

T lymphocytes (green) attacking a cancer cell (with blue nucleus) (TEM)

CHAPTER

21

The Lymphatic and Immune Systems

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Brushing Up

To understand this chapter, it is important that you understand or brush up on the following concepts:

- Endocytosis and exocytosis (p. 112)
- General gland structure: capsule, septa, stroma, and parenchyma (p. 180)
- Leukocyte types (pp. 700–701)
- Mechanisms of venous blood flow (p. 764)

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Of all the body systems, the *lymphatic system* is perhaps the least familiar to most people. Yet without it, neither the circulatory system nor the immune system could function—circulation would shut down from fluid loss, and the body would be over-run by infection for lack of immunity. This chapter discusses the role of the lymphatic and immune systems in maintaining fluid balance and protecting the body from infection and disease.

The Lymphatic System

Objectives

When you have completed this section, you should be able to

- list the functions of the lymphatic system;
- explain how lymph is formed and returned to the bloodstream;
- name the major types of cells in the lymphatic system and state their functions; and
- describe the form and function of the lymph nodes, tonsils, thymus, and spleen.

The **lymphatic system** (fig. 21.1) is composed of a network of vessels that penetrate nearly every tissue of the body, and a collection of tissues and organs that produce immune cells. The lymphatic system has three functions:

1. **Fluid recovery.** Fluid continually filters from our blood capillaries into the tissue spaces. The blood capillaries reabsorb most of it, but by no means all. Each day, they lose an excess of 2 to 4 L of water and one-quarter to one-half of the plasma protein. The lymphatic system absorbs this excess fluid and returns it to the bloodstream by way of the lymphatic vessels. If not for this fluid recovery, the circulatory system would not have enough blood to function properly. Even partial interference with lymphatic drainage can lead to severe edema (fig. 21.2).
2. **Immunity.** As the lymphatic system recovers excess tissue fluid, it also picks up foreign cells and chemicals from the tissues. On its way back to the bloodstream, the fluid passes through lymph nodes, where immune cells stand guard against foreign matter. When they detect it, they activate a protective immune response.
3. **Lipid absorption.** In the small intestine, special lymphatic vessels called *lacteals* absorb dietary lipids that are not absorbed by the blood capillaries (see chapter 25).

The components of the lymphatic system are (1) *lymph*, the recovered fluid; (2) *lymphatic vessels*, which transport the lymph; (3) *lymphatic tissue*, composed of aggregates of lymphocytes and macrophages that populate many organs of the body; and (4) *lymphatic organs*, in which these cells are especially concentrated and which are set off from surrounding organs by connective tissue capsules.

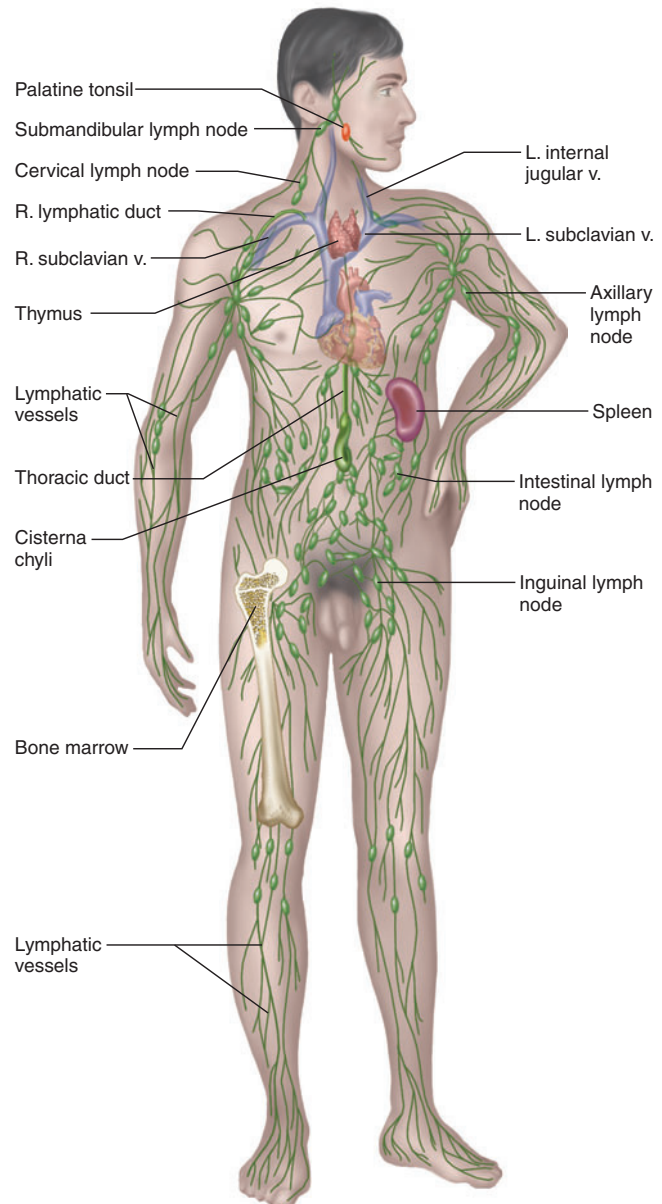


Figure 21.1 The Lymphatic System.

Lymph and the Lymphatic Vessels

Lymph is usually a clear, colorless fluid, similar to blood plasma but low in protein. Its composition varies substantially from place to place. After a meal, for example, lymph draining from the small intestine has a milky appearance because of its high lipid content. Lymph leaving the lymph nodes contains a large number of lymphocytes—indeed, this is the main supply of lymphocytes to the bloodstream.

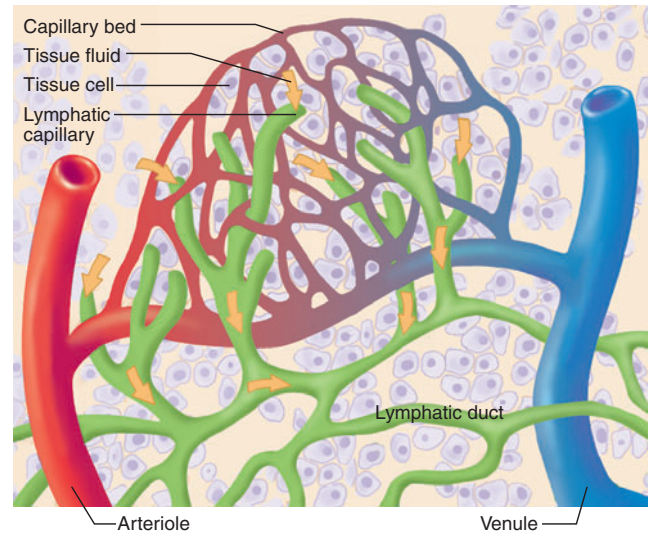


Figure 21.2 Elephantiasis, a Tropical Disease Caused by Lymphatic Obstruction. Mosquito-borne roundworms infect the lymph nodes and block the flow of lymph and recovery of tissue fluid. The resulting chronic edema leads to fibrosis and elephant-like thickening of the skin. The extremities are typically affected as shown here; the scrotum of men and breasts of women are often similarly affected.

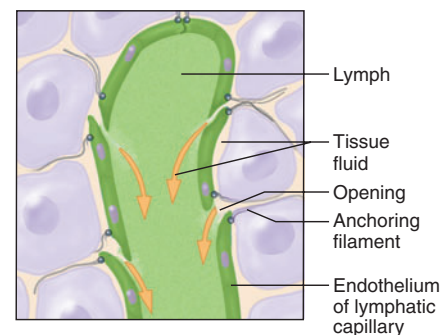
Lymph may also contain bacteria, viruses, cellular debris, or even traveling cancer cells.

Origin of Lymph

Lymph originates in microscopic vessels called **lymphatic capillaries**. These vessels penetrate nearly every tissue of the body but are absent from the central nervous system, cartilage, bone, and bone marrow. They are closely associated with blood capillaries, but unlike them, they are closed at one end (fig. 21.3). A lymphatic capillary consists of a sac of thin endothelial cells that loosely overlap each other like the shingles of a roof. The cells are tethered to surrounding tissue by protein filaments that prevent the sac from collapsing. Unlike the endothelial cells of blood capillaries, lymphatic endothelial cells are not joined by tight junctions. The gaps between them are so large that bacteria and other cells can enter along with the fluid. The overlapping edges of the endothelial cells act as valvelike flaps that can open and close. When tissue fluid pressure is high, it pushes the flaps inward (open) and fluid flows into the lymphatic capillary. When pressure is higher in the lymphatic capillary than in the tissue fluid, the flaps are pressed outward (closed).



(a)



(b)

Figure 21.3 Lymphatic Capillaries. (a) Relationship of the lymphatic capillaries to a bed of blood capillaries. (b) Uptake of tissue fluid by a lymphatic capillary.

Think About It

Contrast the structure of a lymphatic capillary with that of a continuous blood capillary. Explain why their structural difference is related to their functional difference.

Lymphatic Vessels

Lymphatic vessels form in the embryo by budding from the veins, so it is not surprising that the larger ones have a similar histology. They have a *tunica interna* with an endothelium and valves (fig. 21.4), a *tunica media* with elastic fibers and smooth muscle, and a thin outer *tunica externa*. Their walls are thinner and their valves are more numerous than those of the veins.

Lymph takes the following route from the tissues back to the bloodstream: lymphatic capillaries → collecting

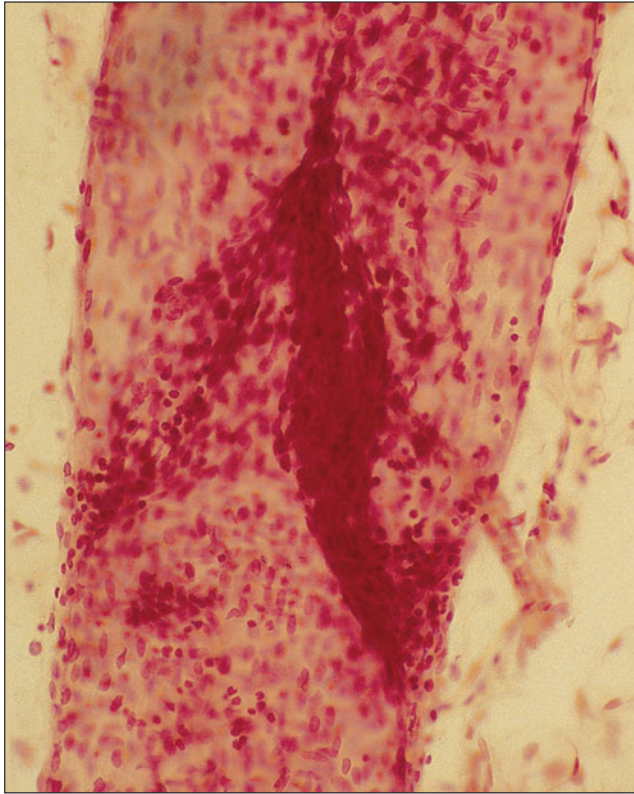


Figure 21.4 Valve in a Lymphatic Vessel. What would be the consequence if these valves did not exist?

vessels → six lymphatic trunks → two collecting ducts → subclavian veins. Thus, there is a continual recycling of fluid from blood to tissue fluid to lymph and back to the blood (fig. 21.5).

