

HUMAN PHYSIOLOGY

AN INTEGRATED APPROACH FOURTH EDITION

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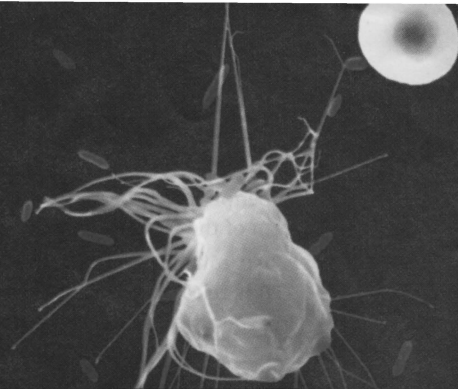


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Although, at first sight, the immune system may appear to be autonomous, it is connected by innumerable structural and functional bridges with the nervous system and the endocrine system, so as to constitute a multisystem.

—Branislav D. Jankovic, *Neuroimmunomodulation: The State of the Art*, 1994



Alveolar macrophage attacking E. coli bacteria (turquoise). A red blood cell is at the upper right.

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BACKGROUND BASICS

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RUNNING PROBLEM

TREATMENT FOR AIDS

In 1996, researchers developed a strategy that might offer long-term suppression of HIV, the virus that causes acquired immunodeficiency syndrome (AIDS). In that year, scientists confirmed that a “cocktail” consisting of several drugs, including a *protease inhibitor*, could be effective against HIV, but questions remained. For how long would the new drug combination keep HIV at bay? Would the new drugs work for everyone carrying the infection? George, 28, pushed these questions to the back of his mind. After three years of relatively good health following his positive test for HIV infection, his T lymphocyte count had begun to slide. It was only a matter of time before George became gravely ill.



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It seems that since the 1980s human civilization has been visited by new plagues of infectious diseases. Some of them, such as tuberculosis and rabies, are old enemies that we thought we had under control. Others, such as SARS (severe acute respiratory syndrome), monkeypox, and the Hanta and Ebola viruses, seem to be cropping up out of nowhere. The conflict between humans and the invaders that cause disease is literally a fight for survival on both sides. The infectious agents need a host such as the human body to reproduce. But if they kill off all the hosts, they, too, will die out. On the human side of the equation, we must fight off the invaders if humans are to continue to survive as a species.

The body's ability to protect itself from viruses, bacteria, and other disease-causing entities is known as **immunity**, from the Latin word *immunis*, meaning *exempt*. The human immune system consists of the lymphoid tissues of the body, the immune cells, and chemicals (both intracellular and secreted) that coordinate and execute immune functions.

OVERVIEW OF IMMUNE SYSTEM FUNCTION

The key features of the immune system are *specificity* and *memory*. Together these processes enable the body to distinguish “self” from “non-self” and mount a targeted response to

specific invaders. The immune system serves three major functions:

1. **It protects the body from disease-causing invaders** known as **pathogens**. Microorganisms (**microbes**) that act as pathogens include bacteria, viruses, fungi, and one-celled protozoans. Larger pathogens include multicellular **parasites**, such as hookworms and tapeworms.
2. **It removes dead or damaged cells**, as well as old red blood cells. Scavenger cells of the immune system patrol the extracellular compartment, gobbling up and digesting dead or dying cells.
3. **It tries to recognize and remove abnormal cells** created when normal cell growth and development go wrong. For example, the diseases we call *cancer* result from abnormal cells that multiply uncontrollably, crowding out normal cells and disrupting function. Scientists believe that cancer cells form on a regular basis but are usually detected and destroyed by the immune system before they get out of control.

Sometimes the body's immune system fails to perform its normal functions. Pathologies of the immune system generally fall into one of three categories: incorrect responses, overactive responses, or lack of response.

1. **Incorrect responses.** If mechanisms for distinguishing self from non-self fail and the immune system attacks the body's normal cells, an *autoimmune disease* results. Type 1 diabetes mellitus, in which proteins made by immune cells destroy pancreatic beta cells, is an example of an autoimmune disease in humans.
2. **Overactive responses.** Allergies are conditions in which the immune system creates a response that is out of proportion to the threat posed by the antigen. In extreme cases, the systemic effects of allergic responses can be life threatening.
3. **Lack of response.** **Immunodeficiency diseases** arise when some component of the immune system fails to work properly. *Primary immunodeficiency* is a family of genetically inherited disorders that range from severe to mild. *Acquired immunodeficiencies* may occur as a result of infection, such as *acquired immunodeficiency syndrome* (AIDS) caused by the *human immunodeficiency virus* (HIV). Acquired immunodeficiencies may also arise as a side effect of drug or radiation therapy, such as those used to treat cancer.

PATHOGENS OF THE HUMAN BODY

In the United States, our most prevalent infectious diseases are of viral and bacterial origin. Worldwide, parasites are an additional significant public health concern. For example, malaria, a pathogenic protozoan whose life cycle alternates between human and mosquito hosts, is estimated to infect as many as 100 million people.

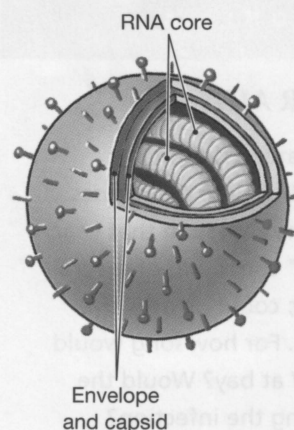
Many parasitic organisms, such as the malaria protozoan, are introduced into the body by biting insects. Others enter the body through the digestive tract, brought in by contaminated food and water. Some, such as the fungi that cause valley fever and histoplasmosis, are inhaled. A few, such as the blood fluke *Schistosoma*, burrow through the host's skin. Once in the body, microbes and parasites may enter host cells in an effort to evade the immune response, or they may remain in the extracellular compartment.

Bacteria and Viruses Require Different Defense Mechanisms

Bacteria and viruses differ from each other in several ways (Table 24-1):

1. **Structure.** Bacteria are cells, with a cell membrane that is usually surrounded by a cell wall. Some *encapsulated* bacteria also produce an additional protective outer layer known as a *capsule*. Viruses are not cells. They consist of a nucleic acid (DNA or RNA) core enclosed in a coat of viral proteins called a *capsid*. Some viruses add an *envelope* of phospholipid and protein made from the host's cell membrane and incorporate viral proteins into the envelope (Fig. 24-1a).
2. **Living conditions and reproduction.** Most bacteria can survive and reproduce outside a host if they have the required nutrients, temperature, pH, and so on. Viruses *must* use the intracellular machinery of a host cell to replicate.
3. **Susceptibility to drugs.** Most bacteria can be killed by the drugs we call **antibiotics**. These drugs act directly on

(a) Influenza, an RNA virus



(b) General steps of viral replication

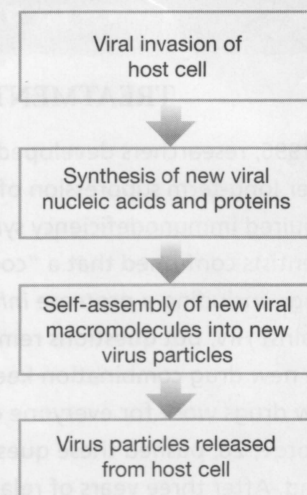


FIGURE 24-1 Viral structure and replication

bacteria and destroy them or inhibit their growth. Viruses cannot be killed by antibiotics. Some viral infections can be treated with *antiviral drugs*, which target viral replication.

Viruses Can Replicate Only Inside Host Cells

The life cycle of a virus begins when the virus invades the host cell (Fig. 24-1b). To cross the human host cell membrane, the virus binds to membrane receptors, triggering endocytosis of the entire virus particle. In an alternative scenario, the virus envelope fuses with the host cell membrane, allowing the core of the virus to enter the cytoplasm.

Once inside the host cell, the virus's nucleic acid takes over the cell's operations. Viruses use their own nucleic acid and the host cell's resources to make new viral nucleic acid and viral proteins. These components assemble into additional virus particles that are released from the host cell to infect other cells.

Viruses can be released from host cells in one of two ways. (1) The virus causes the host cell to rupture, releasing virus particles into the ECF, or (2) virus particles surround themselves with a layer of host cell membrane and then bud off from the surface of the host cell.

Viruses do other kinds of damage to host cells. In taking over a host cell, they may totally disrupt the cell's metabolism so that the cell dies. Some viruses (*Herpes simplex type 1* and varicella-zoster virus, which cause cold sores and chicken pox, respectively) "hide out" in the host cell and replicate only sporadically. Other viruses incorporate their DNA into the host cell DNA. Viruses with this characteristic include HIV and **oncogenic viruses**, which cause cancer.

CONCEPT CHECK

1. Explain the differences between a virus and a bacterium.
2. List the sequence of steps by which a virus replicates itself.

TABLE 24-1 Differences Between Bacteria and Viruses

	BACTERIA	VIRUSES
Structure	Cells; usually surrounded by cell wall	Not cells; nucleic acid core with protein coat
Living conditions	Most can survive and reproduce outside a host	Parasitic; must have a host cell to reproduce
Susceptibility to drugs	Most can be killed or inhibited by antibiotics	Cannot be killed with antibiotics; some can be inhibited with antiviral drugs



EMERGING CONCEPTS

RETROVIRUSES

The RNA viruses known as **retroviruses** replicate in an interesting manner. These viruses do not have DNA that can act as a template for mRNA synthesis; instead they produce an enzyme called **reverse transcriptase**. This enzyme allows the viral RNA to make a complementary strand of DNA. (This is the reverse of the usual process, because normally DNA codes for the synthesis of RNA.) After a period of time (the *latent period*), the virus-infected host cell produces viral mRNA. The viral mRNA then interrupts the host cell's protein synthesis, using host ribosomes to make viral proteins. HIV, the virus that causes AIDS, is a retrovirus.

THE IMMUNE RESPONSE

The body has two lines of defense. Physical and chemical barriers, such as skin, mucus, and stomach acid, first try to keep pathogens out of the body's internal environment. If that line of defense fails, then the internal **immune response** takes over.

Whatever the nature of the foreign material that enters the body, the internal immune response includes the same basic steps: (1) *detection* and *identification* of the foreign substance, (2) *communication* with other immune cells to rally an organized response, (3) *recruitment* of assistance and *coordination* of the response among all participants, and (4) *destruction* or *suppression* of the invader.

Not all invaders can be destroyed by the body's immune system. In some cases the best the body can do is control the damage and keep the invader from spreading. Examples of pathogens that are suppressed by the immune system rather than destroyed include the bacterium that causes tuberculosis; the malaria parasite, which hides inside liver cells; and the herpes viruses, which cause occasional outbreaks of cold sores or genital lesions.

The immune system is distinguished by its extensive use of chemical signaling. Detection, identification, communication, recruitment, coordination, and the attack on the invader all depend on signal molecules such as antibodies and cytokines. **Antibodies**, proteins secreted by certain immune cells, bind antigens and make them more visible to the immune system. **Cytokines** are protein messengers released by one cell that affect the growth or activity of another cell [p. 176].

The human immune response is generally divided into two categories: nonspecific innate immunity and specific acquired immunity. **Innate immunity** is present from birth [*innatus*, inborn] and is the body's **nonspecific immune response** to invasion. Because the nonspecific innate response does not target a particular pathogen, it begins within minutes to hours. **Inflammation**, apparent on the skin as a red, warm, swollen area, is a hallmark reaction of innate immunity.

Acquired immunity (also called *adaptive immunity*) is directed at specific invaders and thus is the body's **specific immune response**. One characteristic of acquired immunity is that a specific immune response to a first exposure to a pathogen may take days. With repeated exposures, however, the immune system "remembers" prior exposure to the pathogen and reacts more rapidly. Acquired immunity can be divided into *cell-mediated immunity* and *humoral immunity*. (The term *humoral*, referring to the blood, comes from the Hippocratic school of medicine, which classified the body's fluids into four *humors*: blood, phlegm, black bile, and yellow bile.)

As we will see later in this chapter, the nonspecific and specific immune responses overlap. Although we have described them as if they are separate, in reality they are two interconnected parts of a single process. The innate response is the more rapid response, but it does not target a specific invader. It is reinforced by the antigen-specific acquired response, which amplifies the efficacy of the innate response. Communication and coordination among all the different pathways of immunity are vital for maximum protective effect.

Because of the huge numbers of molecules involved in human immunity, and because of the complex interactions between different components of the immune system, the field of immunology is continuously expanding. In this chapter we cover the basics.



RUNNING PROBLEM

HIV is a retrovirus that uses the enzyme *reverse transcriptase* to replicate. Two drugs in the AIDS cocktail, AZT and ddC, are anti-retroviral drugs that work by inhibiting reverse transcriptase. The other drug in the cocktail is a protease inhibitor. Protease is an enzyme needed to cleave key proteins during one step of HIV replication.

Question 1:

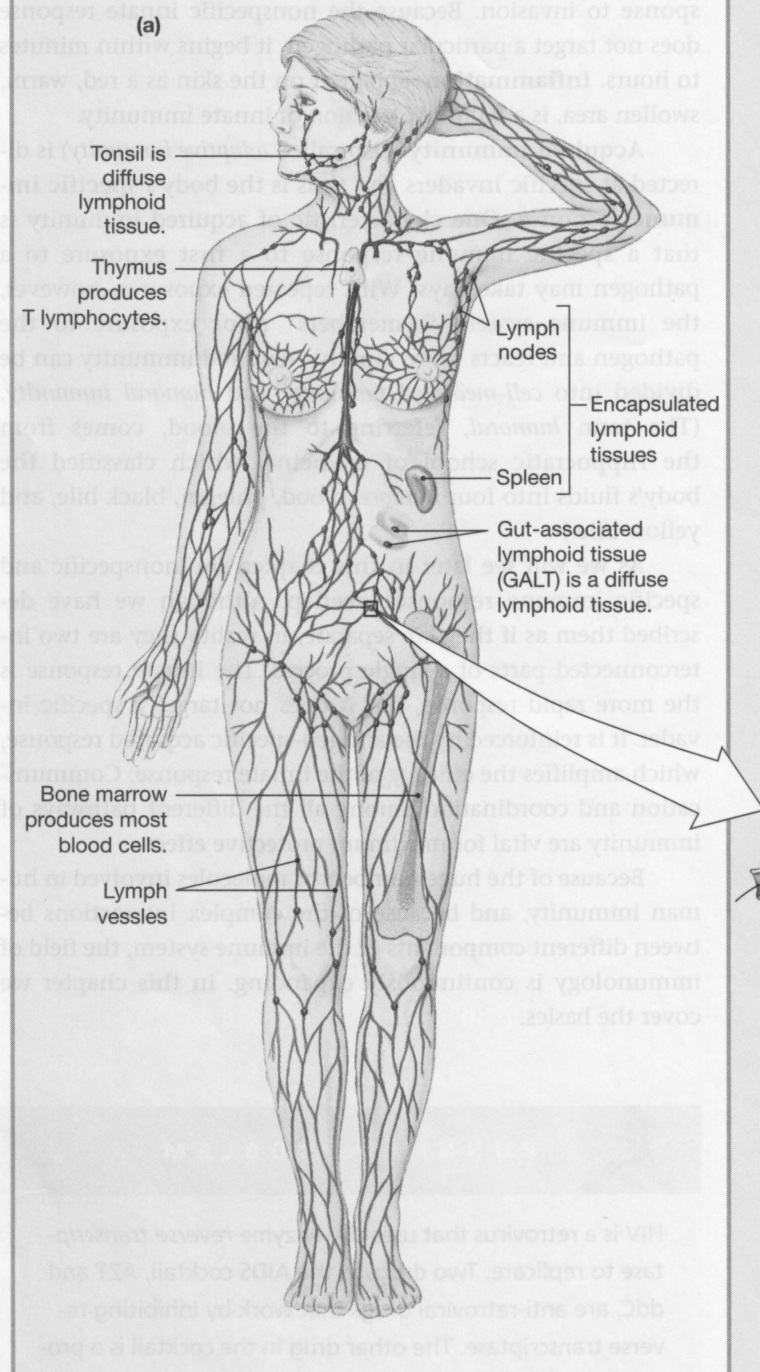
Why can't retroviruses reproduce without reverse transcriptase?



