless bacteria that ordinarily prevent the growth of more dangerous ones. One site in which this may occur is the large intestine, where the loss of harmless bacteria may account for the symptoms of cramps and diarrhea that occur in some individuals taking certain types of antibiotics.

18.6 Harmful Immune Responses

Until now, we have focused on the mechanisms of immune responses and their protective effects. The following section discusses how immune responses can sometimes actually be harmful or unwanted.

Graft Rejection

The major obstacle to successful transplantation of tissues and organs is that the immune system recognizes the transplants, called grafts, as foreign and launches an attack against them. This is called ***graft rejection.*** Although B cells and macrophages have some function, cytotoxic T cells and helper T cells are mainly responsible for graft rejection.

Except in the case of identical twins, the class I MHC proteins on the cells of a graft differ from the recipient's as do the class II molecules present on the macrophages in the graft (recall that virtually all organs and tissues have macrophages). Consequently, the MHC proteins of both classes are recognized as foreign by the recipient's T cells, and the cells bearing these proteins are destroyed by the recipient's cytotoxic T cells with the aid of helper T cells.

Some of the tools aimed at reducing graft rejection are radiation and drugs that kill actively dividing lymphocytes and thereby decrease the recipient's T-cell population. A very effective drug, however, is ***cyclosporine,*** which does not kill lymphocytes but rather blocks the production of IL-2 and other cytokines by helper T cells. This eliminates a critical signal for proliferation of both the helper T cells themselves and the cytotoxic T cells. Synthetic adrenal corticosteroids are also used to reduce the rejection.

Problems with the use of drugs like cyclosporine and potent synthetic adrenal corticosteroids include the following: (1) Immunosuppression with them is nonspecific, so patients taking them are at increased risk for infections and cancer; (2) they exert other toxic side effects; and (3) they must be used continuously to inhibit rejection. An important new kind of therapy, one that may be able to avoid these problems, is under study. Recall that immune tolerance for self proteins is achieved by clonal deletion and/or inactivation and that the mechanism for this is absence of a nonantigenic costimulus at the time the antigen is first encountered. The hope is that, at the time of graft surgery, treatment with drugs that block the complementary proteins constituting the costimulus may induce a permanent state of immune tolerance toward the graft.

Transfusion Reactions

Transfusion reaction, the illness caused when erythrocytes are destroyed during blood transfusion, is a special example of tissue rejection, one that illustrates the fact that antibodies rather than cytotoxic T cells can sometimes be the major factor in rejection. Erythrocytes do not have MHC proteins, but they do have plasma membrane proteins and carbohydrates (the latter linked to the membrane by lipids) that can function as antigens when exposed to another person's blood. There are more than 400 erythrocyte antigens, but the ABO system of carbohydrates is the most important for transfusion reactions.

Some people have the gene that results in synthesis of the A antigen, some have the gene for the B antigen, some have both genes, and some have neither gene. (Genes cannot code for the carbohydrates that function as antigens; rather, they code for the particular enzymes that catalyze the formation of the carbohydrates.) The erythrocytes of those with neither gene are said to have O-type erythrocytes. Consequently, the possible blood types are A, B, AB, and O (**Table 18.8**).

Type A individuals always have anti-B antibodies in their plasma. Similarly, type B individuals have plasma anti-A antibodies. Type AB individuals have neither anti-A nor anti-B antibody, and type O individuals have both. These antierythrocyte antibodies are called **natural antibodies.** How they arise naturally—that is, without exposure to the appropriate antigen-bearing erythrocytes—is not clear.

With this information as background, we can predict what happens if a type A person is given type B blood. There are two incompatibilities: (1) The recipient's anti-B antibodies cause the transfused cells to be attacked; and (2) the anti-A antibodies in the transfused plasma cause the recipient's cells to be attacked. The latter is generally of little consequence, however, because the

TABLE 18.8 Human ABO Blood Groups

			Genetic Possibilities		
Blood Group	**Percentage***	**Antigen on RBC**	**Homozygous**	**Heterozygous**	**Antibody in Blood**
A	42	A	AA	AO	Anti-B
B	10	B	BB	BO	Anti-A
AB	3	A and B	—	AB	Neither anti-A nor anti-B
O	45	Neither A nor B	OO	—	Both anti-A and anti-B

*In the United States.

transfused antibodies become so diluted in the recipient's plasma that they are ineffective in inducing a response. It is the destruction of the transfused cells by the recipient's antibodies that produces the problem.

Similar analyses show that the following situations would result in an attack on the transfused erythrocytes: a type B person given either A or AB blood; a type A person given either B or AB blood; a type O person given A, B, or AB blood. Type O people are, therefore, sometimes called universal donors, whereas type AB people are universal recipients. These terms are misleading, however, because besides antigens of the ABO system, many other erythrocyte antigens and plasma antibodies exist. Therefore, except in a dire emergency, the blood of the donor and recipient must be tested for incompatibilities directly by the procedure called ***cross-matching.*** The recipient's serum is combined on a glass slide with the prospective donor's erythrocytes (a "major" cross-match), and the mixture is observed for rupture (hemolysis) or clumping (agglutination) of the erythrocytes, either of which indicates a mismatch. In addition, the recipient's erythrocytes can be combined with the prospective donor's serum (a "minor" cross-match), looking again for mismatches.

Another group of erythrocyte membrane antigens of medical importance is the Rh system of proteins. There are more than 40 such antigens, but the one most likely to cause a problem is called Rh_o, known commonly as the **Rh factor** because it was first studied in rhesus monkeys. Human erythrocytes either have the antigen (Rh-positive) or lack it (Rh-negative). About 85% of the U.S. population is Rh-positive.

Antibodies in the Rh system, unlike the natural antibodies of the ABO system, follow the classical immunity pattern in that no one has anti-Rh antibodies unless exposed to Rh-positive cells from another person. This can occur if an Rh-negative person is subjected to multiple transfusions with Rh-positive blood, but its major occurrence involves the mother–fetus relationship. During pregnancy, some of the fetal erythrocytes may cross the placental barriers into the maternal circulation. If the mother is Rh-negative and the fetus is Rh-positive, this can induce the mother to synthesize anti-Rh antibodies. This occurs mainly during separation of the placenta at delivery. Consequently, a first Rh-positive pregnancy rarely offers any danger to the fetus because delivery occurs before the mother makes the antibodies. In future pregnancies, however, these antibodies will already be present in the mother and can cross the placenta to attack and hemolyze the erythrocytes of an Rh-positive fetus. This condition, which can cause an anemia severe enough to cause the death of the fetus in utero or of the newborn, is called ***hemolytic disease of the newborn.*** The risk increases with each Rh-positive pregnancy as the mother becomes more and more sensitized.

Fortunately, this disease can be prevented by giving an Rh-negative mother human gamma globulin against Rh-positive erythrocytes within 72 h after she has delivered an Rh-positive infant. These antibodies bind to the antigenic sites on any Rh-positive erythrocytes that might have entered the mother's blood during delivery and prevent them from inducing antibody synthesis by the mother. The administered antibodies are eventually metabolized.