The lymphatic capillaries converge to form **collecting vessels**. These often travel alongside veins and arteries and share a common connective tissue sheath with them. Numerous lymph nodes occur along the course of the collecting vessels, receiving and filtering the lymph. The collecting vessels converge to form larger **lymphatic trunks**, each of which drains a major portion of the body. The principal lymphatic trunks are the *lumbar*, *intestinal*, *intercostal*, *bronchomediastinal*, *subclavian*, and *jugular trunks*. Their names indicate their locations and parts of the body they drain; the lumbar trunk also drains the lower extremities.

The lymphatic trunks converge to form two **collecting ducts**, the largest of the lymphatic vessels: (1) The **right lymphatic duct** begins in the right thoracic cavity with the union of the right jugular, subclavian, and bronchomediastinal trunks. It receives lymphatic drainage from the right arm and right side of the thorax and head and empties into the right subclavian vein (fig. 21.6a).

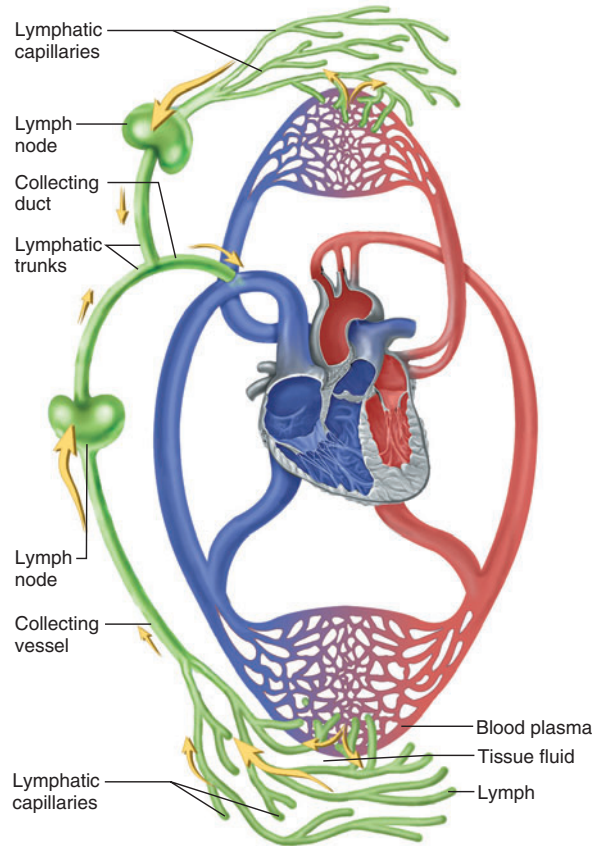


Figure 21.5 Fluid Exchange Between the Circulatory and Lymphatic Systems. Blood capillaries lose fluid to the tissue spaces. The lymphatic system picks up excess tissue fluid and returns it to the bloodstream.

(2) The **thoracic duct**, on the left, is larger and longer. It begins as a prominent sac in the abdominal cavity called the **cisterna chyli** (sis-TUR-nuh KY-lye) and then passes through the diaphragm and up the mediastinum. It receives lymph from all parts of the body below the diaphragm and from the left arm and left side of the head, neck, and thorax (fig. 21.6b). It empties into the left subclavian vein.

Flow of Lymph

Lymph flows under forces similar to those that govern venous return, except that the lymphatic system has no pump like the heart. Lymph flows at even lower pressure and speed than venous blood; it is moved primarily by rhythmic contractions of the lymphatic vessels themselves, which contract when stretched by lymph. The lymphatic vessels, like the veins, are also aided by a skeletal

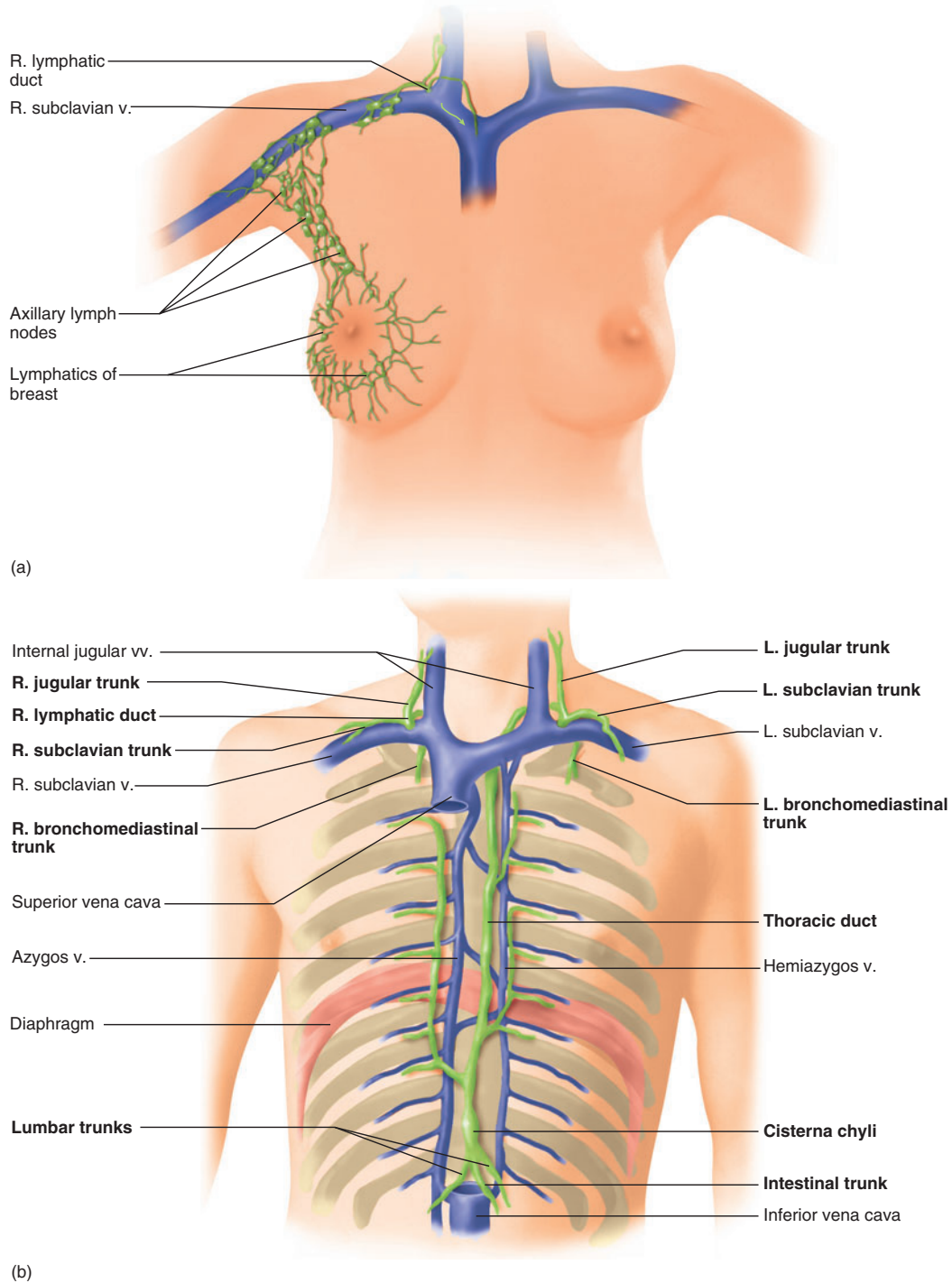


Figure 21.6 Lymphatic Drainage of the Thoracic Region. (a) Drainage of the right mammary and axillary regions. (b) Drainage of the right lymphatic duct and thoracic duct into the subclavian veins.

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muscle pump that squeezes them and moves the lymph along. Also like the medium veins, lymphatic vessels have valves that prevent lymph from flowing backward. Since lymphatic vessels are often wrapped with an artery in a common sheath, arterial pulsation may also rhythmically squeeze the lymphatic vessels and contribute to lymph flow. A thoracic (respiratory) pump aids the flow of lymph from the abdominal to the thoracic cavity as one inhales, just as it does in venous return. Finally, at the point where the collecting ducts join the subclavian veins, the rapidly flowing bloodstream draws the lymph into it. Considering these mechanisms of lymph flow, it should be apparent that physical exercise significantly increases the rate of lymphatic return.

Lymphatic Cells and Tissues

Lymphatic tissues are composed of a variety of lymphocytes and other cells whose roles in the immune system will be examined in this chapter. These include:

1. **T lymphocytes (T cells).** These are so-named because they develop for a time in the thymus and later depend on thymic hormones. The *T* stands for *thymus-dependent*. There are several subclasses of T cells that will be introduced later.
2. **B lymphocytes (B cells).** These are named for an organ in chickens (the *bursa of Fabricius*¹) in which they were first discovered. When activated, B cells differentiate into *plasma cells*, which produce circulating **antibodies**, the protective gamma globulins of the body fluids.
3. **Macrophages.** These cells, derived from monocytes of the blood, phagocytize foreign matter (**antigens**) and “display” fragments of it to certain T cells, thus alerting the immune system to the presence of an enemy. Macrophages and other cells that do this are collectively called **antigen-presenting cells (APCs)**.
4. **Dendritic cells.** These are APCs found in the epidermis, mucous membranes, and lymphatic organs. (In the skin, they are often called *Langerhans cells*.)
5. **Reticular cells.** These are branched cells that contribute to the stroma (connective tissue framework) of the lymphatic organs and act as APCs in the thymus. (They should not be confused with reticular *fibers*, which are fine branched collagen fibers common in lymphatic organs.)

The simplest form of lymphatic tissue is **diffuse lymphatic tissue**—a sprinkling of lymphocytes in the mucous membranes and connective tissues of many organs. It is particularly prevalent in body passages that are open to the exterior—the respiratory, digestive, urinary, and repro-

ductive tracts—where it is called **mucosa-associated lymphatic tissue (MALT)**.

In some places, lymphocytes and other cells congregate in dense masses called **lymphatic nodules (follicles)**, which come and go as pathogens invade the tissues and the immune system answers the challenge. Lymphatic nodules are, however, a relatively constant feature of the lymph nodes and tonsils. They also form clusters called **Peyer² patches** in the ileum, the last segment of the small intestine.