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ANATOMY SUMMARY

THE LYMPHATIC SYSTEM



STRUCTURE OF A LYMPH NODE

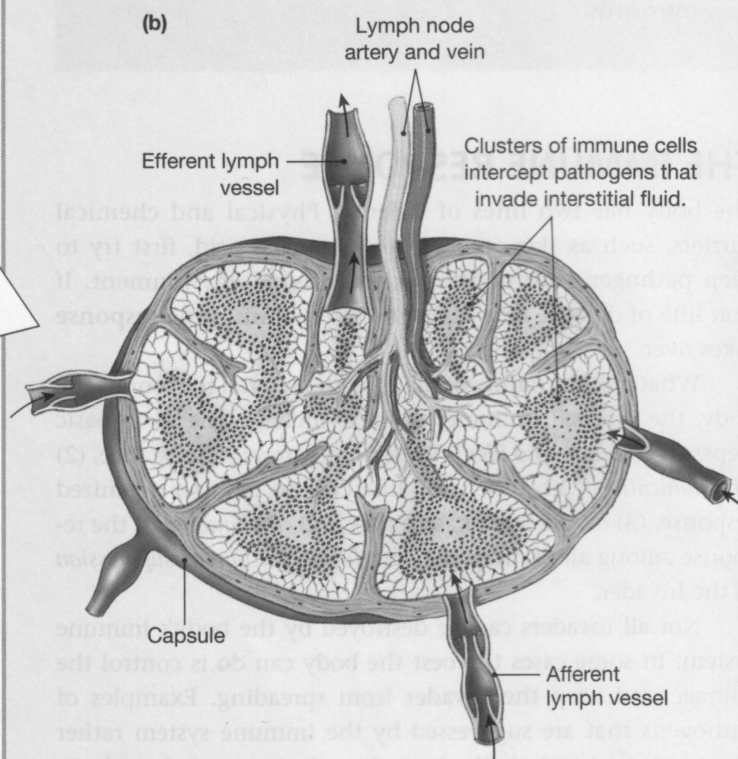


FIGURE 24-2 Anatomy of the immune system

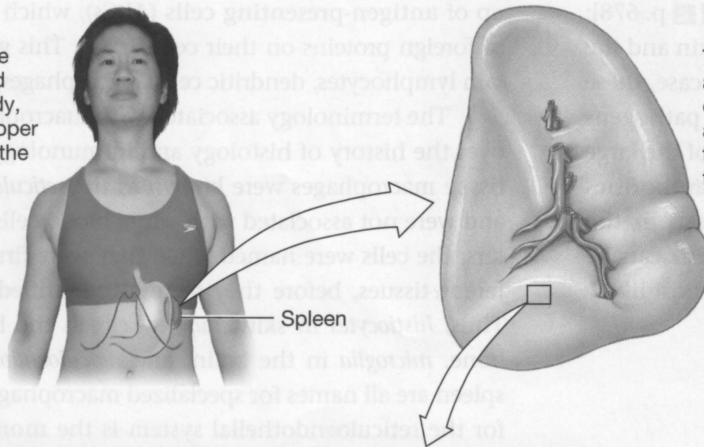
ANATOMY OF THE IMMUNE SYSTEM

The immune system is probably the least anatomically identifiable system of the body because most of it is integrated into the tissues of other organs, such as the skin and gastrointestinal

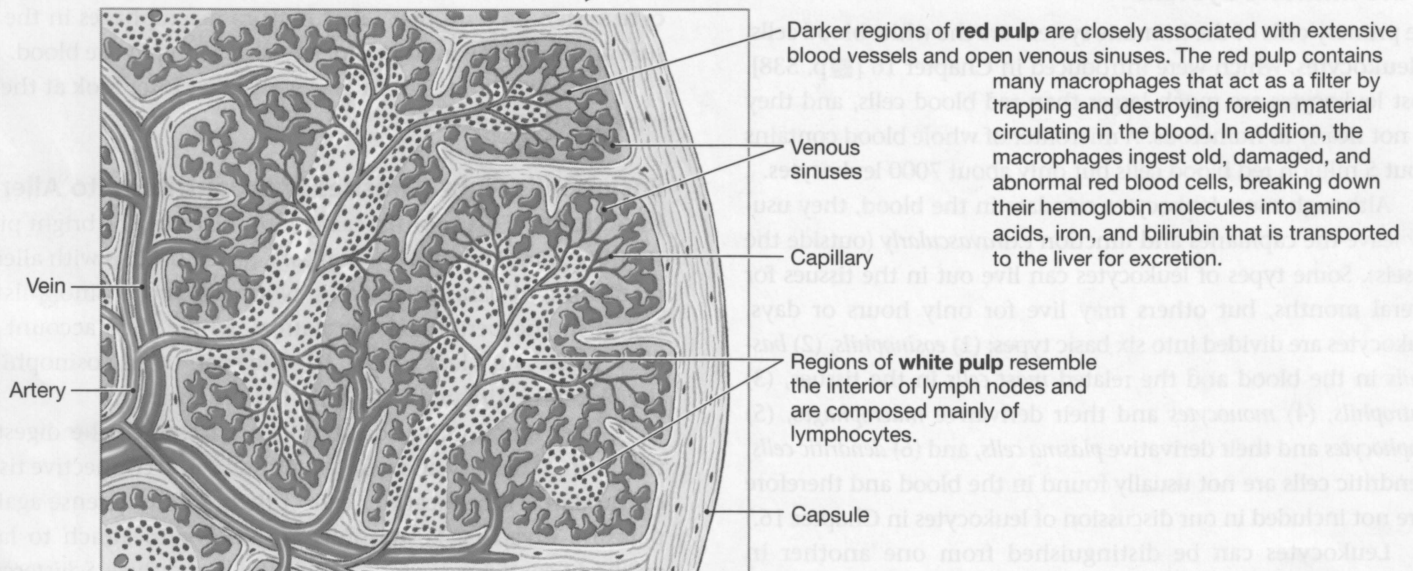
tract. Yet the mass of all immune cells in the body equals the mass of the brain! The immune system has two anatomical components: lymphoid tissues and the cells responsible for the immune response.

FOCUS ON . . . THE SPLEEN

The spleen is the largest lymphoid organ in the body, located in the upper left quadrant of the abdomen close to the stomach.



The outer surface of the spleen is a connective tissue capsule that extends into the interior to create an open framework that supports the blood vessels and lymphoid tissue.



■ FIGURE 24-3

Lymphoid Tissues Are Distributed Throughout the Body

The two primary lymphoid tissues are the **thymus gland** [Focus on the Thymus Gland, p. 792] and the **bone marrow**, both sites where cells involved in the immune response form and mature (Fig. 24-2a ■). Secondary lymphoid tissues are sites where mature immune cells interact with pathogens and initiate a response. Secondary tissues are divided into encapsulated tissues and unencapsulated diffuse lymphoid tissues.

The **encapsulated lymphoid tissues** are the **spleen** (Figs. 24-2a and 24-3 ■) and the **lymph nodes** (Fig. 24-2b). Both have an outer wall formed from fibrous collagenous capsules. The spleen contains immune cells positioned so that they monitor the blood for foreign invaders. Phagocytic cells in the spleen also trap and remove aging red blood cells.

The lymph nodes are associated with the lymphatic circulation. Recall from Chapter 15 that there is net flow of fluid out of capillaries and into the interstitial space [p. 517]. This filtered fluid is picked up by lymph capillaries and passes through the encapsulated lymph nodes on its journey back to the circulation.

Inside lymph nodes, clusters of immune cells intercept pathogens that have entered the interstitial fluid through breaks in the skin or through mucous membranes. Once these microbes have been swept into the lymph, immune cells in the nodes help prevent their spread throughout the body. You have probably noticed that if you have a sinus infection or a sore throat, the lymph nodes in your neck become swollen. These sore, swollen nodes result from the presence of active immune cells that have collected in the nodes to fight the infection.

The unencapsulated **diffuse lymphoid tissues** are aggregations of immune cells that appear in other organs of the body (Fig. 24-2). They include the **tonsils** at the posterior nasopharynx; the **gut-associated lymphoid tissue** (GALT), which lies just under the epithelium of the esophagus and intestines [Fig. p. 678]; and clusters of lymphoid tissue associated with the skin and the respiratory, urinary, and reproductive tracts. In each case, these tissues contain immune cells positioned to intercept pathogens before they get into the general circulation. Because of the large surface area of the digestive tract epithelium, some authorities consider the GALT to be the largest immune organ in the body. Anatomically, the cells of the immune system can be found in highest concentrations wherever they are most likely to encounter antigens that penetrate the epithelia.

Leukocytes Are the Primary Cells of the Immune System

The primary cells of the immune system are the white blood cells, or **leukocytes**, which were introduced in Chapter 16 [Fig. p. 538]. Most leukocytes are much larger than red blood cells, and they are not nearly as numerous. A microliter of whole blood contains about 5 million red blood cells but only about 7000 leukocytes.

Although most leukocytes circulate in the blood, they usually leave the capillaries and function *extravascularly* (outside the vessels). Some types of leukocytes can live out in the tissues for several months, but others may live for only hours or days. Leukocytes are divided into six basic types: (1) *eosinophils*, (2) *basophils* in the blood and the related *mast cells* in the tissues, (3) *neutrophils*, (4) *monocytes* and their derivative *macrophages*, (5) *lymphocytes* and their derivative *plasma cells*, and (6) *dendritic cells*. (Dendritic cells are not usually found in the blood and therefore were not included in our discussion of leukocytes in Chapter 16.)

Leukocytes can be distinguished from one another in stained tissue samples by the shape and size of the nucleus, the staining characteristics of the cytoplasm and cytoplasmic inclusions, and the regularity of the cell border.

Immune Cell Names Reflect Cell Function or Appearance

The terminology associated with immune cells can be very confusing. Some cell types have several variants, and others have been given multiple names (Fig. 24-4 ■). In addition, immune cells can be grouped either functionally or morphologically.

One morphological group is the **granulocytes**, white blood cells whose cytoplasm contains prominent granules. The names of the different cell types come from the staining properties of the granules. Neutrophil granules do not stain darkly with standard blood stains and are therefore “neutral.” Basophil granules stain dark blue with basic (alkaline) dye, and eosinophil granules stain dark pink with the acidic dye *eosin*. In all three types of granulocytes, the granule contents are released into the extracellular space, a process known as *degranulation*.

One functional group of leukocytes is the **phagocytes**, white blood cells that engulf and ingest their targets by phagocytosis [Fig. p. 148]. This group includes the neutrophils, macrophages,

monocytes (which are macrophage precursors), and eosinophils. A second functional group is the **cytotoxic cells**, so named because they kill the cells they attack. This group includes eosinophils and some types of lymphocytes. A third group is made up of **antigen-presenting cells** (APCs), which display fragments of foreign proteins on their cell surface. This group includes certain lymphocytes, dendritic cells, macrophages, and monocytes.

The terminology associated with macrophages has changed over the history of histology and immunology. For many years, tissue macrophages were known as the *reticuloendothelial system* and were not associated with white blood cells. To confuse matters, the cells were named when they were first described in different tissues, before they were all identified as macrophages. Thus, *histiocytes* in skin, *Kupffer cells* in the liver, *osteoclasts* in bone, *microglia* in the brain, and *reticuloendothelial cells* in the spleen are all names for specialized macrophages. The new name for the reticuloendothelial system is the **mononuclear phagocyte system**, a term that refers both to macrophages in the tissues and to their parent monocytes circulating in the blood.

In the sections that follow, we take a closer look at the six basic types of leukocytes.

Eosinophils Fight Parasites and Contribute to Allergic Reactions

Eosinophils, easily recognized by the bright pink-staining granules in their cytoplasm, are associated with allergic reactions and parasitic diseases. Normally, few eosinophils are found in the peripheral circulation, where they account for only 1–3% of all leukocytes. The life span of an eosinophil in the blood is estimated to be only 6–12 hours.

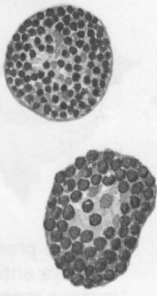
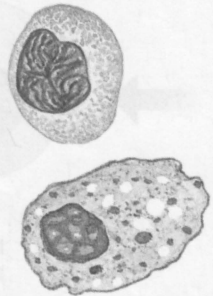
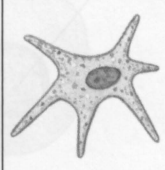
Most functioning eosinophils are found in the digestive tract, lungs, urinary and genital epithelia, and connective tissue of the skin. These locations reflect their role in defense against parasitic invaders. Eosinophils are known to attach to large antibody-coated parasites, such as the blood fluke *Schistosoma*, and release substances from their granules that damage or kill the parasites. Because eosinophils kill pathogens, they are classified as cytotoxic cells.

Eosinophils also participate in allergic reactions, where they contribute to inflammation and tissue damage by releasing toxic enzymes, oxidative substances, and a protein called *eosinophil-derived neurotoxin*. Although eosinophils have been shown *in vitro* to ingest foreign particles, such as pollen, there is no evidence that they do so *in vivo*.

Basophils Release Histamine and Other Chemicals

Basophils are rare in the circulation but are easily recognized in a stained blood smear by the large, dark blue granules in their cytoplasm. They are very similar to the **mast cells** of tissues, and both cell types release mediators that contribute to inflammation. The granules of these cells contain histamine, **heparin** (an anticoagulant that inhibits blood clotting), cytokines, and other chemicals involved in allergic and immune responses.

Mast cells, like eosinophils, are concentrated in the connective tissue of skin, lungs, and the gastrointestinal tract. In

	<i>Basophils and mast cells</i>	<i>Neutrophils</i>	<i>Eosinophils</i>	<i>Monocytes and macrophages</i>	<i>Lymphocytes and plasma cells</i>	<i>Dendritic cells</i>
						
% of WBCs in blood	Rare	50–70%	1–3%	1–6%	20–35%	NA
Subtypes and nicknames		Called “polys” or “segs” Immature forms called “bands” or “stabs”		Called the mononuclear phagocyte system	B lymphocytes Plasma cells T lymphocytes Cytotoxic T cells Helper T cells Natural killer cells Memory cells	Also called Langerhans cells, veiled cells
Primary function(s)	Release chemicals that mediate inflammation and allergic responses	Ingest and destroy invaders	Destroy invaders, particularly antibody-coated parasites	Ingest and destroy invaders Antigen presentation	Specific responses to invaders, including antibody production	Recognize pathogens and activate other immune cells by antigen presentation
Classifications		<i>Phagocytes</i>				
		<i>Granulocytes</i>				
			<i>Cytotoxic cells</i>		<i>Cytotoxic cells (some types)</i>	
				<i>Antigen-presenting cells</i>		

■ **FIGURE 24-4** *Cells of the immune system*

these locations, mast cells are ideally situated to intercept pathogens that are inhaled or ingested or that enter through breaks in the epidermis.

Neutrophils “Eat” Bacteria and Release Cytokines

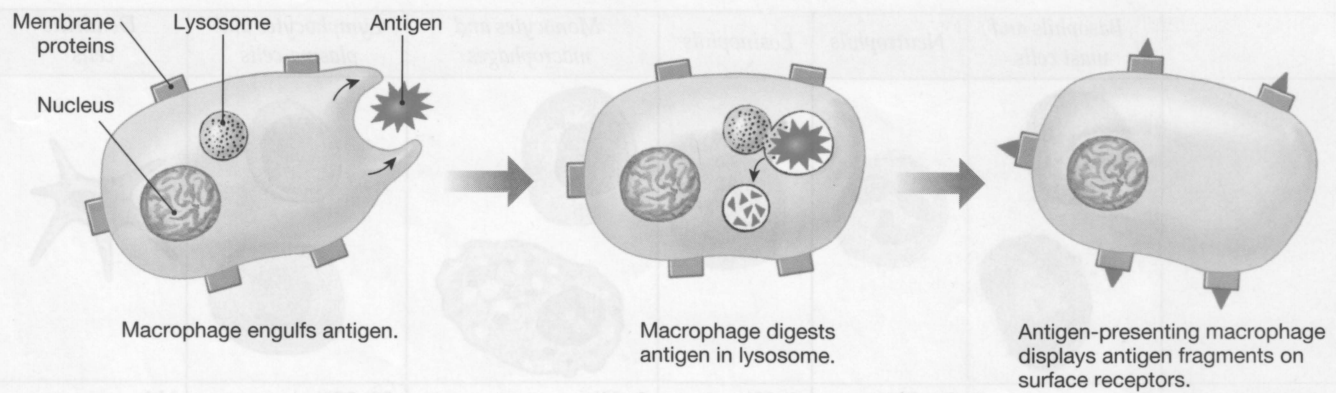
Neutrophils are the most abundant white blood cells (50–70% of the total) and are most easily identified by a segmented nucleus made up of three to five lobes connected by thin strands of nuclear material. Because of the segmented nucleus, neutrophils are also called *polymorphonuclear leukocytes* (“polys”) and “segs.” Immature neutrophils, occasionally found in the circulation, can be identified by their horseshoe-shaped nucleus. These immature neutrophils go by the nicknames of “bands” and “stabs.”

Neutrophils, like other blood cells, are formed in the bone marrow. They are phagocytic cells that typically ingest and kill 5–20 bacteria during their programmed life span of one or two days. Most neutrophils remain in the blood but can leave the circulation if attracted to an extravascular site of damage or infection. In addition to ingesting bacteria and foreign particles, neutrophils release a variety of cytokines, including fever-causing pyrogens [p. 743] and chemical mediators of the inflammatory response.

Monocytes Mature into Macrophages Monocytes are the precursor cells of tissue macrophages. Monocytes are not very common in the blood (1–6% of all white blood cells). By some estimates, they spend only eight hours there in transit from the bone marrow to their permanent positions in the tissues.

Once out of the blood, monocytes enlarge and differentiate into **macrophages**. Some tissue macrophages patrol the tissues, creeping along by amoeboid motion. Others find a location and remain fixed in place. In either case, macrophages are the primary scavengers within tissues. They are larger and more effective than neutrophils, ingesting up to 100 bacteria during their life span. Macrophages also remove larger particles, such as old red blood cells and dead neutrophils.