You may be wondering whether ABO incompatibilities are also a cause of hemolytic disease of the newborn. For example, a woman with type O blood has antibodies to both the A and B antigens. If her fetus is type A or B, this theoretically should cause a problem. Fortunately, it usually does not, partly because the A and B antigens are not strongly expressed in fetal erythrocytes and partly because the antibodies, unlike the anti-Rh antibodies, are of the IgM type, which do not readily cross the placenta.

Allergy (Hypersensitivity)

Allergy (***hypersensitivity***) refers to diseases in which immune responses to environmental antigens cause inflammation and damage to the body itself. Antigens that cause allergy are called ***allergens;*** common examples include those in ragweed pollen and poison ivy. Most allergens themselves are relatively or completely harmless—the immune responses to them cause the damage. In essence, then, allergy is immunity gone wrong, for the response is inappropriate to the stimulus.

A word about terminology is useful here. There are four major types of hypersensitivity, as categorized by the different immunologic effector pathways involved in the inflammatory response. The term *allergy* is sometimes used popularly to denote only one of these types, that mediated by IgE antibodies. We will follow the common practice, however, of using the term *allergy* in its broader sense as synonymous with *hypersensitivity.*

To develop a particular allergy, a genetically predisposed person must first be exposed to the allergen. This initial exposure causes "sensitization." The subsequent exposures elicit the damaging immune responses that we recognize as the disease. The diversity of allergic responses reflects the different immunologic effector pathways elicited. The classification of allergic diseases is based on these mechanisms (**Table 18.9**).

In one type of allergy, the inflammatory response is independent of antibodies. It is due to pronounced secretion of

TABLE 18.9 Major Types of Hypersensitivity

I. Delayed hypersensitivity
   A. Mediated by helper T cells and macrophages
   B. Independent of antibodies

II. Immune-complex Hypersensitivity
   A. Mediated by antigen–antibody complexes deposited in tissue

III. Cytotoxic Hypersensitivity
   A. Mediated by antibodies that lead to damage or destruction of cells, as in hemolytic disease of the newborn

IV. Immediate Hypersensitivity
   A. Mediated by IgE antibodies, mast cells, and eosinophils

cytokines by helper T cells activated by antigen in the area. These cytokines themselves act as inflammatory mediators and also activate macrophages to secrete their potent mediators. Because it takes several days to develop, this type of allergy is known as ***delayed hypersensitivity.*** The tuberculin skin test is an example.

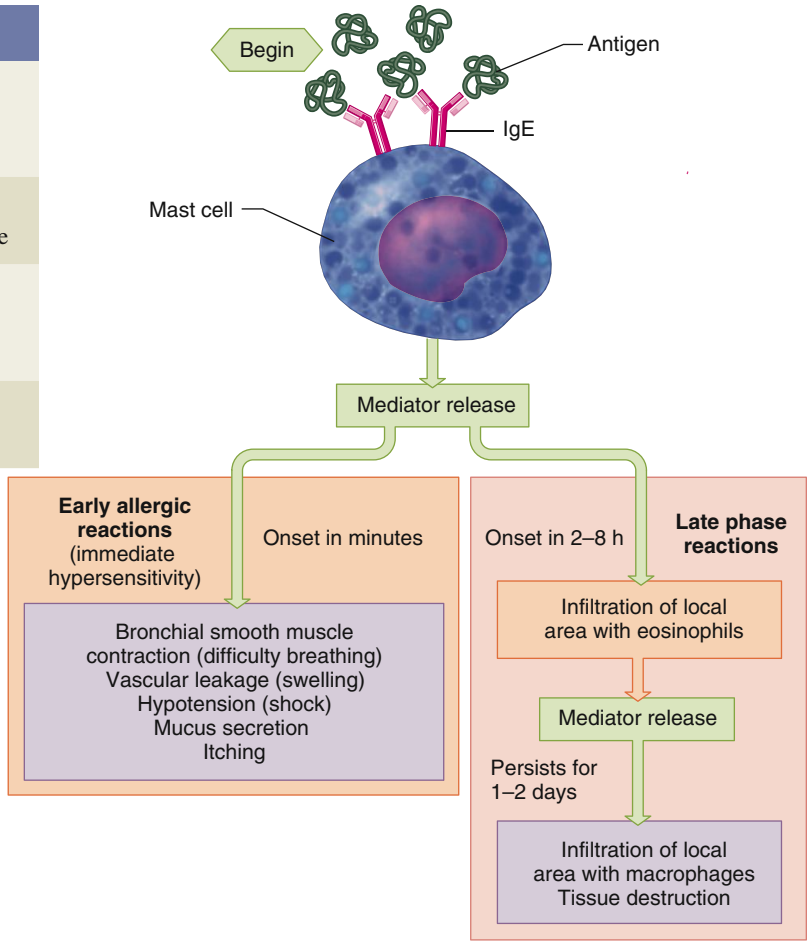
In contrast to this are the various types of antibody-mediated allergic responses. One important type is called ***immune-complex hypersensitivity.*** It occurs when so many antibodies (of either the IgG or IgM types) combine with free antigens that large numbers of antigen–antibody complexes precipitate out on the surface of endothelial cells or are trapped in capillary walls, particularly those of the renal corpuscles. These immune complexes activate complement, which then induces an inflammatory response that damages the tissues immediately surrounding the complexes.

A third type of hypersensitivity or ***cytotoxic hypersensitivity*** occurs when antibodies bind to cell-surface-associated antigens that lead to tissue injury or altered receptor function. An example of this type of hypersensitivity, just discussed, is hemolytic disease of the newborn.

Immediate Hypersensitivity

The more common type of antibody-mediated allergic response is called ***immediate hypersensitivity,*** because the response is usually very rapid in onset. It is also called ***IgE-mediated hypersensitivity*** because it involves IgE antibodies. In immediate hypersensitivity, initial exposure to the antigen leads to some antibody synthesis and, more important, to the production of memory B cells that mediate active immunity. Upon reexposure, the antigen elicits a more powerful antibody response. So far, none of this is unusual; the difference is that the particular antigens that elicit immediate hypersensitivity reactions stimulate, in genetically susceptible persons, the production of type IgE antibodies. Production of IgE requires the participation of a particular subset of helper T cells that are activated by the allergens presented by B cells. These activated helper T cells then release cytokines that preferentially stimulate differentiation of the B cells into IgE-producing plasma cells.

Upon their release from plasma cells, IgE antibodies circulate throughout the body and become attached via binding sites on their Fc portions to connective-tissue mast cells (**Figure 18.24**). When the same antigen type subsequently enters the body and combines with the IgE bound to the mast cell, this triggers the mast cell to secrete many inflammatory mediators, including



AP|R Figure 18.24 Immediate hypersensitivity allergic response. (a) Sequence of events. (b) Colorized electron micrograph of a mast cell, showing numerous secretory vesicles.

histamine, various eicosanoids, and chemokines. All of these mediators then initiate a local inflammatory response. (The entire sequence of events just described for mast cells can also occur with basophils in the circulation.)