Lymphatic Organs

In contrast to the diffuse lymphatic tissue, lymphatic organs have well-defined anatomical sites and at least partial connective tissue capsules that separate the lymphatic tissue from neighboring tissues. These organs include the lymph nodes, tonsils, thymus, and spleen.

Lymph Nodes

Lymph nodes (fig. 21.7) serve two functions: to cleanse the lymph and alert the immune system to pathogens. There are hundreds of lymph nodes in the body. They are especially concentrated in the cervical, axillary, and inguinal

²Johann Conrad Peyer (1653–1712), Swiss anatomist

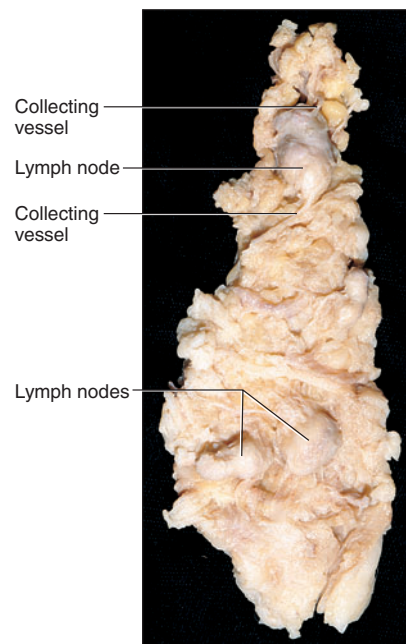


Figure 21.7 Lymph Nodes. Several collecting vessels are especially evident leading to and from the upper lymph node.

¹Hieronymus Fabricius (Giolamo Fabrizzzi) (1537–1619), Italian anatomist

regions close to the body surface, and in thoracic, abdominal, and pelvic groups deep in the body cavities. Most of them are embedded in fat.

A lymph node is an elongated or bean-shaped structure, usually less than 3 cm long, often with an indentation called the *hilum* on one side (fig. 21.8). It is enclosed in a fibrous capsule with extensions (trabeculae) that incompletely divide the interior of the node into compartments. The interior consists of a stroma of reticular connective tissue (reticular fibers and reticular cells) and a

parenchyma of lymphocytes and antigen-presenting cells. Between the capsule and parenchyma is a narrow space called the *subcapsular sinus*, which contains reticular fibers, macrophages, and dendritic cells.

The parenchyma is divided into an outer *cortex* and, near the hilum, an inner *medulla*. The cortex consists mainly of ovoid lymphatic nodules. When the lymph node is fighting a pathogen, these nodules acquire light-staining **germinal centers** where B cells multiply and differentiate into plasma cells. The medulla consists largely of a branching

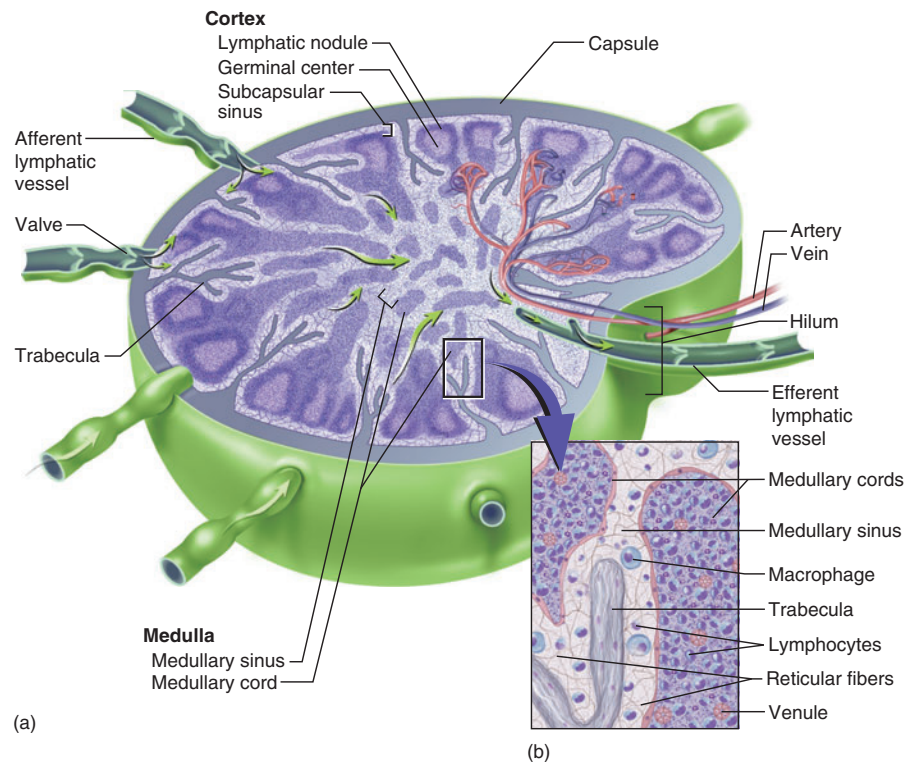


Figure 21.8 Anatomy of a Lymph Node. (a) Bisection of lymph node showing pathway of lymph flow. (b) Detail of the boxed region in a. (c) Stroma and immune cells in a medullary sinus.

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network of *medullary cords* composed of lymphocytes, plasma cells, macrophages, reticular cells, and reticular fibers. The cortex and medulla also contain lymph-filled sinuses continuous with the subcapsular sinus.

Several **afferent lymphatic vessels** lead into the node along its convex surface. Lymph flows from these vessels into the subcapsular sinus, percolates slowly through the sinuses of the cortex and medulla, and leaves the node through one to three **efferent lymphatic vessels** that emerge from the hilum. No other lymphatic organs have afferent lymphatic vessels; lymph nodes are the only organs that filter lymph as it flows along its course. The lymph node is a “bottleneck” that slows down lymph flow and allows time for cleansing it of foreign matter. The macrophages and reticular cells of the sinuses remove about 99% of the impurities before the lymph leaves the node. On its way to the bloodstream, lymph flows through one lymph node after another and thus becomes quite thoroughly cleansed of most impurities.

When a lymph node is under challenge from a foreign antigen, it may become swollen and painful to the touch—a condition called **lymphadenitis**³ (lim-FAD-en-EYE-tis). Physicians routinely palpate the accessible lymph nodes of the cervical, axillary, and inguinal regions for swelling. Lymph nodes are common sites of metastatic cancer because cancer cells from almost any organ can break loose, enter the lymphatic capillaries, and lodge in the nodes. Cancerous lymph nodes are swollen but relatively firm and usually painless. **Lymphadenopathy**⁴ (lim-FAD-eh-NOP-a-tee) is a collective term for all lymph node diseases.

Tonsils

The **tonsils** are patches of lymphatic tissue located at the entrance to the pharynx, where they guard against ingested and inhaled pathogens. Each is covered by an epithelium and has deep pits called **tonsillar crypts** lined by lymphatic nodules (fig. 21.9). The crypts often contain food debris, dead leukocytes, bacteria, and antigenic chemicals. Below the crypts, the tonsils are partially separated from underlying connective tissue by an incomplete fibrous capsule.

There are three main sets of tonsils: (1) a single medial **pharyngeal tonsil (adenoids)** on the wall of the pharynx just behind the nasal cavity, (2) a pair of **palatine tonsils** at the posterior margin of the oral cavity, and (3) numerous **lingual tonsils**, each with a single crypt, concentrated in a patch on each side of the root of the tongue (see fig. 22.3b, p. 844). The palatine tonsils are the largest and most often infected. Their surgical removal, called *tonsillectomy*, used to be one of the most common surgical procedures performed on children, but it is done less often today.

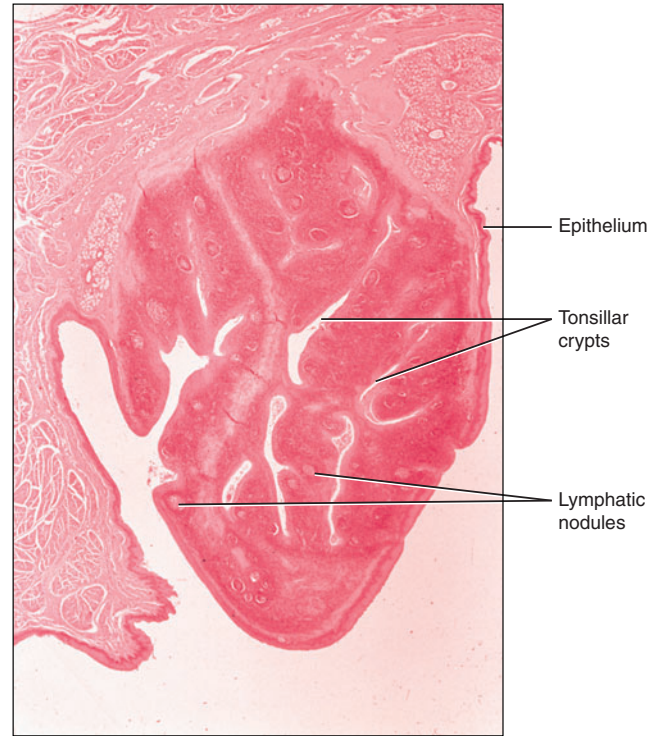


Figure 21.9 A Palatine Tonsil. A vertical tissue section showing a branched tonsillar crypt and lymphatic nodules.

Thymus

The **thymus** is a member of both the lymphatic and endocrine systems. It houses developing lymphocytes and secretes hormones that regulate their later activity. It is located between the sternum and aortic arch in the superior mediastinum. The thymus is very large in the fetus and grows slightly during childhood, when it is most active. After age 14, however, it begins to undergo involution (shrinkage) so that it is quite small in adults (fig. 21.10). In the elderly, the thymus is replaced almost entirely by fibrous and fatty tissue and is barely distinguishable from the surrounding tissues.