Because they are antigen-presenting cells, macrophages play an important role in the development of acquired immunity. After they ingest and digest molecular or cellular antigens, fragments of processed antigen are inserted into the macrophage membrane as part of surface protein complexes (Fig. 24-5 ■). As noted earlier, dendritic cells and the lymphocytes known as *B lymphocytes* also act as antigen-presenting cells.



■ **FIGURE 24-5** *Antigen-presenting cells (APCs)*

Lymphocytes Mediate Acquired Immunity Lymphocytes and their derivatives are the key cells that mediate the acquired immune response of the body. Only 5% of all lymphocytes are found in the circulation, where they constitute 20–35% of all white blood cells. Most lymphocytes are found in lymphoid tissues, where they are likely to encounter invaders.

By one estimate, the adult body contains a trillion lymphocytes at any one time. Although most of these cells look alike under the microscope, they have major differences in function and specificity, as you will learn later in the chapter.

Dendritic Cells Activate Lymphocytes Dendritic cells are antigen-presenting cells characterized by long, thin processes that resemble neuronal dendrites. Dendritic cells are found in the skin (where they are called *Langerhans cells*) and in various organs. When dendritic cells recognize and capture antigens, they migrate to secondary lymphoid tissues, where they present the antigens to lymphocytes. Antigen binding activates the lymphocytes.

INNATE IMMUNITY: NONSPECIFIC RESPONSES

The body's first line of defense is to exclude pathogens by physical and chemical barriers. If those barriers fail to keep invaders out, the innate immune system provides the second line of defense. The innate immune response consists of patrolling and stationary leukocytes that attack and destroy invaders. These leukocytes respond in the same fashion to any material they identify as foreign, which is why innate immunity is considered nonspecific. Innate immunity either clears the infection or contains it until the acquired immune response is activated.

Physical and Chemical Barriers Are the Body's First Line of Defense

Physical barriers of the body include the skin [p. 83], the protective mucous linings of the gastrointestinal and genitourinary tracts, and the ciliated epithelium of the respiratory tract.

The digestive and respiratory systems are most vulnerable to microbial invasion because these regions have extensive areas of thin epithelium in direct contact with the external environment. In women, the reproductive tract is also vulnerable, but to a lesser degree. The opening to the uterus is normally sealed by a mucus plug that keeps bacteria in the vagina from ascending into the uterine cavity.

In the respiratory system, inhaled particulate matter is trapped by mucus lining the upper respiratory system. The mucus is then transported upward on the mucociliary escalator to be expelled or swallowed [p. 568]. Swallowed pathogens may be disabled by the acidity of the stomach. In addition, respiratory tract secretions contain **lysozyme**, an enzyme with antibacterial activity. Lysozyme attacks cell wall components of unencapsulated bacteria and breaks them down. However, it cannot digest the capsules of encapsulated bacteria.

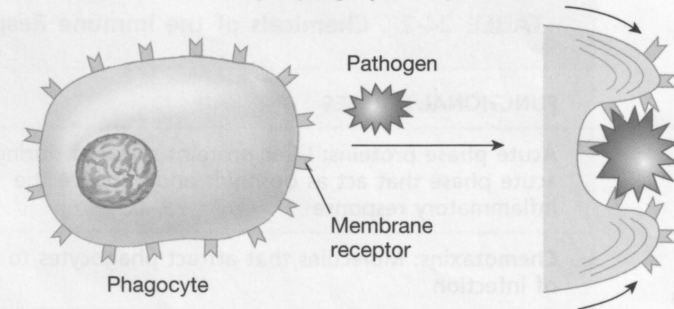
Phagocytes Recognize and Ingest Foreign Material

Pathogens that get past the physical barriers of skin and mucus are dealt with by immune cells and the innate immune response. When patrolling and stationary phagocytes in the tissues detect invaders, their response is twofold: they destroy or suppress the invaders by ingesting them (phagocytosis), and they attract additional immune cells by secreting cytokines. Molecules that attract immune cells are called **chemotaxins**. They include bacterial toxins, products of tissue injury (fibrin and collagen fragments), and cytokines released by leukocytes.

The primary phagocytic cells of the immune system are tissue macrophages and neutrophils. If an invader is in a tissue, phagocytes leave the circulation (*extravasation*) by squeezing through pores in the capillary endothelium. Once the phagocytes reach the pathogen, they identify it by chemical cues and then ingest it.

Phagocytosis is similar in macrophages and neutrophils. It is a receptor-mediated event, which ensures that only unwanted particles are ingested. In the simplest reactions, surface molecules on the pathogen act as ligands that bind directly to receptors on the phagocyte membrane (Fig. 24-6a ■). In a sequence

(a) Pathogen binds directly to phagocyte receptors.



(b) Bacteria with capsules must be coated with antibody before phagocytes can ingest them.

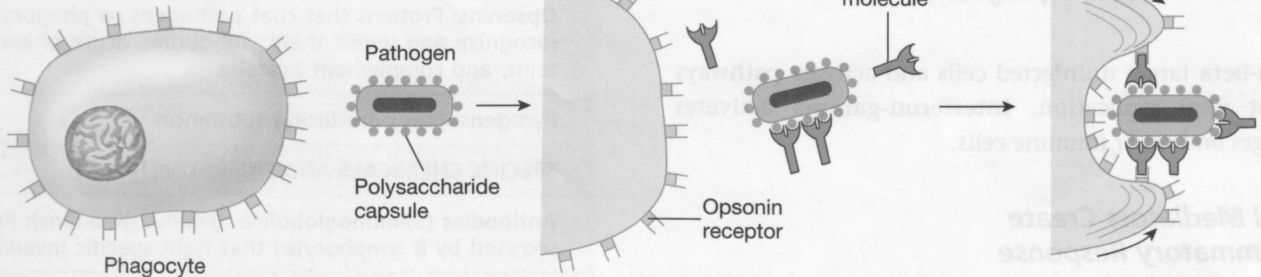


FIGURE 24-6 Phagocytosis

Some foreign materials activate phagocytes directly (a), but others must be coated with antibodies or other proteins before a phagocyte recognizes them (b).

reminiscent of a zipper closing, the ligands and receptors combine sequentially, so that the phagocyte surrounds the unwanted foreign particle. The process is aided by actin filaments that push arms of the phagocytic cell around the invader.

Phagocyte membranes contain receptors that recognize many different types of foreign particles, both organic and inorganic. Phagocytes ingest unencapsulated bacteria, cell fragments, carbon, and asbestos particles, among other materials. In the laboratory, scientists use the ingestion rate of tiny polystyrene beads as an indicator of phagocytic activity.

Phagocytes cannot instantly recognize all foreign substances, however, because some pathogens lack markers that react with the phagocytes' receptors. For example, certain bacteria have evolved a polysaccharide capsule that masks their surface markers (Fig. 24-6b). These encapsulated bacteria are not as quickly recognized by phagocytes and consequently are more pathogenic because they can grow unchecked until the immune system finally recognizes them and makes antibodies against them. Once that happens, the bacteria are "tagged" with a coat of antibodies so that phagocytes recognize them as something to be ingested.

The antibodies that tag encapsulated bacteria, along with additional plasma proteins, are known collectively as **opsonins** [*opsonin*, "to buy provisions."] In the body, opsonins convert unrecognizable particles into "food" for phagocytes. Opsonins act as bridges between pathogens and phagocytes by binding to receptors on the phagocytes.

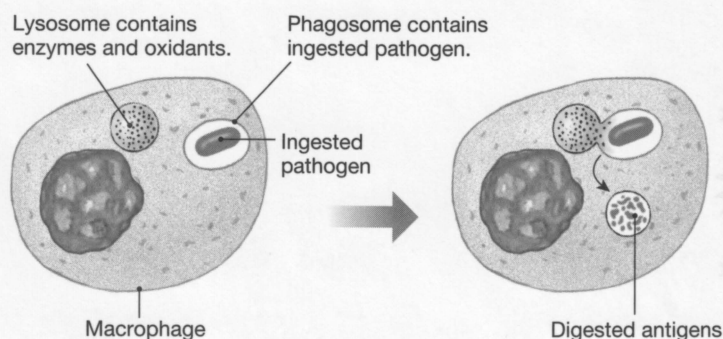
Once a pathogen has been ingested by a phagocyte, the ingested particle ends up in a cytoplasmic vesicle called a **phagosome** (Fig. 24-7 ■). Phagosomes fuse with intracellular lysosomes [p. 66], which contain powerful chemicals that destroy ingested pathogens. Lysosomal contents include enzymes and oxidizing agents, such as hydrogen peroxide (H_2O_2), nitric oxide (NO), and the superoxide anion (O^-).

If an area of infection attracts a large number of phagocytes, the material known as **pus** may form. This thick, whitish to greenish substance is a collection of living and dead neutrophils and macrophages, along with tissue fluid, cell debris, and other remnants of the immune process.

Natural Killer Lymphocytes Eliminate Virally Infected and Tumor Cells

One class of lymphocyte—**natural killer cells**, or **NK cells**—participates in the innate response against viral infections. NK cells act more rapidly than other lymphocytes in a response that can be measured within hours of a primary viral infection. NK cells induce virus-infected cells to commit suicide (apoptosis [p. 81]) before the virus can replicate. Complete elimination of the virus requires activation of a specific immune response. NK cells also attack some tumor cells.

NK cells and other lymphocytes secrete various antiviral cytokines, including **interferons**, which were named for their ability to interfere with viral replication. **Interferon-alpha** and



■ **FIGURE 24-7** *Lysosomal enzymes digest pathogens that have been enclosed in phagosomes*

interferon-beta target uninfected cells and activate pathways to prevent viral replication. **Interferon-gamma** activates macrophages and other immune cells.

Chemical Mediators Create the Inflammatory Response

Inflammation is a hallmark reaction of innate immunity that has three important roles in fighting infection in damaged tissue: (1) attracting immune cells and chemical mediators to the site, (2) producing a physical barrier to retard the spread of infection, and (3) promoting tissue repair once the infection is under control (a non-immunological function).

The inflammatory response is created when activated tissue macrophages release cytokines. These chemicals attract other immune cells, increase capillary permeability, and cause fever. Immune cells attracted to the site in turn release their own cytokines. Some representative examples of chemicals involved in the innate immune response are described below and listed in Table 24-2 ■, a convenient “scorecard” for following the “players” in these complex processes.

Acute-Phase Proteins Are Released Early in the Immune Response In the time immediately following an injury or pathogen invasion (the acute phase), the body responds by increasing the concentration of various plasma proteins. Some of these proteins, produced mostly by the liver, are given the general name of **acute-phase proteins**. They include molecules that act as opsonins, antiprotease molecules that help prevent tissue damage, and *C-reactive protein* (CRP).

Normally, the levels of acute-phase proteins decline to normal as the immune response proceeds, but in *chronic inflammatory diseases*, such as rheumatoid arthritis, elevated levels of acute-phase proteins may persist. For example, increased levels of C-reactive protein are associated with increased risk of coronary heart disease. This is because atherosclerosis is an inflammatory process that begins when macrophages in blood vessels ingest excess cholesterol and become foam cells [p. 526] that secrete CRP, other cytokines, and growth factors. Elevated CRP is not a specific indicator of atherosclerosis, however,

TABLE 24-2 Chemicals of the Immune Response

FUNCTIONAL CLASSES

Acute phase proteins: Liver proteins released during the acute phase that act as opsonins and enhance the inflammatory response

Chemotaxins: Molecules that attract phagocytes to a site of infection

Cytokines: Proteins released by one cell that affect the growth or activity of another cell

Opsonins: Proteins that coat pathogens so phagocytes recognize and ingest them: antibodies, acute phase proteins, and complement proteins

Pyrogens: Fever-producing substances

SPECIFIC CHEMICALS AND THEIR FUNCTIONS

Antibodies (immunoglobulins, gamma globulins): Proteins secreted by B lymphocytes that fight specific invaders

Bradykinin: Stimulates pain receptors; vasodilator

Complement: Plasma and cell membrane proteins that act as opsonins, cytolytic agents, and mediators of inflammation

C-reactive protein: Opsonin that activates complement cascade

Granzymes: Cytotoxic enzymes that initiate apoptosis

Heparin: An anticoagulant

Histamine: Vasodilator and bronchoconstrictor released by mast cells and basophils

Interferons: Proteins that inhibit viral replication and modulate the immune response

Interleukin-1: Macrophage cytokine that mediates inflammatory response and induces fever

Kinins: Plasma proteins that activate to form bradykinin

Lysozyme: An extracellular enzyme that attacks bacteria

Major histocompatibility complex (MHC): A family of membrane protein complexes involved in cell recognition

Membrane attack complex: A membrane pore protein made in the complement cascade; allows ions and water to enter pathogens

Perforin: A membrane pore protein that allows granzymes to enter the cell; made by NK and cytolytic T cells

Superoxide anion (O_2^-): Powerful oxidant in phagocyte lysosomes

T-cell receptors: Membrane receptors on T lymphocytes that recognize and bind antigen presented by MHC receptors

because CRP levels can also be elevated in other acute and chronic inflammatory conditions.

Histamine Initiates Inflammation Histamine is found primarily in the granules of mast cells and basophils, and it is the active molecule that helps initiate the inflammatory response when mast cells degranulate. Histamine's actions bring more leukocytes to the injury site to kill bacteria and remove cellular debris.

Histamine opens pores in capillaries, allowing plasma proteins to escape into the interstitial space. This process causes local edema, or swelling. In addition, histamine dilates blood vessels, increasing blood flow to the area. The result of histamine release is a hot, red, swollen area around a wound or infection site.

Mast cell degranulation is triggered by different cytokines in the immune response. Because mast cells are concentrated under mucous membranes that line the airways and digestive tract, the inhalation or ingestion of certain antigens can trigger histamine release. The resultant edema in the nasal passages leads to one annoying symptom of seasonal pollen allergies: the stuffy nose. Fortunately, pharmacologists have developed a variety of drugs called *antihistamines*, which block the action of histamine at its receptor.

Scientists once believed that histamine was the primary chemical responsible for the bronchoconstriction of asthma and for the severe systemic allergic reaction called *anaphylactic shock* [p. 510]. However, we now know that mast cells release powerful lipid mediators in addition to histamine, including leukotrienes, platelet-activating factor, and prostaglandins. These mediators work with histamine to create the bronchoconstriction and hypotension characteristic of anaphylactic shock.

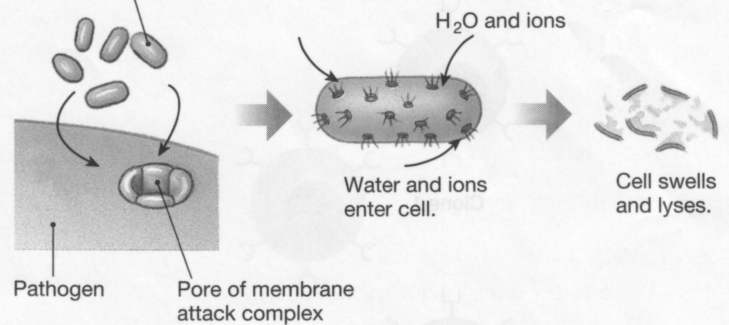
Interleukins Have Widespread Systemic Effects Interleukins [p. 540] are cytokines initially thought to mediate communication among the body's different types of leukocytes. Scientists have since discovered that many different tissues in the body respond to interleukins.

Interleukin-1 (IL-1) is secreted by activated macrophages and other immune cells. Its main role is to mediate the inflammatory response, but it also has widespread systemic effects on immune function and metabolism. Interleukin-1 modulates the immune response by:

1. *Altering blood vessel endothelium* to ease passage of white blood cells and proteins during the inflammatory response.
2. *Stimulating production of acute-phase proteins* by the liver.
3. *Inducing fever* by acting on the hypothalamic thermostat [p. 743]. IL-1 is a known pyrogen.
4. *Stimulating cytokine and endocrine secretion* by a variety of other cells.

Bradykinin Stimulates Pain Receptors *Kinins* are a group of inactive plasma proteins that participate in a cascade similar

Complement proteins insert themselves into the membrane of pathogens, creating a pore.



■ **FIGURE 24-8** Action of a membrane attack complex

to the coagulation cascade [p. 552]. The end product of the kinin cascade is **bradykinin**, a molecule that has the same vasodilator effects as histamine. Bradykinin also stimulates pain receptors, creating the tenderness associated with inflammation. Pain draws the brain's attention to the injury.

Complement Proteins Are Opsonins and Chemotaxins

Complement is a collective term for a group of more than 25 plasma proteins and cell membrane proteins. The *complement cascade* is similar to the blood coagulation cascade. Various intermediates of the complement cascade act as opsonins, chemical attractants for leukocytes, and agents that cause mast cell degranulation.

The complement cascade terminates with the formation of **membrane attack complex**, a group of lipid-soluble proteins that insert themselves into the cell membranes of pathogens and virus-infected cells and form pores (Fig. 24-8 ■). These pores allow ions to enter the pathogen cells, and water follows by osmosis. As a result, the cells swell and lyse.