Consequently, the symptoms of IgE-mediated allergy reflect the various effects of these inflammatory mediators and the body site in which the antigen–IgE–mast cell combination occurs. For example, when a previously sensitized person inhales ragweed pollen, the antigen combines with IgE on mast cells in the respiratory passages. The mediators released cause increased secretion of mucus, increased blood flow, swelling of the epithelial lining, and contraction of the smooth muscle surrounding the airways. As a result, the symptoms that characterize hay fever follow—congestion, runny nose, sneezing, and difficulty breathing. Immediate hypersensitivities to penicillin and insect venoms sometimes occur, and these are usually correlated with IgE production.

Allergic symptoms are usually localized to the site of antigen entry. If very large amounts of the chemicals released by the mast cells (or blood basophils) enter the circulation, however, systemic symptoms may result and cause severe hypotension and bronchiolar constriction. This sequence of events, called ***anaphylaxis,*** can cause death due to circulatory and respiratory failure; it can be elicited in some sensitized people by the antigen in a single bee sting.

The very rapid components of immediate hypersensitivity often proceed to a ***late phase reaction*** lasting many hours or days, during which large numbers of leukocytes, particularly eosinophils, migrate into the inflamed area. The chemoattractants involved are cytokines released by mast cells and helper T cells activated by the allergen. The eosinophils, once in the area, secrete mediators that prolong the inflammation and sensitize the tissues so that less allergen is required the next time to evoke a response.

Given the inappropriateness of most immediate hypersensitivity responses, how did such a system evolve? The normal physiological function of the IgE–mast cell–eosinophil pathways is to repel invasion by multicellular parasites that cannot be phagocytosed. The mediators released by the mast cells stimulate the inflammatory response against the parasites, and the eosinophils serve as the major killer cells against them by secreting several toxins. How this system also came to be inducible by harmless substances is not clear.

Autoimmune Disease

Whereas allergy is due to an inappropriate response to an environmental antigen, ***autoimmune disease*** is due to an inappropriate immune attack triggered by the body's own proteins acting as antigens. The immune attack, mediated by autoantibodies and self-reactive T cells, is directed specifically against the body's own cells that contain these proteins.

We explained earlier how the body is normally in a state of immune tolerance toward its own cells. Unfortunately, there are situations in which this tolerance breaks down and the body does in fact launch antibody-mediated or killer cell–mediated attacks against its own cells and tissues. A growing number of human diseases are being recognized as autoimmune in origin, some of which have been described elsewhere in this textbook. Examples are ***multiple sclerosis,*** in which myelin is attacked (see Chapter 6); ***myasthenia gravis,*** in which the nicotinic receptors for acetylcholine on skeletal muscle cells are the target (see Chapter 9); ***rheumatoid arthritis,*** in which connective tissues in joints are damaged; and ***type 1 diabetes mellitus,*** in which the insulin-producing cells of the pancreas are destroyed (see Chapter 16). Some possible causes for the body's failure to recognize its own cells are summarized in **Table 18.10**. Among the possible treatments for autoimmune disease currently in use are drugs that interfere with the actions of inflammatory mediators. One widely used drug, for example, binds to TNF-α and prevents it from interacting with its receptor.

Excessive Inflammatory Responses

Recall that complement, other inflammatory mediators, and the toxic chemicals secreted by neutrophils and macrophages are not specific with regard to their targets. Consequently, during an inflammatory response directed against pathogens, there can be so much generation or release of these substances that adjacent normal tissues may be damaged. These substances can also cause potentially lethal systemic responses. For example, macrophages release very large amounts of IL-1 and TNF-α, both of which are powerful inflammatory mediators (in addition to their other effects) in response to an infection with certain types of bacteria. These cytokines can cause profound vasodilation throughout the body, precipitating a type of hypotension called ***septic shock.*** This is often accompanied by dangerously high fevers. In other words, the cytokines released in response to the bacteria, not the bacteria themselves, cause septic shock.

TABLE 18.10 Some Possible Causes of Autoimmune Attack

There may be failure of clonal deletion in the thymus or of clonal inactivation in the periphery. This is particularly true for "sequestered antigens," such as certain proteins that are unavailable to the immune system during critical early-life periods.
Normal body proteins may be altered by combination with drugs or environmental chemicals. This leads to an attack on the cells bearing the now "foreign" protein.
In immune attacks on virus-infected bodily cells, so many cells may be destroyed that disease results.
Genetic mutations in the body's cells may yield new proteins that serve as antigens.
The body may encounter pathogens whose antigens are so close in structure to certain of the body's own proteins that the antibodies or cytotoxic T cells produced against these microbial antigens also attack cells bearing the self proteins.
Proteins normally never encountered by lymphocytes may become exposed as a result of some other disease.

Another important example of damage produced by excessive inflammation in response to pathogens is the dementia that occurs in AIDS. HIV does not itself attack neurons, but it does infect microglia. Such invasion causes the microglia, which function as macrophage-like cells, to produce very high concentrations of inflammatory cytokines and other molecules that are toxic to neurons. (Microglia are also implicated in noninfectious brain disorders, like ***Alzheimer's disease,*** that are characterized by inflammation.)

Excessive chronic inflammation can also occur in the absence of pathogen infection. Thus, various major diseases, including ***asthma,*** rheumatoid arthritis, and ***inflammatory bowel disease,*** are categorized as ***chronic inflammatory diseases.*** The causes of these diseases and the interplay between genetic and environmental factors are still poorly understood (see Chapters 13 and 15 for additional details on the nature of asthma and inflammatory bowel disease, respectively). Some, like rheumatoid arthritis, are mainly autoimmune in nature, but all appear to be associated with positive feedback increases in the production of cytokines and other inflammatory mediators.

Yet another example of excessive inflammation in a noninfectious state is the development of atherosclerotic plaques in blood vessels (see Figure 12.69). It is likely that, in response to endothelial cell dysfunction, the vessel wall releases inflammatory cytokines (IL-1, for example) that promote all stages of atherosclerosis—excessive clotting, chemotaxis of various leukocytes (as well as smooth muscle cells), and so on. The endothelial-cell dysfunction is caused by initially subtle vessel-wall injury by lipoproteins and other factors, including increased blood pressure and homocysteine (see Chapter 12).

In summary, the various mediators of inflammation and immunity are a double-edged sword. In usual amounts, they are essential for normal resistance; in excessive amounts, however, they can cause illness.

This completes the section on immunology. **Table 18.11** presents a summary of immune mechanisms in the form of a mini-glossary of cells and chemical mediators involved in immune responses. All of the material in this table has been covered in this chapter.

TABLE 18.11 A Mini-Glossary of Chemical Mediators and Cells Involved in Immune Functions

Chemical Mediators

Acute phase proteins Group of proteins secreted by the liver during systemic response to injury or infection; stimuli for their secretion are IL-1, IL-6, and other cytokines.

Antibodies Immunoglobulins secreted by plasma cells; combine with the type of antigen that stimulated their production and direct an attack against the antigen or a cell bearing it.

C1 The first protein in the classical complement pathway.

Chemoattractants A general name given to any chemical mediator that stimulates chemotaxis of neutrophils or other leukocytes.