The fibrous capsule of the thymus gives off trabeculae that divide the parenchyma into several angular lobules. Each lobule has a cortex and medulla populated by T lymphocytes (fig. 21.11). **Reticular epithelial cells** seal off the cortex from the medulla and surround blood vessels and lymphocyte clusters in the cortex. They thereby form a *blood-thymus barrier* that isolates developing lymphocytes from foreign antigens. After developing in the cortex, the T cells migrate to the medulla, where they spend another 3 weeks. There is no blood-thymus barrier in the medulla; mature T cells enter blood or lymphatic vessels here and leave the thymus. In

³lymph + adeno = gland + itis = inflammation

⁴lymph + adeno = gland + pathy = disease

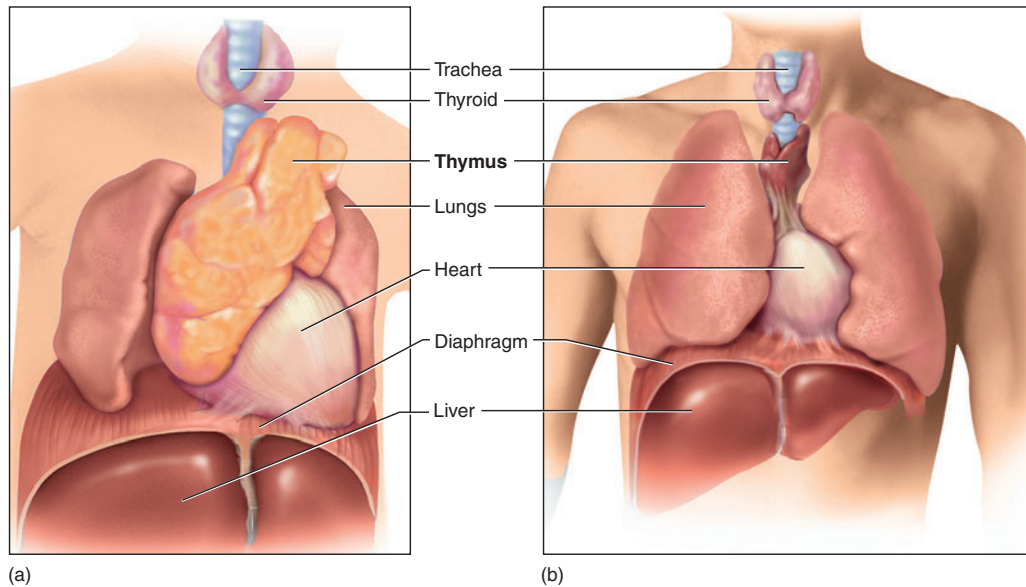


Figure 21.10 The Thymus. (a) The thymus is extremely large in a newborn infant. (b) The adult thymus is atrophied and often barely noticeable.

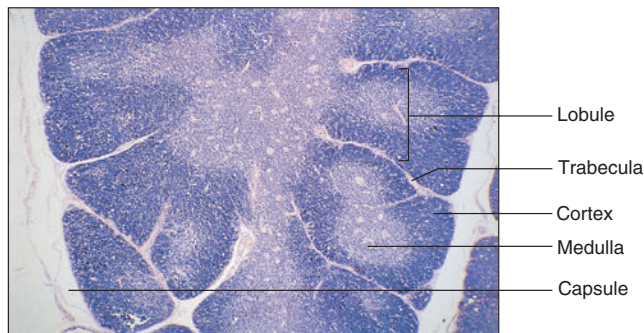


Figure 21.11 Histology of the Thymus.

the medulla, the reticular epithelial cells form whorls called *thymic (Hassall⁵) corpuscles*, useful for identifying the thymus histologically but of no known function. Besides forming the blood-thymus barrier, reticular epithelial cells secrete hormones called **thymosins**, **thymulin**, and **thymopoietin**, which promote the development and action of T cells. If the thymus is removed from newborn mammals, they waste away and never develop immunity. Other lymphatic organs also seem to depend on thymic hormones and develop poorly in thymectomized animals.

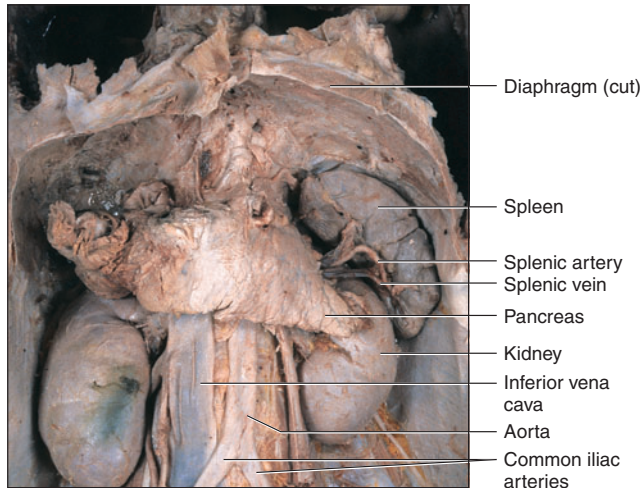
⁵Arthur H. Hassall (1817–94), British chemist and physician

Spleen

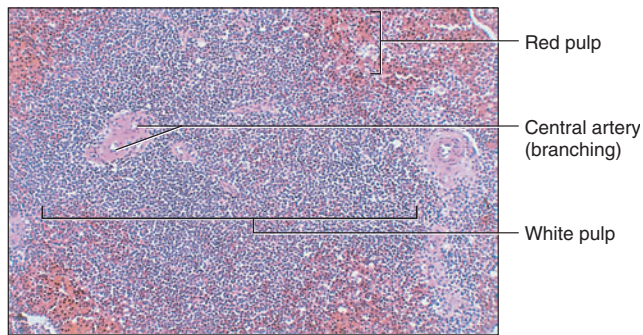
The **spleen** is the body's largest lymphatic organ. It is located in the left hypochondriac region, just inferior to the diaphragm and dorsolateral to the stomach (fig. 21.12; see also fig. A.15, p. 46). It has a medial hilum penetrated by the splenic artery and vein and lymphatic vessels. Its parenchyma exhibits two types of tissue named for their appearance in fresh specimens (not in stained sections): **red pulp**, which consists of sinuses gorged with concentrated erythrocytes, and **white pulp**, which consists of lymphocytes and macrophages aggregated like sleeves along small branches of the splenic artery.

These two tissue types reflect the multiple functions of the spleen. It produces blood cells in the fetus and may resume this role in adults in the event of extreme anemia. It monitors the blood for foreign antigens, much like the lymph nodes do the lymph. Lymphocytes and macrophages of the white pulp are quick to detect foreign antigens in the blood and activate immune reactions. The splenic capillaries are very permeable; they allow RBCs to leave the bloodstream, accumulate in the sinuses of the red pulp, and reenter the bloodstream later. The spleen is an “erythrocyte graveyard”—old, fragile RBCs rupture as they squeeze through the capillary walls into the sinuses. Splenic macrophages phagocytize their remains, just as they dispose of blood-borne bacteria and other cellular debris. The spleen also compensates for excessive blood volume by transferring plasma from the bloodstream into the lymphatic system.

The spleen is highly vascular and vulnerable to trauma and infection. A ruptured spleen can hemorrhage



(a)



(b)

Figure 21.12 The Spleen. (a) Position of the spleen in the upper left quadrant of the abdominal cavity. (b) Histology.

fatally, but is difficult to repair surgically. Therefore a common procedure in such cases is its removal, *splenectomy*. A person can live without a spleen, but is somewhat more vulnerable to infections.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

1. List the primary functions of the lymphatic system. What do you think would be the most noticeable effect of clamping the right lymphatic duct closed?
2. How does fluid get into the lymphatic system? What prevents it from draining back out?
3. List five major cell types of lymphatic tissues and state the function of each.
4. Predict the relative seriousness of removing the following organs from a 2-year-old child: (a) a lymph node, (b) the spleen, (c) the thymus, (d) the palatine tonsils.

Nonspecific Resistance

Objectives

When you have completed this section, you should be able to

- identify the body's three lines of defense against pathogens;
- contrast nonspecific resistance with immunity;
- describe the defensive functions of each kind of leukocyte;
- describe the process of inflammation and explain what accounts for its cardinal signs; and
- describe the body's other nonspecific defenses.

The human body harbors a huge number of microorganisms. Indeed, we contain about 10,000 times as many bacterial cells as we do human cells. We are constantly exposed to countless organisms by the food and water we consume, the air we breathe, and the objects we touch. Without a means of defense, the human body would be an ideal place for microorganisms to live. Our homeostatic mechanisms would ensure a constant warm temperature, ample water, and a continual supply of nutrients. Upon death, the body is quickly overrun by microbial life, but as long as we are alive and maintaining homeostasis, we resist these hordes of would-be invaders. Our mechanisms for doing so are the subject of the rest of this chapter.

Toxins, living organisms, and other agents that cause disease are called **pathogens**.⁶ The living body has three lines of defense against pathogens:

1. External barriers, notably the skin and mucous membranes, which are impenetrable to most of the pathogens that daily assault us.
2. Antimicrobial proteins, inflammation, fever, and other active attacks upon pathogens that break through the first line of defense. These mechanisms are present from birth, are broadly effective against a wide range of pathogens, and work even against pathogens to which the body has never before been exposed.
3. The immune system, which not only defeats a pathogen but leaves the body with a “memory” of it, enabling us to defeat it so quickly in future encounters that the pathogen causes no illness.

The first two mechanisms are called **nonspecific resistance** because they guard equally against a wide variety of pathogens and their effectiveness does not depend on prior exposure to a pathogen. Immunity is called a **specific defense** because it results from prior exposure to a pathogen and usually provides future protection only against that particular pathogen.

In this section we study mechanisms of nonspecific resistance—physical and chemical barriers, phagocytic cells, antimicrobial proteins, inflammation, and fever.

⁶patho = disease + gen = producing

External Barriers

The skin and mucous membranes make it mechanically difficult for microorganisms to enter the body and spread through its tissues. When the skin is broken by a scrape or animal bite or destroyed by a burn, one of the most urgent treatment concerns is the prevention of infection. This attests to the importance of intact skin as a barrier. The skin surface is composed mainly of keratin, a tough protein that few pathogens can penetrate. Furthermore, the surface is hostile to microbial reproduction. With exceptions such as the axillary and pubic areas, it is too dry and poor in nutrients to support much microbial growth. The skin is also coated with antimicrobial chemicals such as defensins and lactic acid. *Defensins* are peptides that kill microbes by creating holes in their membranes; they are produced by neutrophils and other cells and are found on the skin surface. The skin is also coated with a thin film of lactic acid (the *acid mantle*) from sweat, which also inhibits bacterial growth.

The digestive, respiratory, urinary, and reproductive tracts are open to the exterior, making them vulnerable to invasion, but they are protected by mucous membranes. Mucus physically ensnares microbes. Microbes trapped in the respiratory mucus are then moved by cilia to the pharynx, swallowed, and destroyed by stomach acid. Microbes also are flushed from the upper digestive tract by saliva and from the lower urinary tract by urine. Mucus, tears, and saliva also contain **lysozyme**, an enzyme that destroys bacteria by dissolving their cell walls.

Beneath the epithelia of the skin and mucous membranes, there is a layer of areolar tissue. The ground substance of this tissue contains *hyaluronic acid*, which gives it a viscous consistency. It is normally difficult for microbes to migrate through this sticky tissue gel. Some organisms overcome this, however, by producing an enzyme called *hyaluronidase*, which breaks it down to a thinner consistency that is more easily penetrated. Hyaluronidase occurs in some snake venoms and bacterial toxins and is produced by some parasitic protozoans to facilitate their invasion of the connective tissues.