CONCEPT CHECK

3. Why does the action of histamine on capillary permeability result in swelling?

Answers: p. 806

ACQUIRED IMMUNITY: ANTIGEN-SPECIFIC RESPONSES

Acquired immune responses are *antigen-specific responses* in which the body recognizes a particular foreign substance and selectively reacts to it. Acquired immunity is mediated primarily by lymphocytes.

There are three main types of lymphocytes: **B lymphocytes**, **T lymphocytes**, and **natural killer (NK) cells**. Activated B lymphocytes develop into **plasma cells**, which secrete antibodies. Activated T lymphocytes develop either into cells that attack and destroy virus-infected cells or into cells that regulate

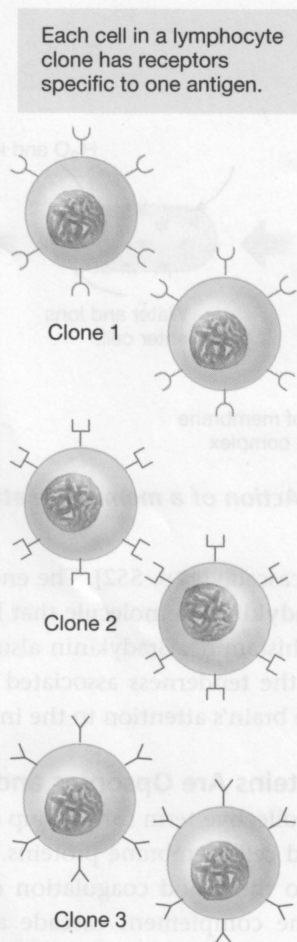


FIGURE QUESTION



Which clone will this antigen activate?

■ **FIGURE 24-9** *Lymphocyte clones*

Each of the three pairs of lymphocytes in this figure is from a different clone.

other immune cells. NK cells attack and destroy virus-infected cells and tumor cells. All lymphocytes secrete cytokines that act on immune cells, on non-immune cells, and, sometimes, on pathogens.

The process of acquired immunity overlaps with the process of innate immunity. Cytokines released by the inflammatory response attract lymphocytes to the site of an immune reaction. The lymphocytes release additional cytokines that enhance the inflammatory response.

Acquired immunity can be subdivided into active immunity and passive immunity. **Active immunity** occurs when the body is exposed to a pathogen and produces its own antibodies. Active immunity can occur naturally, when a pathogen invades the body, or artificially, as when we are given vaccinations containing dead or disabled pathogens.

Passive immunity occurs when we acquire antibodies made by another animal. The transfer of antibodies from mother to fetus across the placenta is one example. Injections containing antibodies are another. Travelers going abroad may be injected with *gamma globulin* (antibodies extracted from donated human plasma), but this passive immunity lasts only about three months.

Lymphocytes Are the Primary Cells Involved in the Acquired Immune Response

On a microscopic level, all lymphocytes look alike. At the molecular level, however, the cells can be distinguished from one another by their membrane receptors, which make each lymphocyte specific for a particular ligand. All lymphocytes that are specific for a given ligand form a group known as a **clone** [*klon*, a twig] (Fig. 24-9 ■).

If a specific type of lymphocyte fights each pathogen that enters the body, millions of different types of lymphocytes must be ready to combat millions of different pathogens. But where do all those lymphocytes come from?

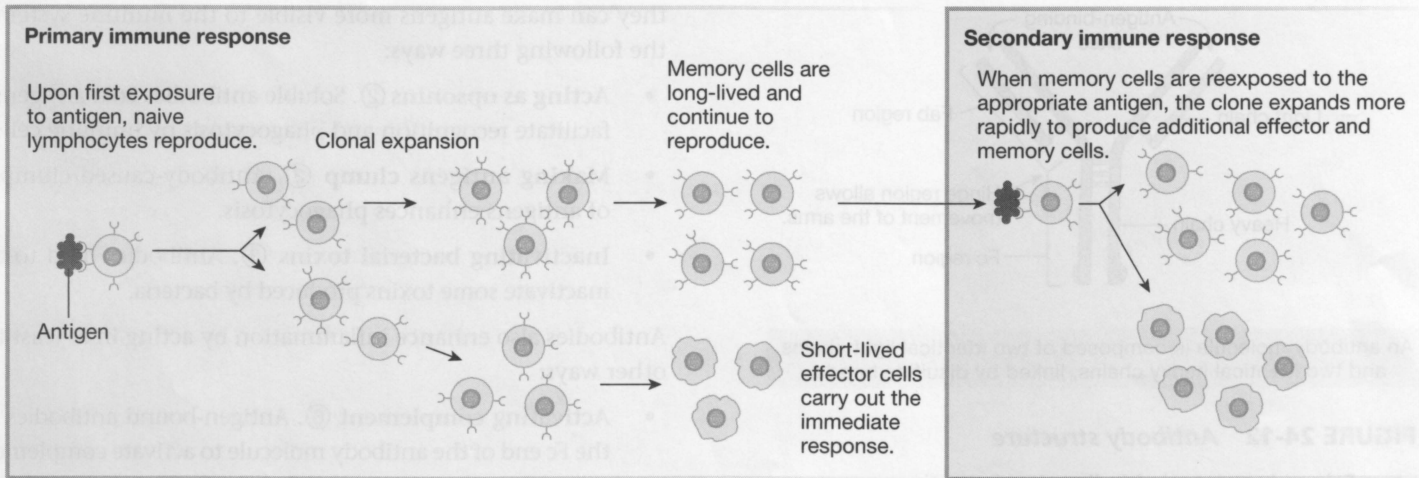
At an individual's birth, each clone of lymphocytes is represented by only a few cells, called **naïve lymphocytes** [*naif*, natural]. Because the small number of cells in each naïve clone is not enough to fight off foreign invaders, the first exposure to an antigen activates the appropriate clone and stimulates it to divide (Fig. 24-10 ■). This process, called **clonal expansion**, creates additional cells in the clone. Naïve cells continue to be generated throughout an individual's lifetime.

The newly formed lymphocytes in a clone differentiate into effector cells and memory cells. **Effector cells** carry out the immediate response and then die within a few days. **Memory cells**, in contrast, are long lived and continue reproducing themselves. Second and subsequent exposures to the antigen activate the memory cells, creating a more rapid and stronger secondary response to the antigen.

B Lymphocytes Differentiate into Plasma Cells and Memory Cells

B lymphocytes (also called **B cells**) develop in the bone marrow. (Memory aid: bone starts with B.) Activated B lymphocytes differentiate primarily into specialized cells that secrete antibodies. The word *antibody* describes what the molecules do: work against foreign bodies. Antibodies are also called **immunoglobulins**, and this alternative name describes what the molecules are: globular proteins that participate in the humoral immune response.

Mature B lymphocytes insert antibody molecules into their cell membranes so that the antibodies become surface receptors marking the members of each clone (Fig. 24-9). When a clone of B cells activates in response to antigen exposure, some of the cells differentiate into plasma cells, which are the effector cells for B lymphocytes. Plasma cells do not have antibody proteins



■ **FIGURE 24-10** How clonal expansion leads to immunologic memory

bound in their membranes. Instead, they synthesize and secrete additional antibody molecules at incredible rates, estimated to be as high as 2000 molecules per second! Plasma cell antibodies form *humoral immunity*, the soluble antibodies of the plasma.

After each invader has been successfully repulsed, a few memory cells of the clone remain behind, waiting to respond to the next exposure to the same antigen. Figure 24-11 ■ compares the antibody responses—expressed as the concentration of antibodies in the plasma—following the first and second exposures to an antigen. The **primary immune response**, which occurs after the initial exposure, is slower and lower in magnitude because the body has not encountered the antigen previously. The **secondary immune response**, which takes place after second and subsequent exposures, is quicker and larger because it is enhanced by lymphocytes that carry a molecular memory of the first exposure to the antigen.

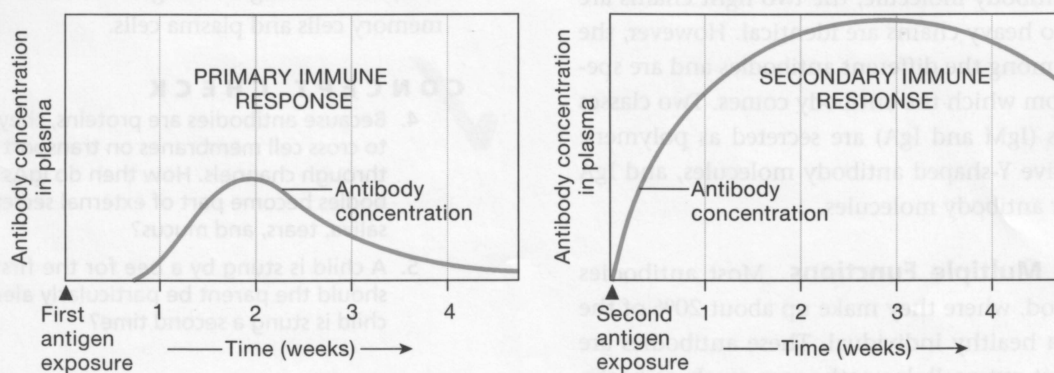
The existence of a secondary immune response is what makes vaccinations work. A vaccine contains an altered pathogen that no longer harms the host but that can be recognized as

foreign by immune cells. The altered pathogen triggers creation of memory cells specific to that particular pathogen. If the vaccinated person is later infected by the pathogen, a stronger and more rapid secondary immune response results. We are now learning, however, that immunity after immunization may not last for a person's lifetime.

Antibodies Are Proteins Secreted by Plasma Cells

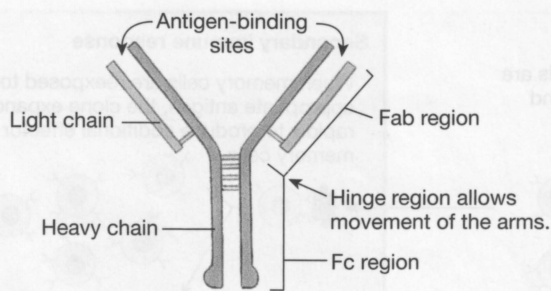
Antibodies were among the first aspects of the immune system to be discovered, and traditionally their names—agglutinins, precipitins, hemolysins, and so on—indicated what they do. Today, however, antibodies or immunoglobulins (Ig) are divided into five general classes: IgG, IgA, IgE, IgM, and IgD (pronounced *eye-gee-[letter]*). Antibodies are collectively referred to as **gamma globulins**.

IgGs make up 75% of plasma antibody in adults because they are produced in secondary immune responses. Maternal IgGs cross the placental membrane and give infants immunity in the first few months of life. IgGs activate complement.



■ **FIGURE 24-11** Memory in the immune system

Antibody production in response to the first exposure to an antigen is both slower and weaker than antibody production following subsequent exposures to the same antigen.



An antibody molecule is composed of two identical light chains and two identical heavy chains, linked by disulfide bonds.

FIGURE 24-12 Antibody structure

The two Fab regions contain binding sites for antigens.

IgA antibodies are found in external secretions, such as saliva, tears, intestinal and bronchial mucus, and breast milk, where they disable pathogens before they reach the internal environment.

IgEs are associated with allergic responses. When mast cell receptors bind with IgEs and antigen, the mast cells degranulate and release chemical mediators, such as histamine.

IgM antibodies are associated with primary immune responses and with the antibodies that react to blood group antigens. IgMs also activate complement.

IgD antibody proteins appear on the surface of B lymphocytes along with IgM, but the physiological role of IgDs is unclear.

Antibodies Are Y-Shaped Proteins The basic antibody molecule has four polypeptide chains linked into a Y-shape (Fig. 24-12 ■). Each side of the Y is identical, with one **light chain** attached to one **heavy chain**. The two arms, or **Fab regions**, form antigen-binding sites that confer the antibody's specificity. The stem of the Y-shaped antibody molecule is known as the **Fc region**. The Fc region determines the Ig class to which the antibody belongs. A **hinge region** between the arms and the stem allows flexible positioning of the arms.

In any given antibody molecule, the two light chains are identical and the two heavy chains are identical. However, the chains vary widely among the different antibodies and are specific for the clone from which the antibody comes. Two classes of immunoglobulins (IgM and IgA) are secreted as polymers: IgM is made up of five Y-shaped antibody molecules, and IgA has from one to four antibody molecules.

Antibodies Have Multiple Functions Most antibodies are found in the blood, where they make up about 20% of the plasma proteins in a healthy individual. These antibodies are most effective against extracellular pathogens (such as bacteria), some parasites, antigenic macromolecules, and viruses before they have invaded their host cells.

Antibody function is summarized in Figure 24-13 ■. Although antibodies are not toxic and cannot destroy antigens,

they can make antigens more visible to the immune system in the following three ways:

- **Acting as opsonins** ②. Soluble antibodies coat antigens to facilitate recognition and phagocytosis by immune cells.
- **Making antigens clump** ③. Antibody-caused clumping of antigens enhances phagocytosis.
- **Inactivating bacterial toxins** ③. Antibodies bind to and inactivate some toxins produced by bacteria.

Antibodies also enhance inflammation by acting in at least two other ways:

- **Activating complement** ⑥. Antigen-bound antibodies use the Fc end of the antibody molecule to activate complement.
- **Activating mast cells** ⑤. Mast cells have IgE antibodies attached to their surface. When antigens or complement proteins bind to IgE, the mast cells degranulate, releasing chemicals that mediate the inflammatory response.

The final role of antibodies is to activate immune cells:

- **Antigen-bound antibody activates immune cells.** In the first three functions listed, the antibody binds first to antigen, then to receptors on the immune cell. Phagocytic and some cytotoxic cells have membrane receptors that attract the Fc region of antigen-bound antibodies. The presence of a single Fc receptor eliminates the need to have millions of different receptors to recognize different antigens. Instead, with one type of receptor the immune cells are activated by any antibody-bound antigen.

If the immune cell is a phagocyte, Fc binding initiates phagocytosis (Fig. 24-13, ③). If the immune cell is a cytotoxic cell (NK cells and eosinophils), Fc binding initiates responses that kill the antibody-bound cell (Fig. 24-13, ④). For example, activated NK cells kill their target cells by triggering apoptosis. This nonspecific response of natural killer cells is called **antibody-dependent cell-mediated cytotoxicity**.

In the case of B lymphocytes, the antibodies are already an integral part of the lymphocyte (Fig. 24-13, ①). In this case, the binding of antigen activates the cell to produce memory cells and plasma cells.

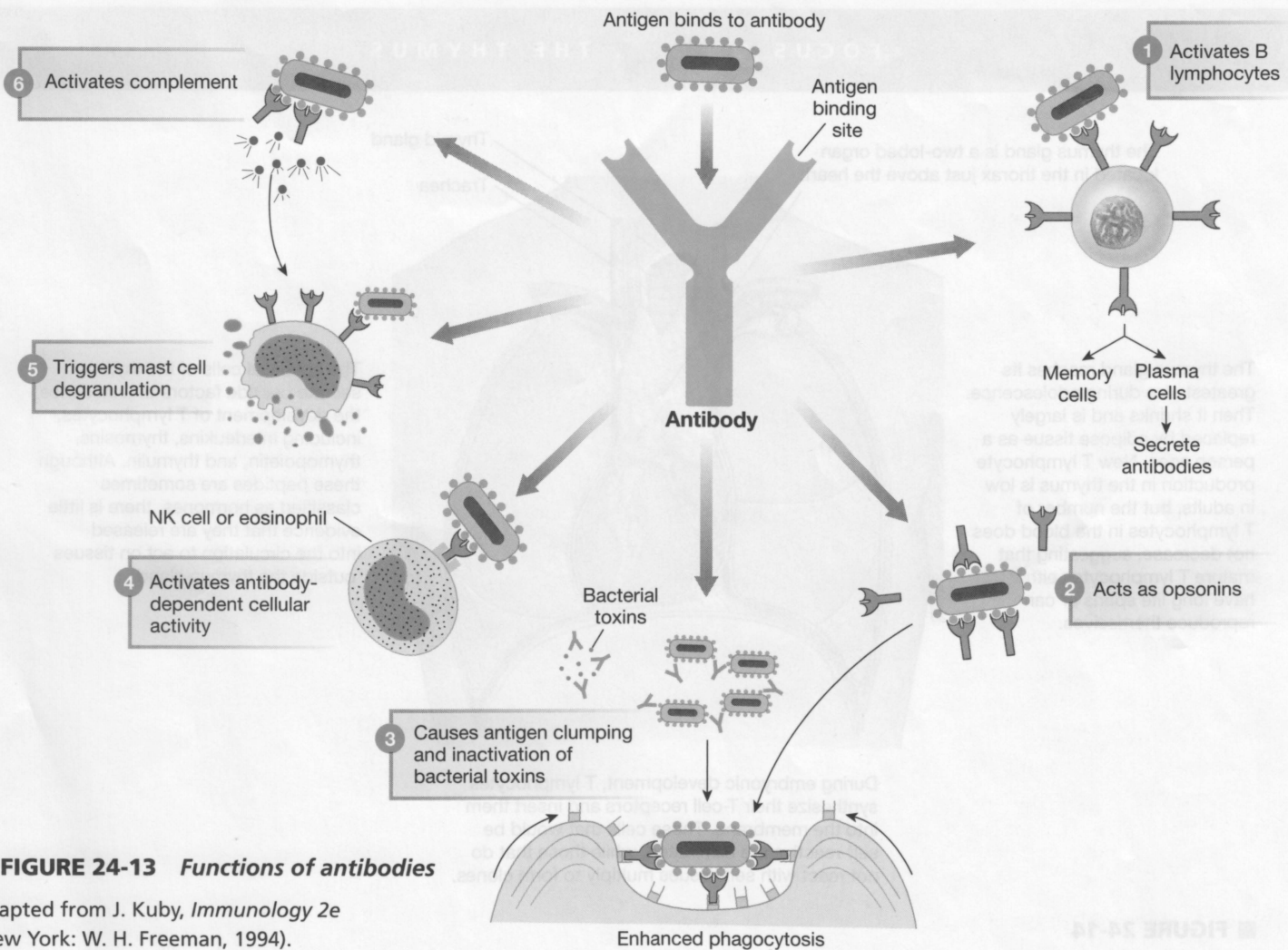
CONCEPT CHECK

4. Because antibodies are proteins, they are too large to cross cell membranes on transport proteins or through channels. How then do IgAs and other antibodies become part of external secretions such as saliva, tears, and mucus?
5. A child is stung by a bee for the first time. Why should the parent be particularly alert when the child is stung a second time?