Chemokines Any cytokine that functions as a chemoattractant.

Chemotaxin A synonym for chemoattractant.

Complement A group of plasma proteins that, upon activation, kill pathogens directly and facilitate the various steps of the inflammatory process, including phagocytosis; the classical complement pathway is triggered by antigen–antibody complexes, whereas the alternative pathway can operate independently of antibody.

C-reactive protein One of several proteins that function as nonspecific opsonins; production by the liver is increased during the acute phase response.

Cytokines General term for protein messengers that regulate immune responses; secreted by macrophages, monocytes, lymphocytes, neutrophils, and several nonimmune cell types; function both locally and as hormones.

Eicosanoids General term for products of arachidonic acid metabolism (prostaglandins, thromboxanes, leukotrienes); function as important inflammatory mediators.

Histamine An inflammatory mediator secreted mainly by mast cells; acts on microcirculation to cause vasodilation and increased permeability to protein.

IgA The class of antibodies secreted by cells lining the GI, respiratory, and genitourinary tracts.

IgD A class of antibodies whose function is unknown.

IgE The class of antibodies that mediates immediate hypersensitivity and resistance to parasites.

IgG The most abundant class of plasma antibodies.

IgM A class of antibodies that is produced first in all immune responses. Along with IgG, it provides the bulk of specific humoral immunity against bacteria and viruses.

(*continued*)

TABLE 18.11 A Mini-Glossary of Chemical Mediators and Cells Involved in Immune Functions *(continued)*

Immunoglobulin (Ig) Proteins that function as B-cell receptors and antibodies; the five major classes are IgA, IgD, IgE, IgG, and IgM.

Interferons (type I) Group of cytokines that nonspecifically inhibit viral replication.

Interferon (type II) Also called interferon-gamma, it stimulates the killing ability of NK cells and macrophages.

Interleukin 1 (IL-1) Cytokine secreted by macrophages (and other cells) that activates helper T cells, exerts many inflammatory effects, and mediates many of the systemic acute phase responses, including fever.

Chemical Mediators

Interleukin 2 (IL-2) Cytokine secreted by activated helper T cells that causes helper T cells, cytotoxic T cells, and NK cells to proliferate, and causes activation of macrophages.

Interleukin 6 (IL-6) Cytokine secreted by macrophages (and other cells) that exerts multiple effects on immune system cells, inflammation, fever, and the acute phase response.

Kinins Polypeptides that split from kininogens in inflamed areas and facilitate the vascular changes associated with inflammation; they also activate neuronal pain receptors.

Membrane attack complex (MAC) Group of complement proteins that forms channels in the surface of a microbe, making it leaky and killing it.

Natural antibodies Antibodies to the erythrocyte antigens (of the A or B type).

Opsonin General name given to any chemical mediator that promotes phagocytosis.

Perforin Protein secreted by cytotoxic T cells and NK cells that forms channels in the plasma membrane of the target cell, making it leaky and killing it; its structure and function are similar to that of the MAC in the complement system.

Tumor necrosis factor-alpha (TNF-α) Cytokine secreted by macrophages (and other cells) that has many of the same actions as IL-1.

Cells

Activated macrophages Macrophages whose killing ability has been enhanced by cytokines, particularly IL-2 and interferon-gamma.

Antigen-presenting cell (APC) Cell that presents antigen, complexed with MHC proteins, on its surface to T cells.

B cells Lymphocytes that, upon activation, proliferate and differentiate into antibody-secreting plasma cells; provide major defense against bacteria, viruses in the extracellular fluid, and toxins; and can function as antigen-presenting cells to helper T cells.

Cytotoxic T cells The class of T lymphocytes that, upon activation by specific antigen, directly attack the cells bearing that type of antigen; are major killers of virus-infected cells and cancer cells; and bind antigen associated with class I MHC proteins.

Dendritic cells Cells that carry out phagocytosis and serve as antigen-presenting cells.

Eosinophils Leukocytes involved in destruction of parasites and in immediate hypersensitivity responses.

Helper T cells The class of T cells that, via secreted cytokines, have a stimulatory function in the activation of B cells and cytotoxic T cells; also can activate NK cells and macrophages; and bind antigen associated with class II MHC proteins.

Lymphocytes The type of leukocyte responsible for adaptive immune responses; categorized mainly as B cells, T cells, and NK cells.

Macrophages Cell type that (1) functions as a phagocyte, (2) processes and presents antigen to helper T cells, and (3) secretes cytokines involved in inflammation, activation of lymphocytes, and the systemic acute phase response to infection or injury.

Mast cells Tissue cells that bind IgE and release inflammatory mediators in response to parasites and immediate hypersensitivity reactions.

Memory cells B cells and cytotoxic T cells that differentiate during an initial immune response and respond rapidly during a subsequent exposure to the same antigen.

Monocytes A type of leukocyte; leaves the bloodstream and is transformed into a macrophage.

Natural killer (NK) cells Class of lymphocytes that bind to cells bearing foreign antigens without specific recognition and kill them directly; major targets are virus-infected cells and cancer cells; participate in antibody-dependent cellular cytotoxicity (ADCC).

Neutrophils Leukocytes that function as phagocytes and also release chemicals involved in inflammation.

Plasma cells Cells that differentiate from activated B lymphocytes and secrete antibodies.

T cells Lymphocytes derived from precursors that differentiated in the thymus; see *Cytotoxic T cells* and *Helper T cells.*

SUMMARY

Cells and Secretions Mediating Immune Defenses

I. Immune defenses may be nonspecific so that the identity of the target is not recognized, or they may be specific so that it is recognized.

II. The cells of the immune system are leukocytes (neutrophils, eosinophils, basophils, monocytes, and lymphocytes), plasma cells, macrophages, dendritic cells, and mast cells. The leukocytes use the blood for transportation but function mainly in the tissues.

III. Cells of the immune system (as well as some other cells) secrete protein messengers that regulate immune responses and are collectively called cytokines.

Innate Immune Responses

I. External barriers to infection are the skin; the linings of the respiratory, gastrointestinal, and genitourinary tracts; the cilia of these linings; and antimicrobial chemicals in glandular secretions.

II. Inflammation, the local response to infection, includes vasodilation, increased vascular permeability to protein, phagocyte chemotaxis, destruction of the invader via phagocytosis or extracellular killing, and tissue repair.
   a. The mediators controlling these processes, summarized in Table 18.3, are either released from cells in the area or generated extracellularly from plasma proteins.
   b. The main cells that function as phagocytes are the neutrophils, monocytes, macrophages, and dendritic cells. These cells also secrete many inflammatory mediators.
   c. One group of inflammatory mediators—the complement family of plasma proteins activated during nonspecific inflammation by the alternative complement pathway—not only stimulates many of the steps of inflammation but mediates extracellular killing via the membrane at tack complex.
   d. The final response to infection or tissue damage is tissue repair.

III. Interferons stimulate the production of intracellular proteins that nonspecifically inhibit viral replication.

IV. Toll-like receptors are evolutionarily ancient proteins that recognize pathogen-associated molecular patterns that are highly conserved features of pathogens. TLRs belong to a family of proteins called pattern-recognition receptors and may be among the first molecules to have evolved in eukaryotic organisms to combat microbial diseases.