Leukocytes and Macrophages

Organisms that penetrate the skin and mucous membranes are attacked by **phagocytes** (phagocytic cells) that have a voracious appetite for foreign matter. Leukocytes and macrophages play especially important roles in both non-specific defense and specific immunity.

Leukocytes

The five types of leukocytes are described in table 18.8 (pp. 700–701). We will now examine in more detail their contributions to resistance and immunity.

1. *Neutrophils* are the nemesis of bacteria. These highly mobile cells spend most of their lives wandering in the connective tissues killing bacteria. They do this in two ways—by phagocytosis and digestion, and by a reaction called the **respiratory burst**. The latter process begins when lysosomes migrate to the neutrophil surface and *degranulate*, or discharge their contents into the tissue fluid. The lysosomal enzymes catalyze the respiratory burst, in which the cell takes up oxygen and reduces it to highly toxic superoxide anions ($O_2^{\bullet -}$). Superoxide reacts with hydrogen ions to form hydrogen peroxide (H_2O_2). Neutrophils also release an enzyme that synthesizes hypochlorite (HClO), the active ingredient in chlorine bleach, from chloride ions in the tissue fluid. Superoxide, hydrogen peroxide, and hypochlorite are highly toxic to bacteria; they form a chemical **killing zone** around the neutrophil that destroys far more bacteria than the neutrophil can destroy by phagocytosis. The killing zone is also deadly to the neutrophils themselves, which die in the course of the attack. These oxidizing agents also damage connective tissues and contribute to rheumatoid arthritis.
2. *Eosinophils* are less avidly phagocytic than neutrophils, but they phagocytize antigen-antibody complexes, allergens (allergy-causing antigens), and inflammatory chemicals, as we will discuss shortly. They are especially abundant in the mucosae of the respiratory, digestive, and lower urinary tracts. In infections with hookworms, tapeworms, and other parasites too large to phagocytize, eosinophils aggregate near the parasites and release enzymes that weaken or destroy them.
3. *Basophils* aid the mobility and action of other leukocytes by secreting two chemicals: the vasodilator histamine, which increases blood flow and speeds the delivery of leukocytes to the area, and the anticoagulant heparin, which inhibits the formation of clots that would impede the mobility of other leukocytes.
4. *Lymphocytes* all look more or less alike in blood films, but there are several functional types, most of which are discussed later in this chapter under immunity. **Natural killer (NK) cells**, however, are large lymphocytes with a nonspecific role. They attack and lyse *host cells* (cells of one's own body) that have either turned cancerous or become infected with viruses, as well as bacteria and cells of transplanted tissues. The continual “patrolling” of the body by NK cells “on the lookout” for abnormal cells is called *immunological surveillance*. When an NK cell recognizes an abnormal cell, it secretes proteins called **perforins**, which bind to the enemy cell surface and make holes in its membrane. This has generally been thought to destroy host cells by

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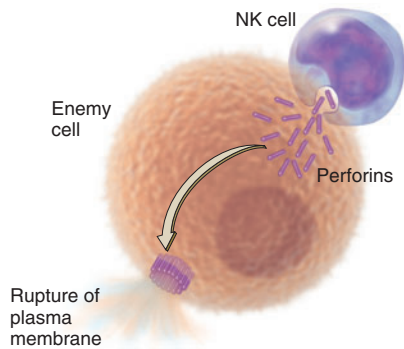


Figure 21.13 The Action of Perforin.

rupturing the membrane (fig. 21.13), although there is a newer theory that perforin induces target cell apoptosis.

5. *Monocytes* are the circulating precursors of macrophages, discussed next.

Macrophages

The **macrophage (lymphoid-macrophage) system** includes all of the body's avidly phagocytic cells except leukocytes. Dendritic cells, which internalize foreign matter by receptor-mediated endocytosis, otherwise function like macrophages and are included in this system. Some of these phagocytes are wandering cells that actively seek pathogens, while reticular cells and others are fixed in place and phagocytize only those pathogens that come to them—although they are strategically positioned for this to occur. The phagocytes include the following cell types:

- **macrophages (histiocytes)** of the loose connective tissues;
- **dendritic cells** of the epidermis, oral mucosa, esophagus, vagina, and lymphatic organs;
- **microglia** in the central nervous system (see chapter 14);
- **alveolar macrophages** in the lungs (see chapter 22); and
- **hepatic macrophages** in the liver (see chapter 25).

Antimicrobial Proteins

Two groups of proteins, the *interferons* and the *complement system*, provide short-term, nonspecific resistance to viral and bacterial infections.

Interferons

Interferons are polypeptides secreted by cells that have been invaded by viruses. They diffuse to neighboring cells

and stimulate them to produce antiviral proteins, which prevent viruses from multiplying within them. Interferons also activate natural killer cells and macrophages, which destroy infected host cells before they release more viruses. Interferons are not specific for a particular virus but provide generalized protection. They also promote the destruction of cancer cells.

Complement System

The **complement system** is a group of 20 or more β globulins that aid in nonspecific resistance and specific immunity. These proteins are continually present in the blood plasma but must be activated by pathogens to exert their effects. There are two pathways of complement activation (fig. 21.14). In the **classical pathway**, antibodies bind to pathogenic organisms and then bind a complex of three complement proteins called C1, C2, and C4. This step is called **complement fixation**. The **alternate pathway** begins with three complement proteins—factors B, D, and P—binding directly to the surface polysaccharides of microbes, without the aid of an antibody. Both pathways converge on a step where complement C3 is split into two fragments, C3a and C3b. From this point on, the pathway to completion, whether initiated by the classical or alternate pathway, is the same, as shown in the figure. Complement helps destroy pathogens in three ways:

1. **Enhanced inflammation.** Complement C3a stimulates mast cells and basophils to secrete chemicals that promote inflammation (discussed shortly).
2. **Opsonization.**⁷ Complement C3b coats bacteria and serves as a binding site for macrophages and neutrophils, enabling these cells to phagocytize them.
3. **Cytolysis.**⁸ Complement C3b leads to the rupture of target cells. It triggers the insertion of a group of proteins called the *membrane attack complex (MAC)* into the target cell membrane. The MAC forms a doughnutlike ring in the membrane that allows the cell contents to escape (fig. 21.15).

Inflammation

Inflammation is a local defensive response to tissue injury of any kind, including trauma and infection. Its general purposes are (1) to limit the spread of pathogens and ultimately destroy them, (2) to remove the debris of damaged tissue, and (3) to initiate tissue repair. Inflammation is characterized by four **cardinal signs**—redness, swelling, heat, and pain. Some authorities list impaired use as a fifth

⁷ *opson* = food

⁸ *cyto* = cell + *lysis* = split apart, break down

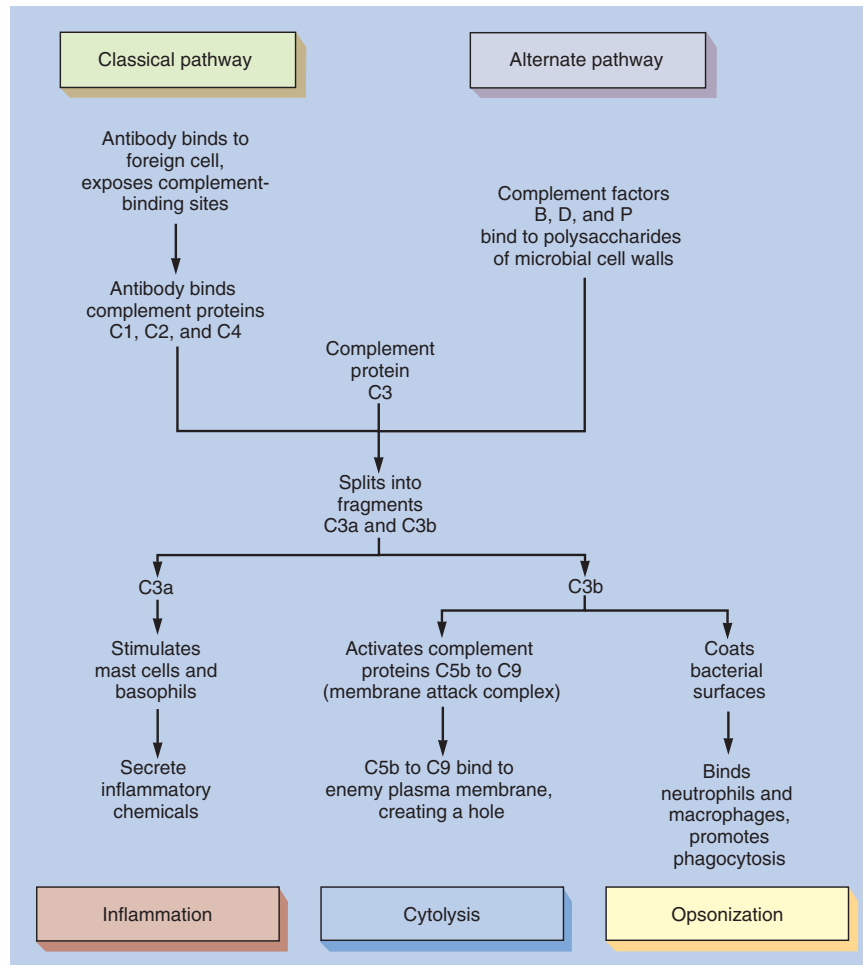


Figure 21.14 Complement Activation. Both the classical pathway and the alternate pathway produce complement fragments C3a and C3b. The process is the same from that point to the end. The C3a and C3b fragments promote inflammation, cytolysis, and opsonization.

sign, but this may or may not occur and when it does, it is mostly because of the pain.

Words ending in the suffix *-itis* denote inflammation of specific organs and tissues: *arthritis*, *encephalitis*, *peritonitis*, *gingivitis*, and *dermatitis*, for example. Inflammation can occur anywhere in the body, but it is most common and observable in the skin, which is subject to more trauma than any other organ. Examples of cutaneous inflammation include an itchy mosquito bite, sunburn, a poison ivy rash, and the redness and blistering produced by manual labor, tight shoes, or a kitchen burn.

The following discussion of the process of inflammation will account for the four cardinal signs and explain how the three purposes of inflammation are achieved. These processes are mediated by several types of cells and

inflammatory chemicals that are summarized in tables 21.1 and 21.2 at the end of this section. Some of these inflammatory chemicals are also classified as **cytokines**⁹—small proteins secreted by leukocytes, macrophages, mast cells, and several other cell types, which mediate the body's immune and nonspecific defenses. Cytokines include interferons, chemotactic factors, growth factors, interleukins, tumor necrosis factor, and other chemicals you will soon encounter in this discussion.