Answers: p. 806

Antigen Binding to B Cell Antibodies Activates the Cell

The surface of each B lymphocyte is covered with as many as 100,000 antibody molecules whose Fc ends are inserted into the lymphocyte membrane (Fig. 24-13, ①). The Fab regions of the antibodies are then free to bind to free-floating extracellular



■ **FIGURE 24-13 Functions of antibodies**

Adapted from J. Kuby, *Immunology 2e* (New York: W. H. Freeman, 1994).

antigens, such as viruses or bacterial toxins. B cell binding neutralizes the pathogen or toxin. Some B cells then differentiate into memory cells that await a subsequent invasion.

For example, *Corynebacterium diphtheriae* is the bacterium that causes diphtheria, an upper respiratory infection. In this disease, the bacterial toxin kills host cells, leaving ulcers that have a characteristic grayish membrane. Natural immunity to the disease occurs when the host develops antibodies that disable the toxin. To develop a vaccine for diphtheria, researchers created an inactivated toxin preparation that did not affect living cells. When administered to a person, the vaccine triggers antibody production without causing any symptoms of the disease. As a result, diphtheria has been almost eliminated in countries with good immunization programs.

T Lymphocytes Must Make Direct Contact with Their Target Cells

Antibodies are effective only against extracellular pathogens. Once a pathogen gets inside a host cell, it can no longer be

“seen” by the humoral immune system. Defending the body against intracellular pathogens is the role of T lymphocytes, which carry out **cell-mediated immunity**. In this process, T cells bind to cells that display foreign antigen fragments as part of a **major histocompatibility complex (MHC)** on their surface.

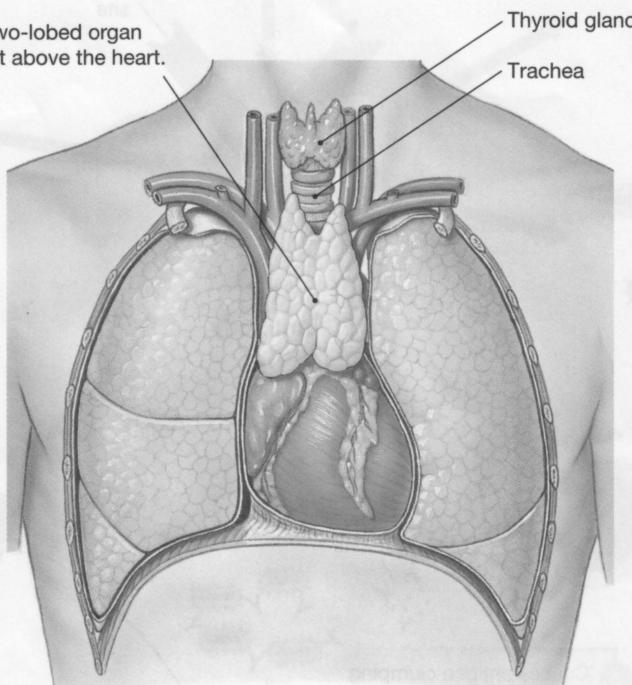
T lymphocytes develop in the thymus gland from immature precursor cells that migrate there from the bone marrow (Fig. 24-14 ■). Mature T cells bind to MHC-antigen-presenting cells with the help of **T-cell receptors** on the T-cell membrane (Fig. 24-15 ■). T-cell receptors are not antibodies (as B-cell receptors are), although proteins of the two receptor types are closely related. Also, T cells cannot bind to free-floating antigens as B cells do. Instead, T cells can only bind MHC-antigen complexes on the surface of a target cell (Fig. 24-15).

Major Histocompatibility Complexes Incorporates Antigen Fragments The major histocompatibility complexes are a family of membrane protein complexes encoded by a specific set of genes. (These proteins were named when they were discovered to play a role in rejection of foreign tissue

FOCUS ON . . . THE THYMUS

The thymus gland is a two-lobed organ located in the thorax just above the heart.

The thymus gland reaches its greatest size during adolescence. Then it shrinks and is largely replaced by adipose tissue as a person ages. New T lymphocyte production in the thymus is low in adults, but the number of T lymphocytes in the blood does not decrease, suggesting that mature T lymphocytes either have long life spans or can reproduce themselves.



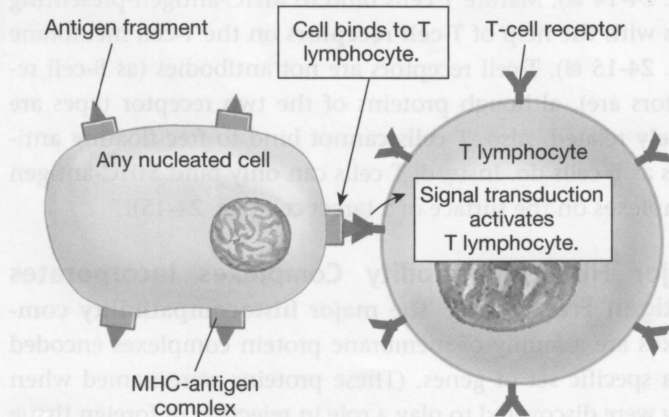
The epithelial cells of the thymus secrete peptide factors that influence the development of T lymphocytes, including interleukins, thymosins, thymopoietin, and thymulin. Although these peptides are sometimes classified as hormones, there is little evidence that they are released into the circulation to act on tissues outside the thymus gland.

During embryonic development, T lymphocytes synthesize their T-cell receptors and insert them into the membrane. Those cells that would be self-reactive are eliminated, while those that do not react with self tissues multiply to form clones.

■ FIGURE 24-14

following organ or tissue transplants.) We know now that every nucleated cell of the body has MHC on its membrane.

MHC proteins combine with fragments of antigens that have been digested within the cell, and the MHC-antigen complex is inserted into the cell membrane by exocytosis (see Fig.



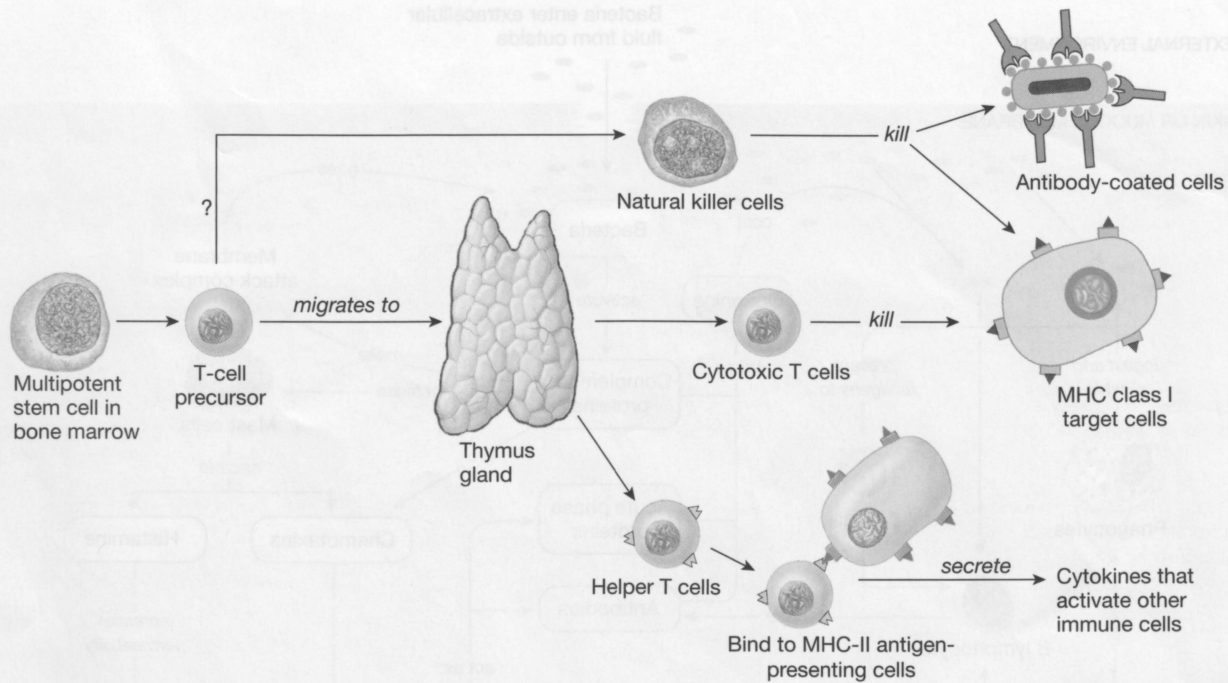
■ FIGURE 24-15 Activation of T lymphocytes

24-5 for an example). Free antigen in the ECF cannot simply bind to unoccupied MHC receptors on the cell surface.

There are two types of MHC molecules. **MHC class I molecules** are found on all nucleated cells. When viruses and bacteria invade the cell, they are digested into peptide fragments and loaded onto MHC-I "platforms." If a **cytotoxic T cell** (T_C cell) encounters a target cell with foreign antigen fragment on its MHC-I, the T_C cell recognizes the target as either a virus-infected cell or as a tumor cell and kills it to prevent it from reproducing (Fig. 24-16 ■).

MHC class II molecules are found primarily on macrophages, B lymphocytes, and dendritic cells. When an immune cell engulfs and digests an antigen, the fragments are returned to the immune cell membrane combined with MHC class II proteins. If a **helper T cell** (T_H cell) encounters a target cell with a foreign antigen fragment on its MHC-II, the T_H cell responds by secreting cytokines that enhance the immune response.

All MHC proteins are related, but they vary from person to person because of the huge number of alleles (variants of a gene) a person can inherit. There are so many alleles that it is unlikely that any two people other than identical twins will inherit exactly the same set. Major histocompatibility complexes



■ **FIGURE 24-16** Roles of T lymphocytes and NK cells in cell-mediated immunity

Cytotoxic and helper T lymphocytes and natural killer cells develop from the same T-cell precursor.

are one reason tissues cannot be transplanted from one person to another without first establishing compatibility. It has recently been discovered that the inheritance of certain MHC alleles is linked to some disorders in which the body fails to recognize its components as “self.”

Cytotoxic T Cells Kill Their Targets Cytotoxic T (T_C) cells attack and destroy cells that display MHC class I-antigen complexes. Although this may be an extreme response, it prevents the reproduction of intracellular invaders such as viruses, some parasites, and some bacteria.

How do cytotoxic T cells kill their targets? They do so in two ways. First they can release a cytotoxic pore-forming molecule called **perforin** along with **granzymes**, enzymes related to the digestive enzymes trypsin and chymotrypsin. When granzymes enter the target cell through perforin channels, they activate an enzyme cascade that induces the cell to commit suicide (*apoptosis*). Second, cytotoxic T cells can induce apoptosis by activating **Fas**, a “death receptor” protein on the target cell membrane that is linked to the enzyme cascade.

Helper T (T_H) cells do not directly attack pathogens and infected cells, but they play an essential role in the immune response by secreting cytokines that influence other cells. The cytokines secreted by helper T cells include (1) *interferon-gamma* ($IFN-\gamma$), which activates macrophages; (2) *interleukins* that activate antibody production and cytotoxic T lymphocytes; (3) *colony-stimulating factors* that enhance leukocyte production; and (4) *interleukins* that support the actions of mast cells and

eosinophils. Helper T cells also bind to B cells and promote their differentiation into plasma cells and memory B cells. HIV, the virus that causes AIDS, preferentially infects and destroys helper T cells, leaving the host unable to respond to pathogens that otherwise could be easily suppressed.



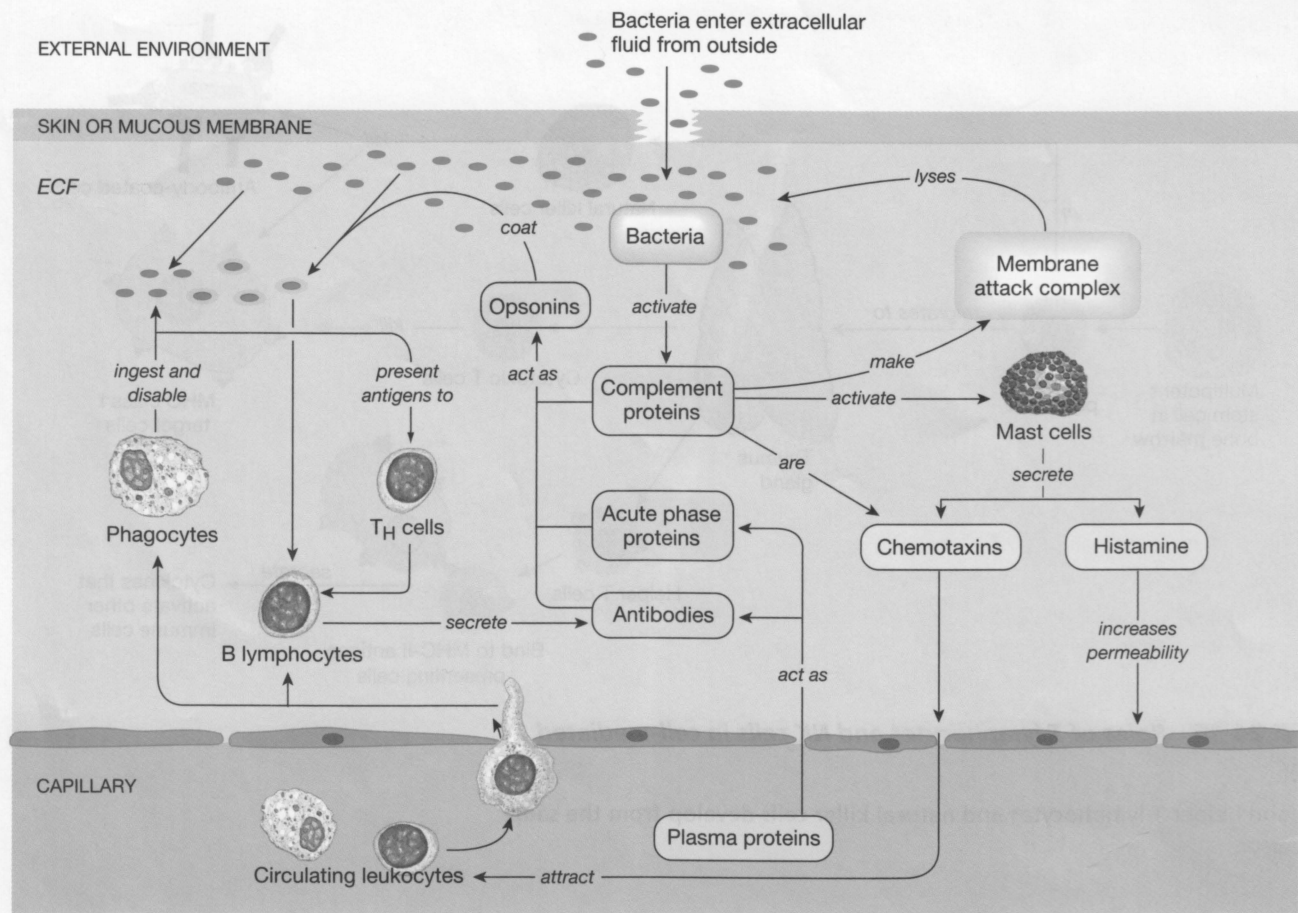
RUNNING PROBLEM

Early in the AIDS epidemic, researchers studied the effectiveness of a drug made with CD4—a naturally occurring protein found on the surface of helper T cells, the primary targets of HIV. When HIV binds to CD4, the virus is taken into the cell and begins replicating. Researchers found that adding high amounts of CD4 to test tubes containing HIV and helper T cells reduced the rate of HIV replication. But in human subjects, the results of clinical trials using the CD4 drug were disappointing. The drug did not slow the rate at which HIV infected helper T cells.

Question 2:

What is the rationale for flooding the body with CD4 protein to prevent HIV replication?