Adaptive Immune Responses

I. Lymphocytes mediate adaptive immune responses.

II. Adaptive immune responses occur in three stages.
   a. A lymphocyte programmed to recognize a specific antigen encounters it and binds to it via plasma membrane receptors specific for the antigen.
   b. The lymphocyte undergoes activation—a cycle of cell divisions and differentiation.
   c. The multiple active lymphocytes produced in this manner launch an attack all over the body against the specific antigens that stimulated their production.

III. The lymphoid organs are categorized as primary (bone marrow and thymus) or secondary (lymph nodes, spleen, tonsils, and lymphocyte collections in the linings of the body's tracts).
   a. The primary lymphoid organs are the sites of maturation of lymphocytes that will then be carried to the secondary lymphoid organs, which are the major sites of lymphocyte cell division and adaptive immune responses.
   b. Lymphocytes undergo a continuous recirculation among the secondary lymphoid organs, lymph, blood, and all the body's organs and tissues.

IV. The three broad populations of lymphocytes are B, T, and NK cells.
   a. B cells mature in the bone marrow and are carried to the secondary lymphoid organs, where additional B cells arise by cell division.
   b. T-cell precursors leave the bone marrow, migrate to the thymus, and undergo maturation there. These cells then circulate between the blood and secondary lymphoid organs. Stimulation with antigen and costimulatory molecules lead to T cells' expansion by cell division.
   c. NK cells originate in the bone marrow.

V. B cells and T cells have different functions.
   a. B cells, upon activation, differentiate into plasma cells, which secrete antibodies. Antibody-mediated responses constitute the major defense against bacteria, viruses, and toxins in the extracellular fluid.
   b. Cytotoxic T cells directly attack and kill virus-infected cells and cancer cells, without the participation of antibodies.
   c. Helper T cells stimulate B cells and cytotoxic T cells via the cytokines they secrete. With few exceptions, this help is essential for activation of the B cells and cytotoxic T cells.

VI. B-cell plasma membrane receptors are copies of the specific antibody (immunoglobulin) that the cell is capable of producing.
   a. Any given B cell or clone of B cells produces antibodies that have a unique antigen-binding site.
   b. Antibodies are composed of four interlocking polypeptide chains; the variable regions of the antibodies are the sites that bind antigen.

VII. T-cell surface plasma membrane receptors are not immunoglobulins, but they do have specific antigen-binding sites that differ from one T-cell clone to another.
   a. The T-cell receptor binds antigen only when the antigen is complexed to one of the body's own plasma membrane MHC proteins.
   b. Class I MHC proteins are found on all nucleated cells of the body, whereas class II MHC proteins are found only on macrophages, B cells, and dendritic cells. Cytotoxic T cells require antigen to be complexed to class I proteins, whereas helper T cells require class II proteins.

VIII. Antigen presentation is required for T-cell activation.
   a. Only macrophages, B cells, and dendritic cells function as antigen-presenting cells (APCs) for helper T cells. The antigen is internalized by the APC and hydrolyzed to polypeptide fragments, which are complexed with class II MHC proteins. This complex is then shuttled to the plasma membrane of the APC, which also delivers a nonspecific costimulus to the T cell and secretes interleukin 1 (IL-1) and tumor necrosis factor-alpha (TNF-α).
   b. A virus-infected cell or cancer cell can function as an APC for cytotoxic T cells. The viral antigen or cancer-associated

antigen is synthesized by the cell itself and hydrolyzed to polypeptide fragments, which are complexed to class I MHC proteins. The complex is then shuttled to the plasma membrane of the cell.

IX. NK cells have the same targets as cytotoxic T cells, but they are not antigen-specific; most of their mechanisms of target identification are not understood.

X. Immune tolerance is the result of clonal deletion and clonal inactivation.

XI. In antibody-mediated responses, the membrane receptors of a B cell bind antigen, and at the same time a helper T cell also binds antigen in association with a class II MHC protein on a macrophage or other APC.
   a. The helper T cell, activated by the antigen, by a nonantigenic protein costimulus, and by IL-1 and TNF-α secreted by the APC, secretes IL-2, which then causes the helper T cell to proliferate into a clone of cells that secrete additional cytokines.
   b. These cytokines then stimulate the antigen-bound B cell to proliferate and differentiate into plasma cells, which secrete antibodies. Some of the activated B cells become memory cells, which are responsible for active immunity.
   c. There are five major classes of secreted antibodies: IgG, IgM, IgA, IgD, and IgE. The first two are the major antibodies against bacterial and viral infection.
   d. The secreted antibodies are carried throughout the body by the blood and combine with antigen. The antigen–antibody complex enhances the inflammatory response, in large part by activating the complement system. Complement proteins mediate many steps of inflammation, act as opsonins, and directly kill antibody-bound cells via the membrane attack complex.
   e. Antibodies of the IgG class also act directly as opsonins and link target cells to NK cells, which directly kill the target cells.
   f. Antibodies also neutralize toxins and extracellular viruses.

XII. Virus-infected cells and cancer cells are killed by cytotoxic T cells, NK cells, and activated macrophages.
   a. A cytotoxic T cell binds via its membrane receptor to cells bearing a viral antigen or cancer-associated antigen in association with a class I MHC protein.
   b. Activation of the cytotoxic T cell also requires cytokines secreted by helper T cells, themselves activated by antigen presented by a macrophage. The cytotoxic T cell then releases perforin, which kills the attached target cell by making it leaky.
   c. NK cells and macrophages are also stimulated by helper T-cell cytokines, particularly IL-2 and interferon-gamma, to attack and kill virus-infected or cancer cells.

Systemic Manifestations of Infection

I. The acute phase response is summarized in Figure 18.22.

II. The major mediators of this response are IL-1, TNF-α, and IL-6.

Factors That Alter the Resistance to Infection

I. The body's capacity to resist infection is influenced by nutritional status, the presence of other diseases, psychological factors, and the intactness of the immune system.

II. AIDS is caused by a retrovirus that destroys helper T cells and therefore reduces the body's ability to resist infection and cancer.

III. Antibiotics interfere with the synthesis of macromolecules by bacteria.

Harmful Immune Responses

I. Rejection of tissue transplants is initiated by MHC proteins on the transplanted cells and is mediated mainly by cytotoxic T cells.

II. Transfusion reactions are mediated by antibodies.
   a. Transfused erythrocytes will be destroyed if the recipient has natural antibodies against the antigens (type A or type B) on the cells.
   b. Antibodies against Rh-positive erythrocytes can be produced following the exposure of an Rh-negative person to such cells.

III. Allergies (hypersensitivity reactions) caused by allergens are of several types.
   a. In delayed hypersensitivity, the inflammation is due to the interplay of helper T-cell cytokines and macrophages. Immune-complex hypersensitivity is due to complement activation by antigen–antibody complexes.
   b. In immediate hypersensitivity, antigen binds to IgE antibodies, which are themselves bound to mast cells. The mast cells then release inflammatory mediators, such as histamine, that produce the symptoms of allergy. The late phase of immediate hypersensitivity is mediated by eosinophils.