Inflammation involves three major processes: mobilization of the body's defenses, containment and destruction of pathogens, and tissue cleanup and repair.

⁹cyto = cell + kine = action, response

Mobilization of Defenses

Some inflammatory chemicals are *vasoactive*—they stimulate vasodilation, causing **hyperemia**, or elevated blood flow to the damaged tissue. Among them are histamine, bradykinin, and leukotrienes, which are secreted by basophils of the blood, mast cells of the connective tissue, and damaged cells of the inflamed tissue. These chemicals also cause endothelial cells of the blood capillaries and venules to separate a little, increasing the permeability of the vessels and thus promoting exudation (filtration) of fluid from the blood into the interstitial spaces of the tis-

sue. The collective effect of these changes is to speed the delivery of cells and chemicals needed to combat pathogens and repair damaged tissue, and to wash away toxins and metabolic wastes more rapidly.

Hyperemia accounts for the redness and heat of inflammation, and the increased filtration of fluid into the tissue accounts for its swelling (edema). *Extravasated* erythrocytes—RBCs that escape from the blood vessels into the tissue—contribute to the redness (as in sunburn). Pain results from direct injury to the nerves, pressure on the nerves caused by edema, and the stimulation of nociceptors (pain receptors) by bradykinin, prostaglandins, and some bacterial toxins.

In an area of injury, endothelial cells of the blood vessels produce *cell-adhesion molecules (CAMs)* that make their membranes sticky and snag leukocytes arriving in the bloodstream. Leukocytes adhere loosely to the CAMs and slowly tumble along the endothelium, sometimes coating it so thickly that they obstruct blood flow. This adhesion to the endothelium is called **margination**. The leukocytes then undergo **diapedesis**¹⁰ (**emigration**), in which they crawl through the spaces between the endothelial cells into the interstitial fluid. Most diapedesis occurs across the walls of the postcapillary venules. Also filtering through the capillary and venule walls are antibodies, fibrinogen and other clotting proteins, and complement, all of which aid in combating the pathogens as described next.

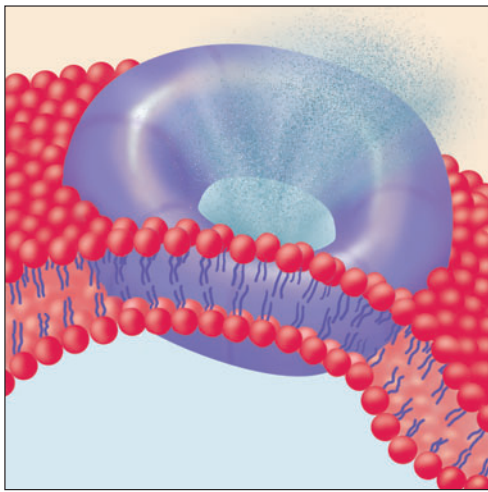


Figure 21.15 The Membrane Attack Complex. Complement proteins form a doughnutlike ring in the plasma membrane of an enemy cell, thus causing cytolysis.

In what way does the action of the membrane attack complex resemble the action of perforin?

Think About It

Review eicosanoid synthesis (p. 665) and explain why aspirin eases the pain of inflammation.

¹⁰*dia* = through + *pedesis* = stepping

Table 21.1 Cellular Agents of Inflammation

Agents	Action
Basophils	Secrete histamine, heparin, bradykinin, serotonin, and leukotrienes
Endothelial cells	Produce cell-adhesion molecules to recruit leukocytes; synthesize platelet-derived growth factor to stimulate fibroblast activity and tissue repair
Eosinophils	Attack parasites too large to phagocytize; phagocytize antigen-antibody complexes
Fibroblasts	Promote tissue repair by secreting collagen, ground substance, and other tissue components; produce scar tissue
Helper T cells	Secrete interleukins that promote inflammation and activate specific immunity
Macrophages	Phagocytize bacteria, tissue debris, dead and dying leukocytes and pathogens; act as antigen-presenting cells, which activate specific immunity
Mast cells	Same actions as basophils
Neutrophils	Phagocytize bacteria; secrete bactericidal oxidizing agents into tissue fluid; secrete cytokines that activate other cells
Platelets	Secrete clotting factors, which initiate tissue fluid coagulation, and platelet-derived growth factor

Table 21.2 Chemical Agents of Inflammation

Substance	Sources	Effects*
Bradykinin	Plasma and basophils	Pain; vasodilation; increased vascular permeability; neutrophil chemotaxis
Clotting factors	Plasma, platelets, and damaged cells	Coagulation of tissue fluid; isolation of pathogens; formation of temporary framework for tissue repair; include fibrinogen and clotting enzymes
Cytokines	Leukocytes, macrophages, mast cells	Mediation of immune and nonspecific defenses; include interferons, interleukins, growth factors, and other signals
Colony-stimulating factors	Macrophages and T cells	Leukopoiesis; increased WBC count
Complement	Plasma	Enhanced histamine release; neutrophil chemotaxis; promotion of phagocytosis
Heparin	Basophils and mast cells	Inhibits clotting in area of infection or injury; thus promotes WBC mobility
Histamine	Basophils and mast cells	Vasodilation; increased vascular permeability
Leukotrienes	Damaged cells, mast cells, and basophils	Vasodilation; increased vascular permeability; neutrophil chemotaxis
Platelet-derived growth factor	Platelets and endothelial cells	Stimulation of fibroblast activity; cell division; replacement of damaged cells
Prostaglandins	Damaged cells	Pain; enhanced action of histamine and bradykinin; neutrophil diapedesis

*Some inflammatory chemicals have additional roles in specific immunity, as described in table 21.6.

Containment and Destruction of Pathogens

One priority in inflammation is to prevent introduced pathogens from spreading through the body. The fibrinogen that filters into the tissue fluid clots in areas adjacent to the injury, forming a sticky mesh that sequesters (walls off) bacteria and other microbes. Heparin, the anticoagulant, prevents clotting in the area of the injury itself, so essentially bacteria or other pathogens are trapped in a fluid pocket surrounded by a gelatinous “capsule” of clotted fluid. They are attacked by antibodies, phagocytes, and other defenses, while the surrounding areas of clotted tissue fluid prevent them from escaping this onslaught.

The chief enemies of bacteria are the neutrophils, which begin to accumulate in the inflamed tissue within an hour of injury. After emigrating from the bloodstream, neutrophils exhibit **chemotaxis**—attraction to chemotactic chemicals such as bradykinin and leukotrienes that guide them to the site of injury or infection. As they encounter bacteria, neutrophils avidly phagocytize and digest them, and destroy many more by the respiratory burst described earlier. The four major stages of neutrophil action are summarized in figure 21.16.

Neutrophils also recruit macrophages and additional neutrophils by secreting cytokines, like shouting “Over here!” to bring in reinforcements. Activated macrophages and T cells in the inflamed tissue also secrete *colony-stimulating factors*, cytokines that pro-

mote the production of more leukocytes (leukopoiesis) by the red bone marrow. Within a few hours of the onset of inflammation, the neutrophil count in the blood can rise from the normal 4,000 or 5,000 cells/ μL to as high as 25,000 cells/ μL , a condition called **neutrophilia**. In the case of an allergy or parasitic infection, an elevated eosinophil count, or **eosinophilia**, may also occur. The task of eosinophils was described earlier.

Tissue Cleanup and Repair

Monocytes are major agents of tissue cleanup and repair. They arrive within 8 to 12 hours of an injury, emigrate from the bloodstream, and turn into macrophages. Macrophages engulf and destroy bacteria, damaged host cells, and dead and dying neutrophils. They also act as antigen-presenting cells, activating immune responses as described later in the chapter.

Edema also contributes to tissue cleanup. The swelling compresses veins and reduces venous drainage, while it forces open the valves of lymphatic capillaries and promotes lymphatic drainage. The lymphatics can collect and remove bacteria, dead cells, proteins, and tissue debris better than blood capillaries can.

As the battle progresses, all of the neutrophils and most of the macrophages die. These dead cells, other tissue debris, and tissue fluid form a pool of yellowish fluid

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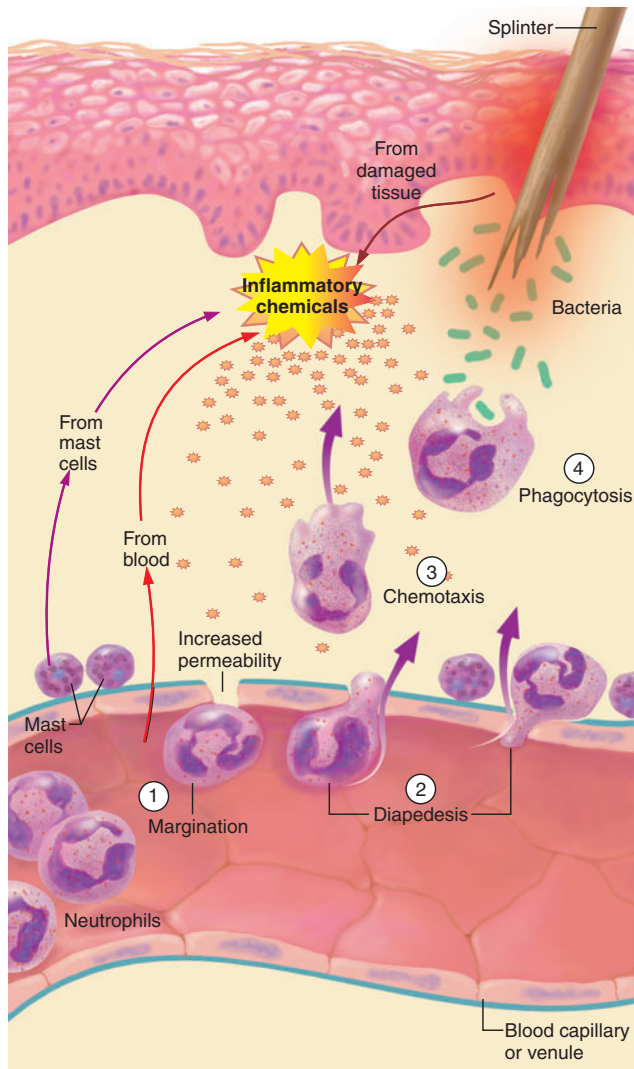


Figure 21.16 Leukocyte Behavior in Inflammation. Chemical messengers are released by basophils, mast cells, blood plasma, and damaged tissue. These inflammatory chemicals stimulate leukocyte margination (adhesion to the capillary wall), diapedesis (crawling through the capillary wall), chemotaxis (movement toward the source of the inflammatory chemicals), and phagocytosis (engulfing bacteria or other pathogens).

called **pus**, which accumulates in a tissue cavity called an **abscess**.¹¹ Pus is usually absorbed, but sometimes it forms a blister between the epidermis and dermis and may be released by its rupture.