■ **FIGURE 24-17** Immune responses to extracellular bacteria

IMMUNE RESPONSE PATHWAYS

How does the body respond to different kinds of immune challenges? Although the details depend on the particular challenge, the basic pattern is the same. The innate response starts first, and is reinforced by the more specific acquired response. The two pathways are interconnected, so cooperation and communication is essential. In the following sections we examine the body's responses in four situations: an extracellular bacterial infection, a viral infection, an allergic response to pollen, and the transfusion of incompatible blood.

Inflammation Is the Typical Response to Bacterial Invasion

What happens when bacteria invade? As we've seen, if the passive barricades of the skin and mucous membranes fail, bacteria reach the extracellular fluid. There they usually cause an inflammatory response that represents the combined effects of many cells working to get rid of the invader. If bacteria enter the lymph, infection-fighting takes place in lymph nodes as well.

Inflammation is characterized by a red, swollen warm area that is tender or painful. In addition to the nonspecific inflammatory response, lymphocytes attracted to the area produce

antibodies keyed to the specific type of bacterium. The entry of bacteria sets off several interrelated reactions (Fig. 24-17 ■):

1. **Activity of the complement system.** Components of the bacterial cell wall activate the complement system. Some complement proteins are chemical signals (*chemotaxins*) that attract leukocytes from the circulation to help fight the infection. The process in which immune cells leave the circulation and enter the interstitial space is called **extravasation**.

Complement causes degranulation of mast cells and basophils. Cytokines secreted by mast cells act as additional chemotaxins, attracting more immune cells. Vasoactive chemicals such as histamine dilate blood vessels and increase capillary permeability. The enhanced blood supply to the site creates the redness and warmth of inflammation. Plasma proteins that escape into the interstitial space pull water with them, leading to tissue edema (swelling).

The complement cascade ends with formation of membrane attack complex molecules that insert themselves into the bacterial wall of unencapsulated bacteria. The subsequent entry of ions and water lyses the bacteria, aided by the enzyme lysozyme. This is a purely chemical process that does not involve immune cells.

2. *Activity of phagocytes.* If the bacteria are not encapsulated, macrophages can begin to ingest the bacteria immediately. But if the bacteria are encapsulated, antibodies must coat the capsule before the bacteria can be ingested by phagocytes. Opsonins enhance the process for bacteria that are not encapsulated. Molecules that act as opsonins include complement, acute phase proteins, and antibodies.
3. *Role of the acquired immune response.* Some elements of the acquired immune response are called into play in bacterial infections. If antibodies against the bacteria are already present, they enhance the innate response by acting as opsonins and neutralizing bacterial toxins.

Memory B cells attracted to the infection site will be activated if they encounter an antigen they recognize. But this process is much slower than the innate response just described, and it may take several days for plasma cells to begin secreting antibodies against the invader.

If the infection is a novel one, some of the bacteria will activate naive B cells, and antigen-presenting cells will present bacterial fragments to helper T cells to activate them. This triggers cytokine secretion from the T_H cells, B cell clonal expansion, antibody production by plasma cells, and formation of memory B and T_H cells.

4. *Initiation of repair.* If the initial wound damaged blood vessels underlying the skin, platelets and the proteins of the coagulation cascade will also be recruited to minimize the damage [p. 548]. Once the bacteria are removed by the immune response, the injured site is repaired under the control of growth factors and other cytokines.

Intracellular Defense Mechanisms Are Needed to Fight Viral Infections

What happens when viruses invade the body? First, they encounter an extracellular phase of immune response similar to that described for bacteria. In the early stages of a viral infection, innate immune responses and antibodies can help control the invasion of the virus.

Once the viruses enter the host's cells, humoral immunity in the form of antibodies is no longer effective. Cytotoxic T lymphocytes (and to a lesser extent, NK cells) are the main defense against intracellular viruses. These cells look for infected host cells, then destroy them.

For years, cell-mediated immunity effected by T lymphocytes, and humoral immunity controlled by B lymphocytes, were considered independent processes. We now know that the two types of immunity are linked. Figure 24-18 ■ depicts how the two types of lymphocytes coordinate to destroy viruses and virus-infected cells. In this figure, we have assumed prior exposure to the virus and the presence of pre-existing antibodies in the circulation. Antibodies can play an important defensive role in the early extracellular stages of a viral infection.

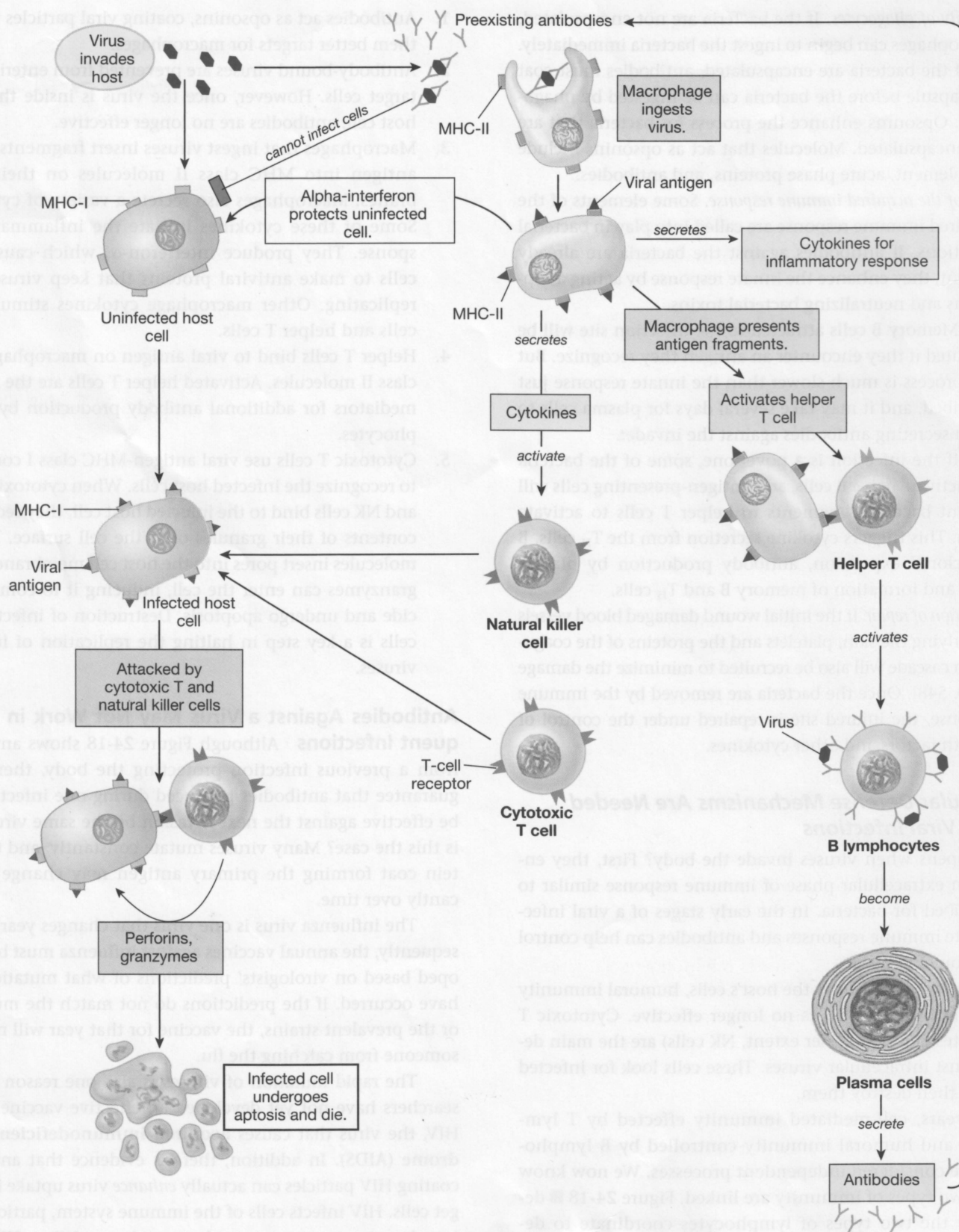
1. Antibodies act as opsonins, coating viral particles to make them better targets for macrophages.
2. Antibody-bound viruses are prevented from entering their target cells. However, once the virus is inside the target host cell, antibodies are no longer effective.
3. Macrophages that ingest viruses insert fragments of viral antigen into MHC class II molecules on their membranes. Macrophages also secrete a variety of cytokines. Some of these cytokines initiate the inflammatory response. They produce interferon- α , which causes host cells to make antiviral proteins that keep viruses from replicating. Other macrophage cytokines stimulate NK cells and helper T cells.
4. Helper T cells bind to viral antigen on macrophage MHC class II molecules. Activated helper T cells are the primary mediators for additional antibody production by B lymphocytes.
5. Cytotoxic T cells use viral antigen-MHC class I complexes to recognize the infected host cells. When cytotoxic T cells and NK cells bind to the infected host cell, they secrete the contents of their granules onto the cell surface. Perforin molecules insert pores into the host cell membrane so that granzymes can enter the cell, inducing it to commit suicide and undergo apoptosis. Destruction of infected host cells is a key step in halting the replication of invading viruses.

Antibodies Against a Virus May Not Work in Subsequent Infections

Although Figure 24-18 shows antibodies from a previous infection protecting the body, there is no guarantee that antibodies produced during one infection will be effective against the next invasion by the same virus. Why is this the case? Many viruses mutate constantly, and the protein coat forming the primary antigen may change significantly over time.

The influenza virus is one virus that changes yearly. Consequently, the annual vaccines against influenza must be developed based on virologists' predictions of what mutations will have occurred. If the predictions do not match the mutations or the prevalent strains, the vaccine for that year will not keep someone from catching the flu.

The rapid mutation of viruses is also one reason that researchers have not yet developed an effective vaccine against HIV, the virus that causes **acquired immunodeficiency syndrome** (AIDS). In addition, there is evidence that antibodies coating HIV particles can actually *enhance* virus uptake into target cells. HIV infects cells of the immune system, particularly T lymphocytes, monocytes, and macrophages. When HIV wipes out the helper T cells, cell-mediated immunity against the virus is lost. The general loss of an immune response in AIDS leaves these patients susceptible to a variety of viral, bacterial, fungal, and parasitic infections.



■ **FIGURE 24-18** *Immune responses to viruses*

This figure assumes prior exposure to the virus and preexisting antibodies.

Allergic Responses Are Inflammatory Responses Triggered by Specific Antigens

An **allergy** is an inflammatory immune response to a nonpathogenic antigen. Left alone, the antigen is not harmful to the body. But if an individual is sensitive to the antigen, the body produces an inflammatory response designed to get rid of it. Allergic inflammatory responses can range from mild tissue damage to fatal reactions.

The immune response in allergies is called **sensitivity** or **hypersensitivity** to the antigen. **Immediate hypersensitivity reactions** are mediated by antibodies and occur within minutes of exposure to antigens, which are called **allergens**. **Delayed hypersensitivity reactions** are mediated by helper T cells and macrophages and may take several days to develop.

Allergens can be practically any exogenous molecule: naturally occurring or synthetic, organic or inorganic. Certain foods, insect venoms, and pollen all trigger immediate hypersensitivity reactions. Allergens can be ingested, inhaled, injected, or simply come in contact with the skin.

Delayed hypersensitivity reactions include contact allergies to copper and other base metals. These are common among people who wear costume jewelry. Poison ivy and poison oak also cause common contact allergies.

Allergies have a strong genetic component, so if parents have a ragweed allergy, chances are good that their children will too. The development of allergies requires exposure to the allergen, a factor that is affected by geographical, cultural, and social conditions.

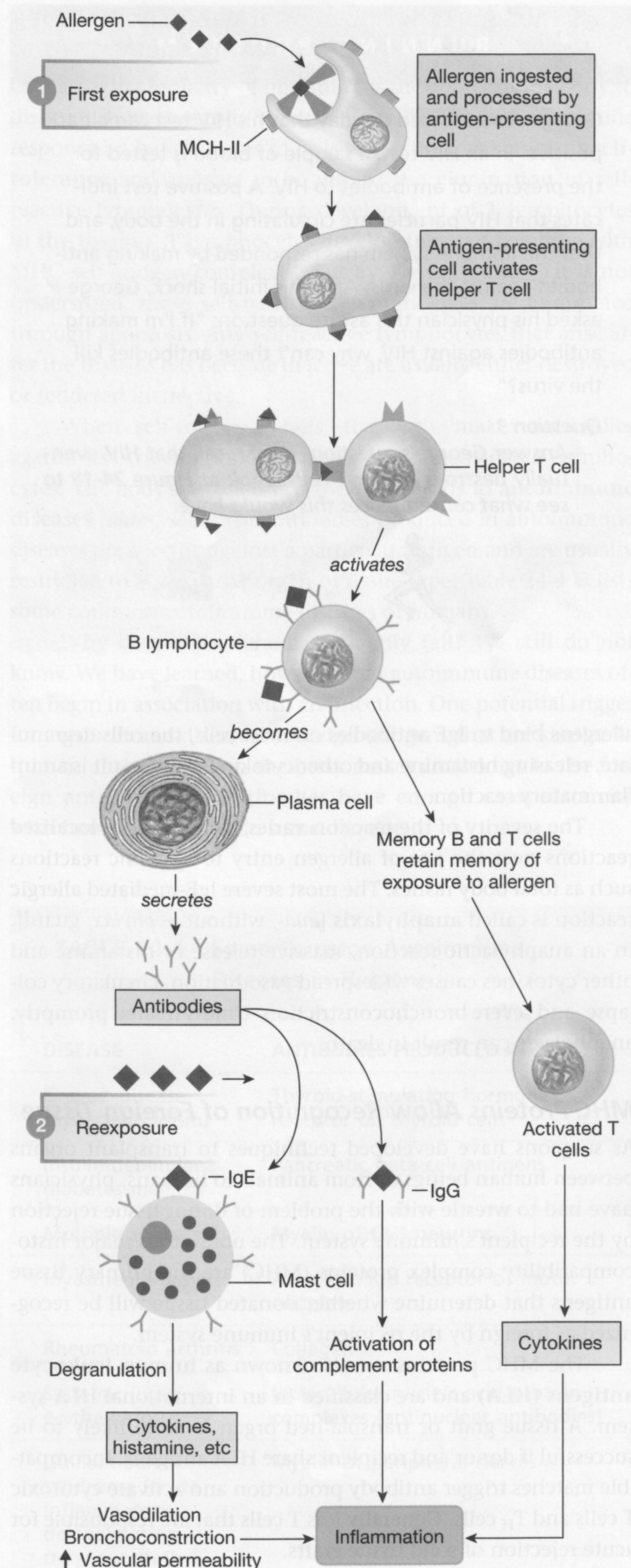
What happens during an immediate hypersensitivity reaction to pollen is depicted in Fig. 24-19 ■.

1. The initial step—first exposure or the sensitization phase ①—is equivalent to the primary immune response discussed previously: the allergen is ingested by and processed by an antigen-presenting cell such as a macrophage, which in turn activates a helper T cell (see the right side of Fig. 24-18).

The helper T cell activates B lymphocytes that have bound the allergen. This results in plasma cell production of antibodies (IgE and IgG) to the allergen. The IgE antibodies are immediately bound by their Fc ends to the surface of mast cells and basophils. Memory T and memory B cells store the record of the initial allergen exposure.

2. Upon reexposure ②, equivalent to the secondary immune response (see Figs. 24-10 and 24-11), the body reacts more strongly and more rapidly. The allergen binds to IgE already present on mast cells, triggering the immediate release of histamine, cytokines, and other mediators that cause allergic symptoms.

The type of allergic reaction depends on the antibody or immune cell involved. Allergen binding to IgE is the most common response to inhaled, ingested, or injected allergens. When



■ FIGURE 24-19 Allergic responses



RUNNING PROBLEM

George remembered the day that his HIV test came back positive. In an HIV test, a sample of blood is tested for the presence of antibodies to HIV. A positive test indicates that HIV particles are circulating in the body, and that the immune system has responded by making antibodies against the virus. After his initial shock, George asked his physician this astute question: "If I'm making antibodies against HIV, why can't these antibodies kill the virus?"

Question 3:

Answer George's question. Hint: recall that HIV eventually destroys helper T cells. Look at Figure 24-18 to see what consequences this would have.



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allergens bind to IgE antibodies on mast cells, the cells degranulate, releasing histamine and other cytokines. The result is an inflammatory reaction.

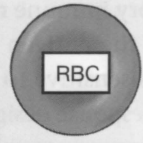
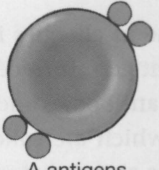
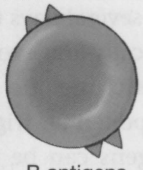
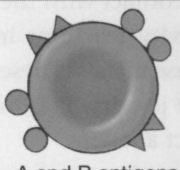
The severity of the reaction varies, ranging from localized reactions near the site of allergen entry to systemic reactions such as total body rashes. The most severe IgE-mediated allergic reaction is called **anaphylaxis** [*ana-*, without + *phylax*, guard]. In an anaphylactic reaction, massive release of histamine and other cytokines causes widespread vasodilation, circulatory collapse, and severe bronchoconstriction. Unless treated promptly, anaphylaxis can result in death.