IV. Autoimmune attacks are directed against the body's own proteins acting as antigens. Reasons for the failure of immune tolerance are summarized in Table 18.10.

V. Normal tissues can be damaged by excessive inflammatory responses to pathogens.

REVIEW QUESTIONS

1. What are the major cells of the immune system and their general functions?
2. Describe the major anatomical and biochemical barriers to infection.
3. Name the three cell types that function as phagocytes.
4. List the sequence of events in an inflammatory response and describe each step.
5. Name the sources of the major inflammatory mediators.
6. What triggers the alternative pathway for complement activation? What functions does complement have in inflammation and cell killing?
7. Describe the antiviral function of type I interferon.
8. Name the lymphoid organs. Contrast the functions of the bone marrow and thymus with those of the secondary lymphoid organs.
9. Name the various populations and subpopulations of lymphocytes and discuss their functions in adaptive immune responses.
10. Contrast the major targets of antibody-mediated responses and responses mediated by cytotoxic T cells and NK cells.
11. How do the Fc and variable regions of antibodies differ?
12. What are the differences between B-cell receptors and T-cell receptors? Between cytotoxic T-cell receptors and helper T-cell receptors?
13. Compare and contrast antigen presentation to helper T cells and cytotoxic T cells.
14. Compare and contrast cytotoxic T cells and NK cells.
15. What two processes contribute to immune tolerance?
16. Diagram the sequence of events in an antibody-mediated response, including the role of helper T cells, interleukin 1, and interleukin 2.
17. Contrast the general functions of the different antibody classes.

18. How is complement activation triggered in the classical complement pathway, and how does complement "know" what cells to attack?
19. Name two ways in which the presence of antibodies enhances phagocytosis.
20. How do NK cells recognize which cells to attack in ADCC?
21. Diagram the sequence of events by which a virus-infected cell is attacked and destroyed by cytotoxic T cells. Include the roles of cytotoxic T cells, helper T cells, interleukin 1, and interleukin 2.
22. Contrast the extracellular and intracellular phases of immune responses to viruses, discussing the role of interferons.
23. List the systemic responses to infection or injury and the mediators responsible for them.
24. What factors influence the body's resistance to infection?
25. What is the major defect in AIDS, and what causes it?
26. What is the major cell type involved in graft rejection?
27. Diagram the sequences of events in immediate hypersensitivity.

KEY TERMS

adaptive immune responses
immune surveillance
immune system
immunology
innate immune responses
microbes
pathogens

18.1 Cells and Secretions Mediating Immune Defenses

basophils
B cells
B lymphocytes
cytokines
dendritic cells
eosinophils
histamine
leukocytes
lymphocytes
macrophages
mast cells
monocytes
natural killer (NK) cells
neutrophils
phagocytes
phagocytosis
plasma cells
T cells
T lymphocytes

18.2 Innate Immune Responses

alternative complement pathway
chemoattractants
chemokines
chemotaxins
chemotaxis
C1
classical complement pathway
complement
C-reactive protein
C3b
diapedesis
hydrogen peroxide
inflammation
kinins
margination
membrane attack complex (MAC)
nitric oxide
opsonin
pathogen-associated molecular patterns (PAMPs)
pattern-recognition receptors (PRRs)
phagolysosome
phagosome
Toll-like receptors (TLRs)
type I interferons
type II interferons (interferon-gamma)

18.3 Adaptive Immune Responses

activated macrophages
active immunity
adenoids
antibodies
antibody-dependent cellular cytoxicity (ADCC)
antibody-mediated responses
antigen
antigen-binding site
antigen presentation
antigen-presenting cells (APCs)
class I MHC proteins
class II MHC proteins
clonal deletion
clonal expansion
clonal inactivation
clone
costimulus
cytotoxic T cells
epitopes
Fc
gamma globulin
helper T cells
IgA
IgD
IgE
IgG
IgM
immune tolerance
immunoglobulins
interleukin 1 (IL-1)
interleukin 2 (IL-2)
lymph nodes
lymphocyte activation
lymphoid organs
major histocompatibility complex (MHC)
memory cells
MHC proteins
passive immunity
perforin
primary lymphoid organs
regulatory T cells
secondary lymphoid organs
spleen
thymus
tonsils
tumor necrosis factor-alpha (TNF-α)

18.4 Systemic Manifestations of Infection

acute phase proteins
acute phase response
interleukin 6 (IL-6)

18.6 Harmful Immune Responses

natural antibodies
Rh factor

CLINICAL TERMS

Because of the subject matter of this chapter, it is difficult to distinguish between physiological key terms and "clinical" terms. This list is limited largely to specific diseases, their causes, symptoms and signs, and treatments.

bacteria
viruses

18.3 Adaptive Immune Responses

oncogenes
vaccine

18.5 Factors That Alter the Resistance to Infection

acquired immune deficiency syndrome (AIDS)
antibiotic
erythromycin
HAART
human immunodeficiency virus (HIV)
Kaposi's sarcoma
penicillin
severe combined immunodeficiency (SCID)

18.6 Harmful Immune Responses

allergens
allergy (hypersensitivity)
Alzheimer's disease
anaphylaxis
asthma
autoimmune disease
chronic inflammatory diseases
cross-matching
cyclosporine
cytotoxic hypersensitivity
delayed hypersensitivity
graft rejection
hemolytic disease of the newborn
IgE-mediated hypersensitivity
immediate hypersensitivity
immune-complex hypersensitivity
inflammatory bowel disease
late phase reaction
multiple sclerosis
myasthenia gravis
rheumatoid arthritis
septic shock
transfusion reaction
type 1 diabetes mellitus

CHAPTER 18

Clinical Case Study: A Teenage Girl with Widespread Pain and Severe Facial Rash

A 17-year-old Caucasian girl returned from a long day at the beach one sunny, late-summer day complaining of a sunburn and fatigue. Over the next few days, the "sunburn" took on the form of a rash across her cheeks and the bridge of her nose, and the girl began to feel sick, tired, and "achy all over." She assumed her symptoms were from severe sunburn. After a few days, the rash subsided a bit, but over the next several weeks she regularly felt pain and stiffness in her knees, wrists, and fingers. She did not alert her parents of this, however, thinking it was of no importance and would eventually subside. During this time, she spent considerable time outdoors in after-school activities and on weekends, being exposed to the sun. One day, while sitting at the computer, her fingers became so stiff that she had to stop typing. She could see that her fingers were swollen. She also felt nauseated, and upon standing, her knees felt stiff and very painful. At this point, she told her parents she was feeling very ill, and a visit was scheduled to see her physician.