Blood platelets and endothelial cells in an area of injury secrete a cytokine called **platelet-derived growth**

factor, an agent that stimulates fibroblasts to multiply and synthesize collagen. Hyperemia, at the same time, delivers the oxygen, amino acids, and other necessities of protein synthesis, while the heat of inflamed tissue increases metabolic rate and the speed of mitosis and tissue repair. The fibrin clot in inflamed tissue may provide a scaffold for tissue reconstruction. Pain also contributes importantly to recovery. It is an important alarm signal that calls our attention to the injury and makes us limit the use of a body part so it has a chance to rest and heal.

Fever

Fever is an abnormal elevation of body temperature. It is also known as **pyrexia**, and the term **febrile** means pertaining to fever (as in a “febrile attack”). Fever can result from trauma, infections, drug reactions, brain tumors, and several other causes. Because of variations in human body temperature, there is no exact criterion for what constitutes a fever—a temperature that is febrile for one person may be normal for another.

Fever was long regarded as an undesirable side effect of illness, and efforts were (and still are) made to reduce it for the sake of comfort. It is now recognized, however, as an adaptive defense mechanism that, in moderation, does more good than harm. People with colds, for example, recover more quickly and are less infective to others when they allow a fever to run its course rather than using **antipyretic** (fever-reducing) medications such as aspirin. Fever is beneficial in that (1) it promotes interferon activity, (2) it elevates metabolic rate and accelerates tissue repair, and (3) it inhibits reproduction of bacteria and viruses.

When neutrophils and macrophages phagocytize bacteria, they secrete a **pyrogen**¹² (fever-producing agent) called *interleukin-1 (IL-1)*. IL-1 stimulates the anterior hypothalamus to secrete prostaglandin E (PGE). PGE, in turn, raises the hypothalamic set point for body temperature—say to 39°C (102°F) instead of the usual 37°C. Aspirin and ibuprofen reduce fever by inhibiting PGE synthesis.

When the set point rises, a person shivers to generate heat and the cutaneous blood vessels constrict to reduce heat loss. In the stage of fever called *onset*, one has chills, feels cold and clammy to the touch, and has a rising temperature (fig. 21.17). In the next stage, *stadium*, the body temperature oscillates around the new set point for as long as the pathogen is present. The elevated temperature stimulates the liver and spleen to hoard zinc and iron, depriving bacteria of minerals they need to reproduce. When the infection is defeated, pyrogen secretion ceases and the hypothalamic thermostat is set back to normal. This activates heat-losing mechanisms, especially cutaneous vasodilation and sweating. The skin is warm and flushed during this phase. The phase of falling temperature is

¹¹ab = away + scss (from *cedere*) = to go

¹²pyro = fire, heat + gen = producing

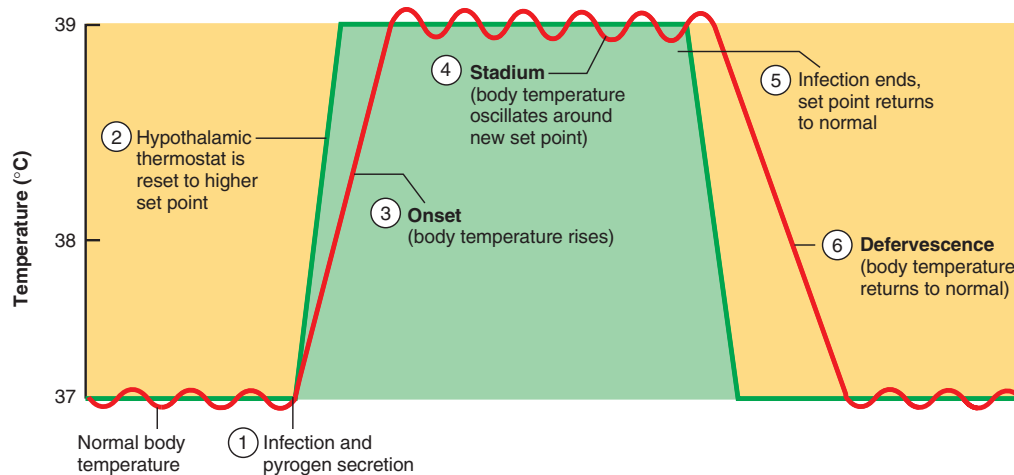


Figure 21.17 The Course of a Fever.

called *defervescence* in general, *crisis (flush)* if the temperature drops abruptly, or *lysis* if it falls slowly.

Even though most fevers are beneficial, excessively high temperature can be dangerous because it speeds up different enzymatic pathways to different degrees, thus causing metabolic discoordination and cellular dysfunction. Fevers above 40.5°C (105°F) can make a person delirious. Convulsions and coma ensue at higher temperatures, and death or irreversible brain damage commonly results from fevers that range from 44° to 46°C (111° to 115°F).

Insight 21.1 Clinical Application

Reye Syndrome

In children under 15, an acute viral infection such as chickenpox or influenza is sometimes followed by a serious disorder called *Reye¹³ syndrome*. First recognized in 1963, this disease is characterized by swelling of brain neurons and by fatty infiltration of the liver and other viscera. Neurons die from hypoxia and the pressure of the swelling brain, which results in nausea, vomiting, disorientation, seizures, and coma. About 30% of victims die, and the survivors sometimes suffer mental retardation. Reye syndrome can be triggered by the use of aspirin to control fever; parents are now strictly advised never to give aspirin to children with chickenpox or flulike symptoms.

¹³R. Douglas Reye (1912–77), Australian pathologist

Before You Go On

Answer the following questions to test your understanding of the preceding section:

- What are macrophages? Give four examples and state where they are found.
- List the cardinal signs of inflammation and state the cause of each.

- How do interferons and the complement system protect against disease?
- Summarize the benefits of fever and the limits of these benefits.

General Aspects of Specific Immunity

Objectives

When you have completed this section, you should be able to

- define *specific immunity*;
- contrast cellular and humoral immunity, active and passive immunity, and natural and artificial immunity;
- describe the chemical properties of antigens; and
- describe the general roles played by lymphocytes, antigen-presenting cells, and interleukins in the immune response.

The remainder of this chapter is concerned with the immune system and specific immunity, the third line of defense. The **immune¹⁴ system** is not an organ system but a group of widely distributed cells that recognize foreign substances and act to neutralize or destroy them. Two characteristics distinguish immunity from nonspecific resistance:

- Specificity.** Immunity is directed against a particular pathogen. Immunity to one pathogen usually does not confer immunity to others.
- Memory.** When reexposed to the same pathogen, the body reacts so quickly that there is no noticeable illness. The reaction time for inflammation and other nonspecific defenses, by

¹⁴*immuno* = free

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contrast, is just as long for later exposures as it was for the initial one.

These properties of immunity were recognized even in the fifth century B.C.E., when Thucydides remarked that people who recover from a disease often become immune to that one but remain susceptible to others. A person might be immune to measles but still susceptible to polio, for example.

Forms of Immunity

In the late 1800s, it was discovered that immunity can be transferred from one animal to another by way of the blood serum. In the mid-1900s, however, it was found that serum does not always confer immunity; sometimes only donor lymphocytes do so. Thus, we now recognize two types of immunity, called cellular and humoral immunity, although these two mechanisms interact extensively and often respond to the same pathogen.

Cellular (cell-mediated) immunity is based on the action of lymphocytes that directly attack diseased or “suspicious” cells, including those of transplanted tissues, cells infected with viruses or parasites, and cancer cells. Lymphocytes lyse these cells or release chemicals that enhance other defenses such as inflammation.

Humoral (antibody-mediated) immunity, named for the fluids or “humors” of the body, is an indirect attack that employs antibodies. Antibodies occur in the body fluids and on the plasma membranes of some lymphocytes. Circulating antibodies bind to bacteria, toxins, and extracellular viruses, tagging them for destruction by mechanisms described later. You will find cellular and humoral immunity summarized and compared in table 21.7 following discussion of the details of the two processes.

Other ways of classifying immunity are active versus passive and natural versus artificial. In *active immunity* the body makes its own antibodies or T cells against a pathogen, whereas in *passive immunity* the body acquires antibodies or T cells produced by another person or an animal. Either type of immunity can occur naturally or, for treatment and prevention purposes, it can be induced artificially. Thus we can recognize four classes of immunity under this scheme:

1. **Natural active immunity.** This is the production of one’s own antibodies or T cells as a result of infection or other natural exposure to an antigen.
2. **Artificial active immunity.** This is the production of one’s own antibodies or T cells as a result of **vaccination** against diseases such as smallpox, tetanus, or influenza. A **vaccine** consists of either dead or *attenuated* (weakened) pathogens which can stimulate an immune response but normally cause little or no discomfort or disease. In some cases, periodic “booster shots” are given to restimulate immune memory and maintain a high level of protection. Vaccination has eliminated smallpox

worldwide and greatly reduced the incidence of life-threatening childhood diseases, but many people continue to die from influenza and other diseases that could be prevented by vaccination.

3. **Natural passive immunity.** This is a temporary immunity that results from acquiring antibodies produced by another individual. The only natural way for this to happen is for a fetus to acquire antibodies from the mother through the placenta before birth or for a baby to acquire it through the colostrum or breast milk after birth.
4. **Artificial passive immunity.** This is a temporary immunity that results from the injection of an *immune serum* obtained from another individual or from animals (such as horses) that produced antibodies against a certain pathogen. Immune serum is used for emergency treatment of snakebites, botulism, tetanus, rabies, and other diseases.

Only the two forms of active immunity involve immune memory and thus provide future protection. Passive immunity typically lasts for only 2 or 3 weeks, until the acquired antibody is degraded. The remaining discussion is based on natural active immunity.

Antigens

An **antigen**¹⁵ (**Ag**) is any molecule that triggers an immune response. Some antigens are free molecules such as venoms and toxins; others are components of plasma membranes and bacterial cell walls. Small universal molecules such as glucose and amino acids are not antigenic; if they were, our immune systems would attack the nutrients and other molecules essential to our very survival. Most antigens have molecular weights over 10,000 amu and are generally complex molecules that are unique to each individual: proteins, polysaccharides, glycoproteins, and glycolipids. Their uniqueness enables the body to distinguish its own (“self”) molecules from those of any other individual or organism (“nonself”). The immune system “learns” to distinguish self- from nonself-antigens prior to birth; thereafter, it normally attacks only nonself-antigens.