MHC Proteins Allow Recognition of Foreign Tissue

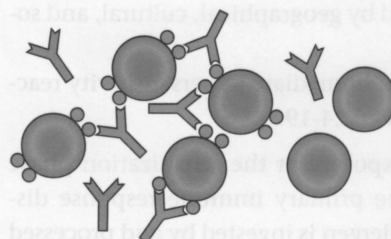
As surgeons have developed techniques to transplant organs between human beings or from animals to humans, physicians have had to wrestle with the problem of donor tissue rejection by the recipient's immune system. The ubiquitous major histocompatibility complex proteins (MHC) are the primary tissue antigens that determine whether donated tissue will be recognized as foreign by the recipient's immune system.

The MHC proteins are also known as **human leukocyte antigens (HLA)** and are classified in an international HLA system. A tissue graft or transplanted organ is more likely to be successful if donor and recipient share HLA antigens. Incompatible matches trigger antibody production and activate cytotoxic T cells and T_H cells. Generally it is T cells that are responsible for acute rejection of solid tissue grafts.

One of the most common examples of tissue donation is a blood transfusion. Human red blood cell (RBC) membranes

(a) Blood type	Antigen on red blood cell	Antibodies in plasma
O	 No A or B antigens	 "Anti-A" and "anti-B"
A	 A antigens	 "Anti-B"
B	 B antigens	 "Anti-A"
AB	 A and B antigens	None to A or B

(b) A mixture of type O and type A blood



When red blood cells with group A antigens on their membranes are mixed with plasma containing antibodies to group A, the antibodies cause the blood cells to clump, or agglutinate.

FIGURE 24-20 ABO blood groups

The antigens and antibodies characteristic of each blood type are shown.

contain antigenic proteins and glycoproteins, but RBCs lack the MHC protein markers for recognizing foreign tissue that are found on nucleated cells. In the absence of MHC proteins, two surface proteins—the ABO blood group antigens and the Rh* antigens—become the most important causes of a rejection reaction after a blood transfusion.

The ABO blood groups consist of four blood types created by combinations of two different glycoprotein antigens (designated A and B) found on the membrane of red blood cells (Fig. 24-20a ■). Each person inherits two alleles (one from each parent) of three possible ABO alleles: A, B, and O (neither A nor B

*Rh stands for Rhesus, a kind of monkey. Rh antigens are also called D antigens.

TABLE 24-3 ABO Blood Group Frequency in the United States

BLOOD GROUP	U.S. POPULATION (%)			
	WHITE	BLACK	ASIAN	NATIVE AMERICAN
O	45	49	40	79
A	40	27	28	16
B	11	20	27	4
AB	4	4	5	<1

antigen will be produced). Because alleles A and B are dominant to allele O, the various combinations of two alleles produces four blood types: A (AA or AO), B (BB or BO), AB, and O (OO) (Table 24-3 ■).

Problems with blood transfusions arise because plasma normally contains antibodies to the ABO group antigens. These antibodies are thought to be stimulated early in life by common substances such as bacteria and food components. They can be measured in the blood of infants as early as age 3–6 months.

People express antibodies to the red blood cell antigen(s) that they do not possess. Thus, people with blood type A have anti-B antibodies in their plasma, people with no antigens on their red blood cells (blood type O) have both anti-A and anti-B antibodies, and people with both antigens on their red blood cells (blood type AB) have no antibodies to A or B antigens.

How does the body respond to a transfusion of incompatible blood? If a person with blood type O is mistakenly given a transfusion of type A blood, for example, an immune reaction takes place. The anti-A antibodies of the type O recipient bind to the transfused type A red blood cells, causing them to clump (*agglutinate*). This reaction is easily seen in a blood sample and forms the basis for the blood-typing tests often performed in student laboratories.

Antibody binding also activates the complement system, resulting in production of membrane attack complexes that cause the transfused cells to swell and leak hemoglobin. Free hemoglobin released into the plasma can result in acute renal failure as the kidneys try to filter the large molecules from the blood. Cross-matching donor and recipient blood is critical prior to giving a blood transfusion.

CONCEPT CHECK

6. A person with AB blood type is transfused with type O blood. What happens and why?
7. A person with O blood type is transfused with type A blood. What happens? Why?

Answers: p. 806

Recognition of Self Is an Important Function of the Immune System

One amazing property of immunity is the ability of the body to distinguish its own cells from foreign cells. The lack of immune response by lymphocytes to cells of the body is known as **self-tolerance** and appears to be due to the elimination of self-reactive lymphocytes. During development of T lymphocytes in the thymus, T lymphocytes develop that can combine with MHC-self-antigen complexes. But by a mechanism that is not understood, these self-reactive T lymphocytes are eliminated through apoptosis. Any self-reactive lymphocytes that arise after the thymus has become inactive are usually either destroyed or rendered ineffective.

When self-tolerance fails, the body makes antibodies against its own components through T cell-activated B lymphocytes. The body's attack on its own cells leads to **autoimmune diseases** [*auto-*, self]. The antibodies produced in autoimmune diseases are specific against a particular antigen and are usually restricted to a particular organ or tissue type. Table 24-4 ■ lists some common autoimmune diseases of humans.

Why does self-tolerance suddenly fail? We still do not know. We have learned, however, that autoimmune diseases often begin in association with an infection. One potential trigger for autoimmune diseases is foreign antigens that are similar to human antigens. When the body makes antibodies to the foreign antigen, those antibodies have enough cross-reactivity with human tissues to do some damage.

TABLE 24-4 Some Common Autoimmune Diseases in Humans

DISEASE	ANTIBODIES PRODUCED AGAINST
Graves' disease (hyperthyroidism)	Thyroid-stimulating hormone receptor on thyroid cells
Insulin-dependent diabetes mellitus	Pancreatic beta cell antigens
Multiple sclerosis	Myelin of CNS neurons
Myasthenia gravis	Acetylcholine receptor of motor endplate
Rheumatoid arthritis	Collagen
Systemic lupus erythematosus	Intracellular nucleic acid protein complexes (antinuclear antibodies)
Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy)	Myelin of peripheral nerves



BIOTECHNOLOGY

ENGINEERED ANTIBODIES

One goal of cancer treatments is to destroy cancerous cells while minimizing damage to normal body cells. Scientists have used both chemotherapy and radiation for this approach but with mixed success. The newest cancer treatments are based on the genetic engineering of antibodies against tumor surface proteins, such as the growth factor receptor HER2 that occurs in high density on some breast cancer tumors. The engineered antibody then binds to its antigen on the tumor cell. In the case of the HER2 receptor, the antibody blocks the action of a growth factor the tumor cell needs to reproduce. Other antibodies have been engineered to carry chemotherapy drugs or radioactive molecules that specifically target cancer cells.

One strategy for developing these antibody treatments involves injecting the antigen into mice, which then produce antibodies against the antigen. Murine (mouse) antibodies injected into humans normally would trigger an immune response against the mouse protein, so scientists have used genetic engineering to create “humanized antibodies.” In this procedure, the antigen-binding portion of the mouse Fab region is integrated into the Fab region of a human antibody, resulting in a protein that is less likely to be rejected in the human body.

One example of an autoimmune disease is type 1 diabetes mellitus, in which the body makes *islet cell antibodies* that destroy pancreatic beta cells but leave other endocrine cells untouched [p. 735]. Another autoimmune condition, discussed in Chapter 23, is the hyperthyroidism of Graves’ disease [p. 761]. The body makes *thyroid-stimulating immunoglobulins* that mimic thyroid-stimulating hormone and cause the thyroid gland to oversecrete hormone.

Severe autoimmune diseases are sometimes treated by administering glucocorticosteroids, such as cortisol and its derivatives. Glucocorticoids depress immune system function by suppressing bone marrow production of leukocytes and decreasing the activity of circulating immune cells. Although helpful in suppressing symptoms of the autoimmune disease, large doses of steroids may trigger the same signs and symptoms as hormone oversecretion, causing patients to develop the central obesity and moon-face characteristic of Cushing’s syndrome [p. 755].

Immune Surveillance Allows the Body to Remove Abnormal Cells

What is the role of the human immune system in protecting the body against cancer? This question holds considerable interest for scientists. One theory, known as **immune surveillance**, proposes that although cancerous cells develop on a regular basis, they are detected and destroyed before they can spread. Some evidence supports that theory, but it does not explain why so many cancerous tumors develop every year, or why people with depressed immune function do not develop cancerous tumors in all types of tissues. However, immune surveillance does appear to recognize and control virus-associated tumors, presumably because of the viral antigen presented to NK and cytotoxic T cells.

Many types of endogenous tumors lack surface antigens that allow them to be recognized as abnormal by the immune system. One active area of cancer research is investigating ways to activate the immune system to fight cancerous tumor cells.

NEURO-ENDOCRINE-IMMUNE INTERACTIONS

One of the most fascinating and rapidly developing areas in physiology involves the link between the mind and the body. Although serious scientists scoffed at the topic for many years, the interaction of emotions and somatic illnesses has been described for centuries. The Old Testament says, “A merry heart doeth good like a medicine; but a broken spirit drieth the bones” (Proverbs 17:22). Most societies have tales of people who lost the will to live and subsequently died without obvious illness, or of people given up for dead who made remarkable recoveries.

Today, the medical field is beginning to recognize the reality of the mind-body connection. Psychosomatic illnesses and the placebo effect have been accepted for many years. Why should we not investigate the possibility that cancer patients can enhance their immune function by visualizing their immune cells gobbling up the abnormal cancer cells?

The study of brain-immune interactions is now a recognized field known as **neuroimmunomodulation**. Currently the field is still in its infancy, and the results of many studies raise more questions than they answer. In one experiment, for example, mice were repeatedly injected with a chemical that suppressed the activity of their lymphocytes. During each injection, they were also exposed to the odor of camphor, a chemical that does not affect the immune system. After a period of conditioning, the mice were exposed only to the camphor odor. When the researchers checked the mice’s lymphocyte function, they found that the odor of camphor had suppressed the activity of the immune cells, just as the chemical suppressant had

done previously. The pathways through which this conditioning occurred are still largely unexplained.

What do we know at this point about the relationship between the immune, nervous, and endocrine systems?

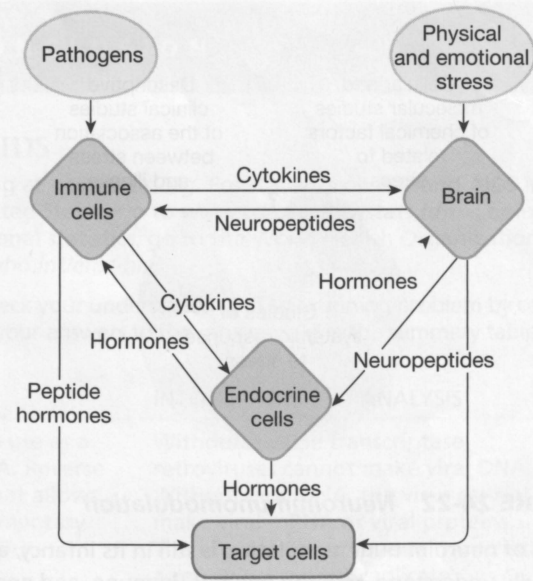
1. **The three systems share common signal molecules and common receptors for those molecules.** Chemicals once thought to be exclusive to a single cell or tissue are being discovered all over the body. Immune cells secrete hormones, and leukocyte cytokines are produced by non-immune cells. For example, lymphocytes secrete thyrotropin (TSH), ACTH, growth hormone, and prolactin, as well as hypothalamic corticotropin-releasing hormone (CRH).

Receptors for hormones, neurotransmitters, and cytokines are being discovered everywhere. Neurons in the brain have receptors for cytokines produced by immune cells. Natural killer cells have opiate receptors and beta adrenergic receptors. Everywhere we turn, the nervous, endocrine, and immune systems seem to share chemical signal molecules and their receptors.

2. **Hormones and neuropeptides can alter the function of immune cells.** It has been known for years that increased cortisol levels due to stress were associated with decreased antibody production, depressed lymphocyte proliferation, and diminished activity of natural killer cells. Substance P, a neuropeptide, has been shown to induce degranulation of mast cells in the mucosa of the intestines and the respiratory tract. And sympathetic innervation of the bone marrow increases antibody synthesis and production of cytotoxic T cells.
3. **Cytokines from the immune system can affect neuroendocrine function.** Stressors such as bacterial and viral infections or tumors can induce stress responses in the central nervous system through cytokines released by immune cells. Interleukin-1 is probably the best-studied cytokine in this response, but the induction of cortisol release by lymphocyte ACTH is receiving considerable attention.

It was once believed that cortisol secretion depended on neural signals translated through the hypothalamic CRH-anterior pituitary ACTH pathway. Now it appears that pathogenic stressors can activate the cortisol pathway by causing immune cells to secrete ACTH.

The interaction of the three systems is summarized in the model shown in Fig. 24-21 ■. The nervous, endocrine, and immune systems are closely linked through bidirectional communication carried out using cytokines, hormones, and neuropeptides. The brain is linked to the immune system by autonomic neurons, CNS neuropeptides, and leukocyte cytokines. The nervous system controls endocrine glands by secretion of hypothalamic-releasing hormones, but immune cells secrete some of the same trophic hormones. Hormones from endocrine



■ FIGURE 24-21 Model for interaction between nervous, endocrine, and immune systems

glands feed back to influence both the nervous and immune systems.

The result is a complex network of chemical signals subject to modulation by outside factors. These outside factors include physical and emotional stimuli integrated through the brain, pathogenic stressors integrated through the immune system, and a variety of miscellaneous factors, including magnetic fields, chemical factors from brown adipose tissue, and melatonin from the pineal gland. It will probably take years for us to decipher these complex pathways.



RUNNING PROBLEM

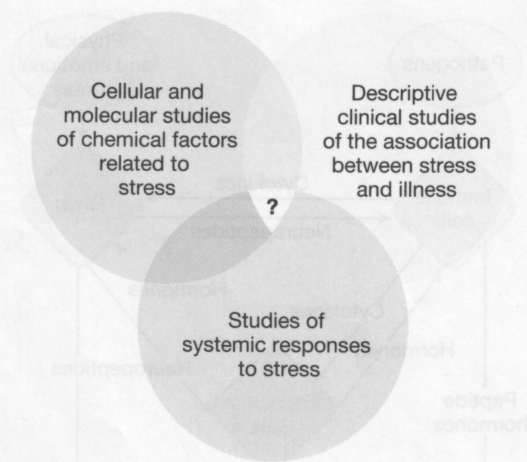
George began taking the AIDS drug cocktail. On the day he filled the prescription, his T-cell count was 338. (A normal T-cell count is 1000.) Within four weeks, his T-cell count was 489. Within two months, it was inching toward 900. The amount of virus in George's blood (called the "viral load") had also decreased significantly. George was thrilled. "I don't know if this will last forever," he told his doctor. "But I'm going to enjoy this reprieve while I can."

Question 4:

What correlation can be made between T-cell count and the viral load of HIV in George's blood?



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■ **FIGURE 24-22 Neuroimmunomodulation**

The field of neuroimmunomodulation is still in its infancy, and we do not fully understand how the nervous, immune, and endocrine systems interact to affect health and well-being.

Stress Alters Immune System Function

One area of interest is the link between inability to cope with stress and the development of illnesses. The modern study of stress is attributed to Hans Selye, beginning in 1936. He defined **stress** as nonspecific stimuli that disturb homeostasis and elicit an invariable stress response that he termed the *general adaptation syndrome*.

Selye's stress response consisted of stimulation of the adrenal glands, followed by suppression of the immune system due to high levels of circulating glucocorticoids [p. 751]. For many years, Selye's experiment was the benchmark for defining stress. However, since the 1970s, the definition of stress and the stress response has broadened.

Stressors—the events or items that create stress—are highly variable and difficult to define in experimental settings. Acute stress is different from chronic stress. A person's reaction to stress is affected by loneliness and by whether the person feels in control of the stressful situation. Many stressors are sensed and interpreted by the brain, leading to modulation of the stressor by experience and expectations. A stressor to one person may not affect another.

Most physical and emotional stressors are integrated through the central nervous system. The two classic stress responses are (1) the rapid, neurally mediated **fight-or-flight reaction**, and (2) the elevation of adrenal cortisol levels with associated suppression of the immune response. Fight-or-flight is a rapid reaction to acute stress. The cortisol response is a better indicator of chronic or repetitive stress.

One difficulty in studying the body's response to stress is the complexity involved in integrating information from three levels of response (Fig. 24-22 ■). Scientists have gathered

a good deal of information at each of three levels: cellular and molecular factors related to stress, systemic responses to stress, and clinical studies describing the relationships between stress and illness. In some cases, we have linked two different levels together, although in other cases the experimental evidence is scanty or even contradictory. What we still do not understand is the big picture, the way that all three levels of response overlap.

Experimental progress is slow because many traditional study animals, such as rodents, are not good models for studying stress in humans. At the same time, controlled experiments that create stress in humans are difficult to design and execute for both practical and ethical reasons. Much of our research is observational. One study, for example, followed natural killer cell activity over an 18-month period in two groups of people: spouse caregivers of Alzheimer's disease patients (a group that reports high psychosocial stress) and a matched group of controls. For a subset of the caregivers, high perceived stress at the beginning of the study was associated with low NK cell activity at the end. However, many variables—including age, gender, exercise, and use of alcohol and prescription drugs—must be taken into account before we can conclude that stress was the causative factor.