The physician noted that the girl had an unremarkable medical history with no chronic illnesses, had until recently been very fit and active, and had no history of major allergies or disease. Upon examination, however, she did appear extremely fatigued and weak. The joints in her fingers, wrists, knees, and toes were slightly swollen and had restricted movement. The rash had also reappeared on her face. At the time of her visit, the girl had a slightly increased body temperature of 37.6°C (99.7°F). Also, the girl indicated that recently it "hurt to breathe" and that she felt "winded" all the time, which the physician took to mean that the girl was experiencing ***dyspnea*** (shortness of breath). The physician listened to her heart and chest sounds through a stethoscope and detected sounds that suggested inflammation. A chest radiograph revealed fluid buildup in the pleural membranes around the lungs and in the pericardium around the heart. Blood tests indicated an increased concentration of liver enzymes, suggesting that some liver cells were damaged or dying and had released their contents into the blood. The concentration of albumin, the major protein in blood, was lower than normal. Because albumin is made in the liver, this was another sign that the liver was not functioning normally. The tests also revealed that the concentration of creatinine in the blood was slightly elevated, and a urinalysis revealed trace amounts of protein and blood in the urine. This suggested that the girl's kidneys were not functioning properly.

Reflect and Review #1

- What is creatinine, and what might an increase in its concentration in the blood suggest about renal function? (Refer back to Chapter 14, Section 14.4, for a discussion of clearance.)

Finally, the girl's hematocrit was 34.1%, which is below normal (see Chapter 12). Taken together, these test results were sufficiently serious that the physician admitted the girl to the hospital so that her condition could be carefully monitored and treated and additional tests could be performed.

The physician concluded that the girl may have an autoimmune disease known as ***systemic lupus erythematosus*** (***SLE***). Although a relatively uncommon disease (about 1.5 million total cases in the United States), all of the signs in this girl were consistent with a diagnosis of SLE. As with many autoimmune diseases, the majority (>90%) of SLE sufferers are female. The disease can occur at any age, but it most commonly appears in women of childbearing age and its onset can be quite sudden.

The two major immune dysfunctions in SLE are hyperactivity of T and B cells, with overexpression of "self" antibodies, and decreased negative regulation of the immune response.

Reflect and Review #2

- What class of immune cells are important in negatively regulating immune function? (Recall the three major types of T cells.) What steroid hormone inhibits immune function? (Refer back to Figure 18.22.)

In some other autoimmune diseases, one or a small number of antigens appear to be the target of the immune attack, and these are often localized to one or a few organs. In SLE, however, the reaction is much more widespread. The most common antigens are proteins and double-stranded DNA in the nuclei of all nucleated cells. Because all nucleated cells share most of the same DNA and nuclear proteins, few—if any—parts of the body are not susceptible to immune attack in SLE. A subsequent blood test in this patient was positive for the presence of circulating antibodies that recognize cell nuclear material, confirming the diagnosis of SLE.

Exactly what initiates the immune response in SLE is unclear. However, it is known that most people with this disease are photosensitive—that is, their skin cells are readily damaged by ultraviolet light from the sun. When these cells die, their nuclear contents become exposed to phagocytes and other components of the immune system. It is also believed that UV light induces intact skin cells to express certain proteins that are antigenic in SLE. As a result, symptoms of SLE tend to flare up when a person with the disease is exposed to excessive sunlight. This is what happened to our subject after a day at the beach without sunscreen and as she continued to spend considerable time outdoors thereafter.

SLE has a strong genetic component, as evidenced by the fact that approximately 40% to 50% of identical twins share the disease when one is afflicted. Moreover, there is an increased frequency of five specific class II MHC variants in people with SLE, as well as deficient or abnormal complement proteins. Still, environmental triggers almost certainly elicit the disease in genetically susceptible people (because, as stated, in half the cases in which one twin has SLE, the other does not). There is no conclusive evidence that infections due to viral invasion are a trigger for the development of SLE. In addition to sunlight, other triggers associated with the appearance of SLE are certain chemicals and foods, such as alfalfa sprouts.

SLE can be mild or severe, intermittent or chronic. In most cases, though, the effects are widespread. Typically, connective-tissue involvement is extensive, with repeated episodes of inflammation in joints and skin. The outer covering of the heart (pericardium) and the pleural membranes of the lungs may become inflamed.

Gastrointestinal function may be affected, resulting in nausea or diarrhea, and retinal damage is sometimes observed. Even the brain is not spared, as cognitive dysfunction and even seizures may arise in severe cases. The skin often develops inflamed patches, notably on the face along the cheeks and bridge of the nose, forming the so-called ***butterfly*** (***malar***) ***rash*** seen in some patients with SLE (Figure 18.25). One of the most serious manifestations of SLE occurs when immune complexes and immunoglobulins accumulate in the glomeruli of the nephrons of the kidney (see Chapter 14 for description of nephrons). This often leads to ***nephritis*** (inflammation of the nephrons) and results in damaged, obstructed, or leaky glomeruli. The appearance of protein or blood in the urine, therefore, is a clinical finding often associated with SLE.

Finally, certain proteins on the plasma membranes of red blood cells and platelets may also become antigenic in SLE. When the immune system attacks these structures, the results are lysis of red blood cells and destruction and loss of platelets (***thrombocytopenia***). Loss of red blood cells in this manner contributes to the condition known as ***hemolytic anemia,*** a common manifestation of SLE. Our subject demonstrated widespread organ malfunction, evidenced by blood tests assessing liver and kidney function, radiograph results, and urinalysis. She also had mild hemolytic anemia. Considering the extent to which her disease affected her skin and other organs, it is not surprising that she felt ill and "achy all over."

In addition to the production of self antibodies in large numbers, there also appears to be a failure of the immune system to regulate itself in SLE. Consequently, the immune attacks, once begun, do not stop after a few days but instead continue. Some investigators believe this may be related to a deficiency or inactivity of regulatory T cells, but this has not been proven. It is clear, however, that the circulating concentrations of numerous cytokines—notably, IL-10, IL-12, and TNF-α—are abnormal in persons with SLE.

Figure 18.25 Characteristic butterfly or malar rash in a patient with systemic lupus erythematosus.

The treatments for SLE depend on its severity and the overall physical condition of the patient. In mild flare-ups, nonsteroidal anti-inflammatory drugs (NSAIDs) may be sufficient to control pain and inflammation, together with changes in lifestyle to avoid potential triggers. In more advanced cases, immunosuppression with high doses of synthetic adrenal corticosteroids (such as prednisone) or other potent immunosuppressant drugs is employed. Our patient was started on prednisone at an initially high dosage to control the widespread inflammation and immune attacks. The dose was tapered off once her blood tests were restored to nearly normal, because chronic high dosages of prednisone can have severe side effects (see Section D of Chapter 11 for a discussion of the effects of high concentrations of glucocorticoids). She was additionally started on ***hydroxychloroquine,*** an antimalarial drug commonly used in treatment of SLE due to its immunomodulatory effects. She was advised to immediately begin taking ibuprofen (an NSAID) whenever her symptoms worsened in the future and to use hydrocortisone skin cream if she developed rashes again. She was counseled on lifestyle changes that she would need to follow for the rest of her life. These included eating a healthy diet and exercising to promote cardiovascular health, to avoid smoking (which is a major risk factor for blood vessel disease and hypertension), and most significantly to avoid exposure to the sun when possible. This meant using sunscreen and a wide-brimmed hat at all times when outdoors, not just when at the beach, and even indoors because fluorescent and halogen lights emit sufficient UV light to trigger symptoms in some SLE patients. As she was of reproductive age, she was counseled about the possible effects of SLE on pregnancy and was advised against the use of estrogen-containing oral contraceptives, as estrogen has been reported to trigger or worsen flare-ups of SLE. After several days, a follow-up urinalysis indicated an absence of protein; therefore, kidney damage was minimal. Additional blood tests were near normal for liver and kidney function, and a chest radiograph was normal. She was released from the hospital but returned 2 weeks later for follow-up tests, which were all nearly or completely normal. One month after beginning treatment, she was able to resume normal activities and most of the stiffness in her joints had disappeared. Her steroid dosage was reduced to a very low dose every other day and then stopped. She was advised to call her physician if and when symptoms flared so that a new course of therapy could be initiated quickly.