Modern Medicine Incorporates Mind-Body Therapeutics

The role of mind-body interactions in traditional medicine is receiving more attention in recent years. The U.S. National Center for Complementary and Alternative Medicine (<http://nccam.nih.gov>) supports rigorously designed research studies on the efficacy of complementary medical therapies, such as meditation, yoga, hypnosis, visual imagery, and biofeedback. Although the placebo and nocebo effects [p. 11] are widely accepted in the traditional medical community, the role of complementary therapies such as laughter therapy is still being studied. Can watching a funny movie really help your immune system? Recent studies suggest that it can. In these studies, researchers measured the activity of immune cells in subjects before and after watching a humorous movie or video. In both studies, immune cells became more active. You can learn more about *humor therapy* from the Association for Applied and Therapeutic Humor (www.aath.org).

In spite of the difficulties of studying the integration of the immune, endocrine, and nervous systems, scientists are beginning to piece together the intricate tapestry of mind-body interactions. When we can explain at the molecular level why students tend to get sick just before exam time, and why relaxation therapy enhances the immune response, we will be well on the way to understanding the complex connections between the brain and the immune system.



RUNNING PROBLEM CONCLUSION

TREATMENT FOR AIDS

In this running problem you learned about a treatment for AIDS that consists of two anti-retroviral drugs and a protease inhibitor. The combination of these drugs seems to stem the tide of HIV replication more effectively than either of the drugs used alone. Other drugs have been developed, and tests for an HIV vaccine are still in progress. To learn more about current treatments, see www.aidsinfo.nih.gov or

AIDS.org at www.aids.org. For statistics on HIV and AIDS in the United States, go to www.cdc.gov/hiv/stats.htm. For international statistics, go to the World Health Organization at www.who.int/emc-hiv/

Now check your understanding of this running problem by comparing your answers to the information in the summary table.

QUESTION	FACTS	INTEGRATION AND ANALYSIS
1 Why can't retroviruses reproduce without reverse transcriptase?	Retroviruses have no DNA to use as a template to make viral mRNA. Reverse transcriptase is an enzyme that allows retroviruses to make complementary DNA from their own viral RNA.	Without reverse transcriptase, retroviruses cannot make viral DNA. Without viral DNA, the virus cannot make viral mRNA or viral proteins. Therefore, without reverse transcriptase, a retrovirus cannot replicate.
2 What is the rationale for flooding the body with CD4 protein to prevent HIV replication?	CD4 is one receptor on helper T cells to which HIV binds. Binding causes the virus to be taken into the T cell.	Introducing large amounts of CD4 protein into the body might "trick" HIV into binding to these free proteins instead of to CD4 on helper T cells. This would reduce the number of virus particles that could invade T cells.
3 George asks, "If I'm making antibodies against HIV, why can't these antibodies kill the virus"? Answer George's question.	Viruses can only be affected by antibodies when they are outside host cells. HIV bound to antibody is taken up into helper T cells.	HIV enters helper T cells and, over time, destroys them.
4 What correlation can be made between T-cell count and the viral load?	George's T-cell count increases while the viral load decreases.	Apparently, the drug cocktail is effective in decreasing the rate of T-cell infection by HIV. This has two results. As fewer T cells are killed by the virus, the T-cell count rises. As the drugs suppress viral replication, viral load decreases.

777 779 793 798 801 803



CHAPTER SUMMARY

In this chapter you learned how the immune system protects the body from pathogens and how it removes damaged tissue and abnormal cells. An immune response requires detection of the foreign substance, communication with other immune cells, and coordination of the response. These functions depend on *chemical communication* and

Overview of Immune System Function

1. **Immunity** is the ability of the body to protect itself from pathogens. The human immune system consists of lymphoid tissues, immune cells, and cytokines. (p. 777)
2. **Antigens** are substances that trigger an immune response and react with products of that response. (p. 777)

molecular interactions between receptors, antibodies, and antigens. The *compartmentation* of the body affects how the immune system fights pathogens: some pathogens hide inside cells while others remain in the extracellular compartment.

Pathogens of the Human Body

3. Bacteria are cells that can survive and reproduce outside of a living host. Antibiotic drugs kill bacteria. (p. 778)
4. Viruses are DNA or RNA cores enclosed in protective proteins. They invade host cells and reproduce using the host's intracellular

machinery. The immune system must destroy infected host cells to kill a virus. (p. 778; Fig. 24-1)

The Immune Response

5. The immune response includes: (1) *detection and identification*, (2) *communication* with other immune cells, (3) *recruitment* of assistance and *coordination* of the response, and (4) *destruction or suppression* of the invader. (p. 779)
6. **Innate immunity** is the rapid, **nonspecific immune response**. **Acquired immunity** is slower and is an **antigen-specific response**. The two types of immunity overlap. (p. 779)

Anatomy of the Immune System

7. Immune cells form and mature in the **thymus gland** and **bone marrow**. The **spleen** and **lymph nodes** are encapsulated lymphoid tissues. Unencapsulated **diffuse lymphoid tissues** include **tonsils** and the **gut-associated lymphoid tissue (GALT)**. (p. 781; Figs. 24-2, 24-3, 24-14)
8. **Eosinophils** are **cytotoxic cells** that kill parasites. **Basophils** and **mast cells** release histamine, **heparin**, and other cytokines. (p. 782; Fig. 24-4)
9. **Neutrophils** are phagocytic cells that release pyrogens and cytokines that mediate inflammation. (p. 783; Fig. 24-4)
10. **Monocytes** are the precursors of tissue **macrophages**. **Antigen-presenting cells (APCs)** display antigen fragments in proteins on their membrane. (p. 783; Figs. 24-4, 24-5)
11. **Lymphocytes** and **plasma cells** mediate antigen-specific immune responses. (p. 784)
12. **Dendritic cells** capture antigens and present them to lymphocytes. (p. 784)

Innate Immunity: Nonspecific Responses

13. Physical and chemical barriers, such as skin and mucus, are the first line of defense. (p. 784)
14. **Chemotaxins** attract immune cells to pathogens. (p. 784)
15. Phagocytosis requires that surface molecules on the pathogen bind to membrane receptors on the phagocyte. **Opsonins** are antibodies or complement proteins that coat foreign material. (p. 785; Figs. 24-6, 24-7)
16. **Natural killer cells** kill certain tumor cells and virus-infected cells. They bind to the Fc stem of antibodies that are bound to a target cell. This is called **antibody-dependent cell-mediated cytotoxicity**. (pp. 785, 790)
17. **Inflammation** results from cytokines released by activated tissue macrophages. (p. 787)
18. Inflammatory cytokines include **acute phase proteins**, histamine, **interleukins**, **bradykinin**, and **complement proteins**. (pp. 786–787)
19. The complement cascade forms **membrane attack complex**, pore-forming molecules that cause pathogens to rupture. (p. 787; Fig. 24-8)

Acquired Immunity: Antigen-Specific Responses

20. Lymphocytes mediate the acquired immune response. Lymphocytes that react to one type of antigen form a **clone**. (p. 788; Fig. 24-9)
21. First exposure to an antigen activates a **naive lymphocyte clone** and causes it to divide (**clonal expansion**). Newly formed lymphocytes differentiate into **effector cells** or **memory cells**. Additional

exposure to the antigen creates a faster and stronger **secondary immune response**. (p. 788; Figs. 24-10, 24-11)

22. Lymphocyte cytokines include **interleukins** and **interferons**, which interfere with viral replication. **Interferon-gamma** activates macrophages and other immune cells. (p. 793)
23. **B lymphocytes** secrete antibodies. **T lymphocytes** and natural killer cells attack and destroy infected cells. (p. 788)
24. **Antibodies** bind to pathogens. Mature B lymphocytes are covered with antibodies that act as surface receptors. Activated B lymphocytes differentiate into **plasma cells**, which secrete soluble antibodies. (p. 788)
25. The five classes of immunoglobulins (Ig), or antibodies, are IgG, IgA, IgE, IgM, and IgD, collectively known as **gamma globulins**. (p. 789)
26. The antibody molecule is Y shaped, with four polypeptide chains. The arms, or **Fab regions**, contain antigen-binding sites. The stem, or **Fc region**, can bind to immune cells. Some immunoglobulins are polymers. (p. 790; Fig. 24-12)
27. Soluble antibodies act as opsonins, serve as a bridge between antigens and leukocytes, activate complement proteins and mast cells, and disable viruses and toxins. (p. 790; Fig. 24-13)
28. B cell antibodies bind antigens to activate B lymphocytes and initiate the production of additional antibodies. (p. 790; Fig. 24-13)
29. **T lymphocytes** are responsible for **cell-mediated immunity**, in which the lymphocytes bind to target cells using **T-cell receptors**. (p. 791; Fig. 24-15)
30. T lymphocytes react to antigen bound to **major histocompatibility complex** proteins on the target cell. **MHC class I molecules** displaying antigen cause cytotoxic T (T_C) cells to kill the target cell. **MHC class II molecules** with antigen activate helper T (T_H) cells to secrete cytokines. (pp. 791–792; Fig. 24-16)
31. **Cytotoxic T (T_C) cells** release **perforin**, a pore-forming molecule that allows **granzymes** to enter the target cell and trigger it into committing suicide (**apoptosis**). (p. 793)
32. **Helper T (T_H) cells** secrete cytokines that influence other cells. (p. 793; Fig. 24-16)

Immune Response Pathways

33. Bacteria usually cause a nonspecific inflammatory response. In addition, lymphocytes produce antibodies keyed to the specific type of bacterium. (p. 794; Fig. 24-17)
34. Innate immune responses and antibodies help control the early stages of a viral infection. Once the viruses enter the host's cells, cytotoxic T cells must destroy infected host cells. (p. 795; Fig. 24-18)
35. An **allergy** is an inflammatory immune response to a nonpathogenic **allergen**. The body gets rid of the allergen through the inflammatory response. (p. 797; Fig. 24-19)
36. **Immediate hypersensitivity reactions** to allergens are mediated by antibodies and occur within minutes of exposure to antigen. **Delayed hypersensitivity reactions** are mediated by T lymphocytes and may take several days to develop. (p. 797)
37. The major histocompatibility complex (MHC) proteins found on all nucleated cells determine tissue compatibility. Lymphocytes will attack any MHC complexes they do not recognize as self proteins. (p. 798)
38. Human red blood cells lack MHC proteins but contain other antigenic membrane proteins and glycoproteins, such as the ABO and Rh antigens. (p. 798; Fig. 24-20)

39. **Self-tolerance** is the body's ability to distinguish its own cells and not produce an immune response. When self-tolerance fails, the body makes antibodies against its own components, creating an **autoimmune disease**. (p. 799)
40. The theory of **immune surveillance** proposes that cancerous cells develop on a regular basis but are detected and destroyed by the immune system before they can spread. (p. 800)

QUESTIONS

(Answers to the Review Questions begin on page A1.)

THE PHYSIOLOGY PLACE

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LEVEL ONE REVIEWING FACTS AND TERMS

1. Define immunity. What is meant by memory and specificity in the immune system?
2. Name the anatomical components of the immune system.
3. List and briefly summarize the three main functions of the immune system.
4. Name two ways viruses are released from a host cell. Give three ways in which viruses damage host cells or disrupt their function.
5. Suppose a pathogen has invaded the body. What four steps occur if the body is able to destroy the pathogen? What compromise may be made if the pathogen cannot be destroyed?
6. Define the following terms and explain their significance:
 - (a) anaphylaxis
 - (b) agglutinate
 - (c) extravascular
 - (d) degranulation
 - (e) acute phase protein
 - (f) clonal expansion
 - (g) immune surveillance
7. How are histiocytes, Kupffer cells, osteoclasts, and microglia related?
8. What is the mononuclear phagocytic system, and what role does it play in the immune system?
9. Match each of the following cell types with its description:
 - (a) lymphocyte
 - (b) neutrophil
 - (c) monocyte
 - (d) dendritic cell
 - (e) eosinophil
 - (f) basophil
 1. most abundant leukocyte; phagocytic; lives 1–2 days
 2. cytotoxic; is associated with allergic reactions and parasitic infestations
 3. precursor of macrophages; relatively rare in blood smears
 4. related to mast cells; releases cytokines such as histamine and heparin
 5. most of these cells reside in the lymphoid tissues
 6. these cells capture antigens, then migrate to the lymphoid tissues
10. Give examples of physical and chemical barriers to infection.
11. Name the three main types of lymphocytes and their subtypes. Explain the functions and interactions of each group.
12. Define self-tolerance. Which cells are responsible? Relate self-tolerance to autoimmune disease.

Neuro-Endocrine-Immune Interactions

41. The nervous, endocrine, and immune systems are linked together by signal molecules and receptors. The study of these interactions is a field known as **neuroimmunomodulation**. (p. 800; Fig. 24-21)
42. The link between inability to cope with stress and the development of illnesses is believed to result from neuroimmunomodulation. (p. 802)

13. What is meant by the term **neuroimmunomodulation**?
14. Explain the terms **stress**, **stressor**, and **general adaptation syndrome**.

LEVEL TWO REVIEWING CONCEPTS

15. **Concept map:** Map the following terms. You may add additional terms.

acquired immunity	helper T cell
antibody	innate immunity
antigen	memory cell
antigen-presenting cell	MHC class I
B lymphocyte	MHC class II
bacteria	monocyte
basophil	natural killer cell
chemotaxin	neutrophil
cytokine	opsonin
cytotoxic cell	phagocyte
cytotoxic T cell	phagosome
dendritic cell	plasma cell
eosinophil	T lymphocyte
Fab region	viruses
Fc region	
16. Why do lymph nodes often swell and become tender or even painful when you are sick?
17. Summarize the effects of histamine, interleukin-1, acute phase proteins, bradykinin, complement, and interferon- γ . Are these chemicals antagonistic or synergistic to one another?
18. Compare and contrast the terms in the following sets of terms:
 - (a) pathogen, microbe, pyrogen, antigen, antibody, antibiotic
 - (b) infection, inflammation, allergy, autoimmune disease
 - (c) virus, bacteria, allergen, retrovirus
 - (d) chemotaxin, opsonin, cytokine, interleukin, bradykinin, interferon
 - (e) acquired immunity, innate immunity, humoral immunity, cell-mediated immunity, specific immunity, nonspecific immunity
 - (f) immediate and delayed hypersensitivity
 - (g) membrane attack complex, granzymes, perforin
19. Diagram and label the parts of an antibody molecule. What is the significance of each part?
20. Diagram the steps in the process of inflammation.
21. Diagram the steps in the process of fighting viral infections.
22. Diagram the steps in the process of an allergic reaction.

LEVEL THREE PROBLEM SOLVING

23. One ABO blood type is called the "universal donor," and one is called the "universal recipient." Which types are these, and why are they given those names?

24. Maxie Moshpit claims that Snidley Superstar is the father of her child. Maxie has blood type O. Snidley has blood type B. Baby Moshpit has blood type O. Can you rule out Snidley as the father of the baby with only this information? Explain.
25. Every semester around exam time more students visit the Student Health Center with colds and viral infections. The physicians attribute the increased incidence of illness to stress. Can you explain the biological basis for that relationship? What are some other possible explanations?
26. Barbara is troubled with rheumatoid arthritis, characterized by painful, swollen joints from inflamed connective tissue. She notices

that it flares up when she is tired and stressed. This condition is regarded as an autoimmune disease. Outline the physiological reactions that would lead to this condition.

27. The differential white cell count [Fig. 16-3, p. 541] is an important diagnostic tool in medicine. If a patient's "diff" shows an increase in the number of immature neutrophils ("bands"), do you think the cause is more likely to be a bacterial or a viral infection? If the count shows an increase in eosinophils (*eosinophilia*), is the cause more likely to be a viral infection or a parasitic infection? Explain your reasoning.

ANSWERS

Answers to Concept Check Questions

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1. Bacteria are cells; viruses are not. Bacteria can reproduce outside a host; viruses cannot. Bacteria can be killed by antibiotics; viruses cannot.
2. Virus enters host cell and uses its viral nucleic acids to tell host cell to make viral nucleic acids and proteins. These assemble into new virus particles, which are then released from the host cell.

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3. When capillary permeability increases, proteins move from plasma to interstitial fluid. This decreases the colloid osmotic force opposing capillary filtration, and additional fluid accumulates in the interstitial space (swelling or edema).

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4. Antibodies can be moved across cells by transcytosis or released from cells by exocytosis.
5. The child developed antibodies to bee venom on first exposure, so if the child will have a severe allergic reaction to bee venom, it will occur

on the second exposure. Allergic reactions are mediated by IgE. After the first bee sting, IgE antibodies secreted in response to the venom are bound to the surface of mast cells. At the second exposure, bee venom binding to the IgE causes the mast cells to degranulate, causing an allergic reaction that may be severe enough to cause anaphylaxis.

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6. Type O blood has neither A nor B antigens, but even if it did, type AB blood does not produce anti-A or anti-B antibodies. Therefore, no immune reaction will occur.
7. If type A blood is given to a type O recipient, the recipient's anti-A antibodies will cause agglutination.

Answers to Figure Questions

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Figure 24-9: The antigen will activate clone 1.