Clinical terms: butterfly (malar) rash, dyspnea, hemolytic anemia, hydroxychloroquine, nephritis, systemic lupus erythematosus (SLE), thrombocytopenia.

See Chapter 19 for complete, integrative case studies.

CHAPTER 18 TEST QUESTIONS *Recall and Comprehend*

Answers appear in Appendix A.

These questions test your recall of important details covered in this chapter. They also help prepare you for the type of questions encountered in standardized exams. Many additional questions of this type are available on Connect and LearnSmart.

1. Which of the following is an opsonin?
   a. IL-2
   b. C1 protein
   c. C3b protein
   d. C-reactive protein
   e. membrane attack complex
2. Which is/are important in innate immune responses?
   a. interferons
   b. clonal inactivation
   c. lymphocyte activation
   d. secretion of antibodies from plasma cells
   e. class 1 MHC proteins
3. A second exposure to a given foreign antigen elicits a rapid and pronounced immune response because
   a. passive immunity occurs after the first exposure.
   b. some B cells differentiate into memory B cells after the first exposure.
   c. a greater number of antigen-presenting cells are available due to the earlier exposure.
   d. the array of class II MHC proteins expressed by antigen-presenting cells is permanently altered by the first exposure.
   e. Both a and b are correct.
4. Which statement is incorrect?
   a. The most abundant immunoglobulins in serum are IgG and IgM antibodies.
   b. IgG antibodies are involved in adaptive immune responses against bacteria and viruses in the extracellular fluid.
   c. IgM antibodies are primarily involved in immune defense mechanisms found in the surface or lining of the gastrointestinal, respiratory, and genitourinary tracts.
   d. All antibodies of a given class have an Fc portion that is identical in amino acid sequence.
   e. Antibodies can exist at the surface of a B cell or be circulating freely in the blood.

True or False

5. Antibiotics are useful for treating illnesses caused by viruses.
6. Chronic inflammatory diseases may occur even in the absence of any infection.
7. All T cells are lymphocytes, but not all lymphocytes are T cells.
8. Edema (swelling), which occurs during inflammation, has important adaptive value in helping defend against infection or injury.
9. Bone marrow and the thymus are examples of secondary lymphoid organs.
10. Toll-like receptors are the major defense against specific pathogens and therefore have an important function in adaptive immunity.

CHAPTER 18 TEST QUESTIONS *Apply, Analyze, and Evaluate*

Answers appear in Appendix A.

These questions, which are designed to be challenging, require you to integrate concepts covered in the chapter to draw your own conclusions. See if you can first answer the questions without using the hints that are provided; then, if you are having difficulty, refer back to the figures or sections indicated in the hints.

1. If an individual failed to develop a thymus because of a genetic defect, what would happen to the immune responses mediated by antibodies and those mediated by cytotoxic T cells? *Hint:* Think how helper T cells and B cells are functionally related, and see Figure 18.10.
2. What abnormalities would a person with a neutrophil deficiency display? A person with a monocyte deficiency? *Hint:* Refer to Table 18.1 and recall that monocytes also differentiate into another type of cell.
3. An experimental animal is given a drug that blocks phagocytosis. Will this drug prevent the animal's immune system from killing foreign cells via the complement system? *Hint:* Does the complement system work in more than one way? See Figure 18.7.
4. If the Fc portion of a person's antibodies is abnormal, what effects could this have on antibody-mediated responses? *Hint:* See text associated with Figure 18.12.
5. Would you predict that patients with AIDS would develop fever in response to an infection? Explain. *Hint:* Which cells are affected in AIDS, and which cells secrete substances that cause fever? See Figure 18.22.

CHAPTER 18 TEST QUESTIONS *General Principles Assessment*

Answers appear in Appendix A.

These questions reinforce the key theme first introduced in Chapter 1, that general principles of physiology can be applied across all levels of organization and across all organ systems.

1. *Homeostasis is essential for health and survival.* Using Figure 18.22 as your guide, describe several ways in which infection may result in a disruption of homeostasis.

CHAPTER 18 ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS

Figure 18.6 The C3b receptor should have a ligand-binding site that is *specific* for C3b and that binds C3b with high *affinity*.

Figure 18.8 Many molecules in the body act this way. For example, somatostatin acts locally in the stomach to control acid production (paracrine) and is secreted into the hypothalamo–pituitary portal veins to control growth hormone secretion (endocrine). Testosterone acts locally within the testes (paracrine) and reaches other targets through the blood (endocrine).

Figure 18.9 Vasodilation and increased protein permeability of the microcirculation both contribute to an increase in the rate of filtration of fluid from the plasma into the interstitial space. Because lymph vessels are the main route by which fluid and protein are returned from the interstitial space to the circulatory system (see Figure 12.50), these changes will lead to increased flow of lymph. As that fluid flows through the lymph nodes, lymphocytes are exposed to antigens from the invading pathogen, thus activating the adaptive immune response.

Figure 18.10 Myeloid stem cells differentiate into four types of leukocytes (neutrophils, eosinophils, basophils, and monocytes). Via another developmental pathway, myeloid cells also differentiate into mast cells and dendritic cells. Macrophages differentiate from monocytes.

Figure 18.12 The structures of a ligand and the protein to which it binds determine the function of both the ligand and protein. Nowhere is this more evident than in the incredible array of specific antigen:immunoglobulin interactions. Which antigen binds to which immunoglobulin is determined entirely by the structure of the ligand *and* the structures of the variable ends of each immunoglobulin molecule. It is this specificity that imparts a function to the immunoglobulin. The structure of the constant ends of immunoglobulins is also important in their function, because it is this structure that is recognized by phagocytes when the immunoglobulin is a circulating antibody attached to a pathogen.

Figure 18.16 The body may encounter many common pathogens multiple times over the course of a lifetime. By establishing a population of memory cells, each subsequent infection can be defended against more efficiently and quickly.

Figure 18.19 Note the log scale of the y-axis. The first exposure to antigen elicited a response from about 2 units to 10 units (fivefold), whereas the second exposure elicited a response from about 2 units up to nearly 10,000 (5000-fold). Roughly, then, the second response was about 1000-fold greater in magnitude.

Figure 18.21 This is an example of positive feedback (refer back to Chapter 1), because the stimulus (interferon-gamma) results in an activated cell that produces more of the stimulus.

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