Only certain regions of an antigen molecule, called **epitopes (antigenic determinants)**, stimulate immune responses. One antigen molecule typically has several different epitopes, however, that can stimulate the production of different antibodies.

Some molecules called **haptens**¹⁶ are too small to be antigenic in themselves, but they can stimulate an immune response by binding to a host macromolecule and creating a unique complex that the body recognizes as foreign. After the first exposure, a hapten may stimulate an immune response without needing to bind to another molecule.

¹⁵acronym from *antibody generating*

¹⁶from *haptēin* = to fasten

Many people are allergic to haptens in cosmetics, detergents, industrial chemicals, poison ivy, and animal dander. Penicillin is a hapten that sometimes binds to erythrocytes and triggers an allergic reaction that destroys them.

Lymphocytes

The major cells of the immune system are lymphocytes and macrophages, which are especially concentrated at strategic places such as the lymphatic organs and mucous membranes. Lymphocytes fall into three classes: natural killer (NK) cells (which we have already discussed), T lymphocytes, and B lymphocytes. In circulating blood, about 80% of the lymphocytes are T cells, 15% B cells, and 5% NK and stem cells.

T Lymphocytes (T cells)

During fetal development, the bone marrow releases undifferentiated stem cells into the blood. Some of these colonize the thymus and become T cells. In the thymic cortex, reticular epithelial (RE) cells secrete thymic hormones that stimulate these T cells to develop surface antigen receptors. With receptors in place, the T cells are now **immunocompetent**, capable of recognizing antigens presented to them by APCs. The RE cells then test these T cells by presenting self-antigens to them. There are two ways to fail the test: inability to recognize the RE cells at all (specifically, their MHC proteins, described later), or reacting to the self-antigens. T cells that fail the test are eliminated—a process called **negative selection**. There are two forms of negative selection: **clonal deletion**, in which self-reactive T cells die and macrophages phagocytize them, and **anergy**,¹⁷ in which they remain alive but unresponsive. Negative selection leaves the body in a state of **self-tolerance** in which the surviving, active T cells respond only to foreign antigens, not to one's own.

T cells that recognize the RE cells but do not react strongly to self-antigens undergo **positive selection**—they multiply and form **clones** of identical T cells programmed to respond to a particular foreign antigen. Only about 2% of the T cells survive negative selection and move on to the medulla. These T cells, which are immunocompetent but have not yet encountered the “enemy” (foreign antigens), constitute the **virgin lymphocyte pool**. These virgin (*naive*) T cells leave the thymus and colonize lymphatic tissues and organs everywhere.

Think About It

Is clonal deletion a case of apoptosis or necrosis? Explain your answer. (Review these concepts in chapter 5 if necessary.)

B Lymphocytes (B cells)

Another group of fetal stem cells remain in the bone marrow to differentiate into B cells. Those that respond to self-antigens undergo either anergy or clonal deletion, much like self-reactive T cells. Self-tolerant B cells, on the other hand, go on to produce surface receptors for antigens, divide, and produce immunocompetent B cell clones. These cells disperse throughout the body, colonizing the same organs as T cells. They are abundant in the lymph nodes, spleen, bone marrow, and mucous membranes.

Antigen-Presenting Cells

In addition to their other roles, B cells, macrophages, reticular cells, and dendritic cells function as **antigen-presenting cells (APCs)**. T cells usually cannot recognize free antigen molecules but require the help of APCs. APC function hinges on a family of genes on chromosome 6 called the **major histocompatibility complex (MHC)**. These genes code for **MHC proteins**, which are structurally unique to every person except for identical twins. MHC proteins act as “identification tags” that label every cell of your body as belonging to you. An MHC protein is shaped a little like a hotdog bun—an elongated protein with a central groove.

An antigen-presenting cell internalizes an antigen by endocytosis, digests it into molecular fragments (*antigen processing*), and “displays” the epitopes in the grooves of its MHC proteins (fig. 21.18). Wandering T cells regularly inspect APCs for displayed antigens (fig. 21.19). If an MHC protein carries a self-antigen, the T cells disregard it. If it carries a nonself-antigen, however, the T cells initiate an immune attack. APCs thus alert the immune system to the presence of a foreign antigen. The key to a successful defense is then to quickly mobilize immune cells against the antigen.

Interleukins

With so many cell types involved in immunity, it is not surprising that they require chemical messengers to coordinate their activities. **Interleukins**¹⁸ are chemical signals (cytokines) sent from one leukocyte (or leukocyte derivative) to another. Those produced by lymphocytes are called *lymphokines*,¹⁹ and those produced by macrophages are called *monokines* (after monocytes, the macrophage precursors).

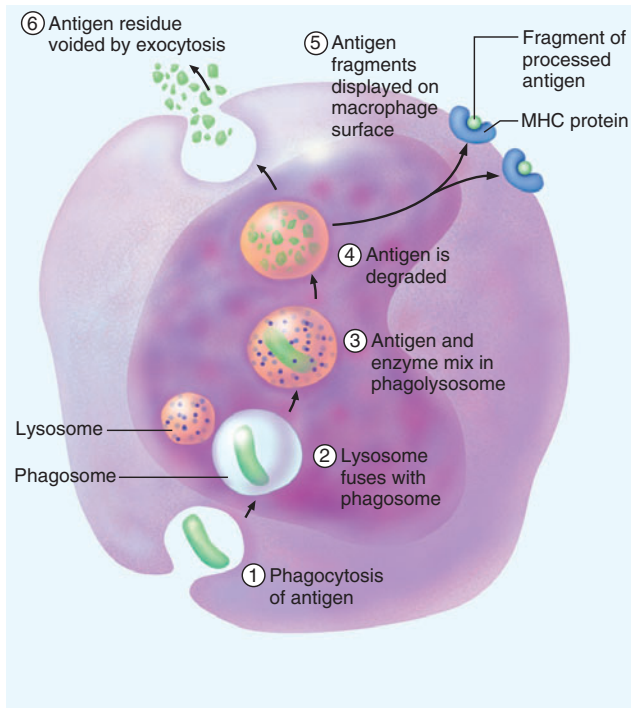
Since the terminology of immune cells and chemicals is quite complex, you may find it helpful to refer often to tables 21.5 and 21.6 (pp. 826–827) as you read the following discussions of cellular and humoral immunity.

¹⁷*an* = without + *erg* = action, work

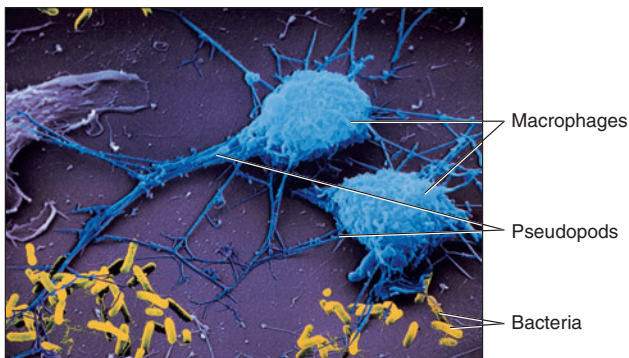
¹⁸*inter* = between + *leuk* = leukocytes

¹⁹*kine* = motion, action

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(a)



(b)

Figure 21.18 The Action of an Antigen-Presenting Cell (APC). (a) Stages in the processing and presentation of an antigen by an APC such as a macrophage. (b) Macrophages phagocytizing bacteria. Filamentous extensions of the macrophage snare the rod-shaped bacteria and draw them to the cell surface, where they are engulfed.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

9. How does specific immunity differ from nonspecific defense?
10. How does humoral immunity differ from cellular immunity?
11. Contrast active and passive immunity. Give a natural and an artificial example of each.

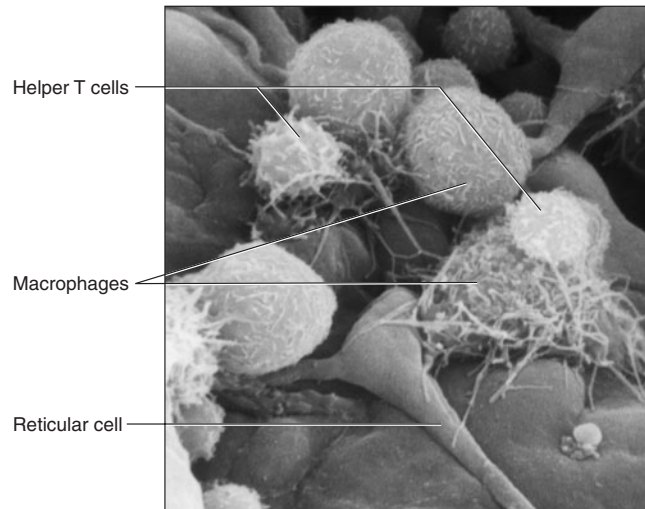


Figure 21.19 T Cells “Inspecting” Macrophages in a Lymph Node for Antigen Presentation. From R. G. Kessel and R. H. Kardon, *Tissues and Organs: A Text-Atlas of Scanning Electron Microscopy* (W. H. Freeman & Co., 1979).

12. What structural properties distinguish antigenic molecules from those that are not antigenic?
13. What is an immunocompetent lymphocyte? What does a lymphocyte have to produce in order to be immunocompetent?
14. Define *T cell* and *B cell*.
15. Define *interleukin*, *lymphokine*, and *monokine*.

Cellular Immunity

Objectives

When you have completed this section, you should be able to

- list the types of lymphocytes involved in cellular immunity and describe the roles they play;
- explain how antigen-presenting cells activate T lymphocytes;
- explain how interleukins coordinate the actions of immune system cells; and
- explain the role of memory cells in cellular immunity.

Cellular immunity involves four classes of T cells:

1. **Cytotoxic T (T_C) cells** are the “effectors” of cellular immunity which carry out the attack on foreign cells. They are also called *killer T cells*, but are not the same as *natural killer cells*.
2. **Helper T (T_H) cells** promote the action of T_C cells as well as playing key roles in humoral immunity and nonspecific defense. All other T cells are involved in cellular immunity only.
3. **Suppressor T (T_S) cells** limit the cell-mediated attack and keep the immune system from running out of

control. T_H and T_S cells are regulatory lymphocytes that act somewhat like an accelerator and brake on T_C action.

- Memory T cells** are descended from the cytotoxic T cells and are responsible for memory in cellular immunity.

T_H cells are also known as T4, CD4, or CD4+ cells, because they have a surface glycoprotein called CD4. Cytotoxic (T_C) and suppressor (T_S) cells are collectively known as T8, CD8, or CD8+ cells after their glycoprotein, CD8. (CD stands for *cluster of differentiation*, a classification system for many cell surface molecules.) These glycoproteins enable T cells to bind to other cells in the events to be described shortly.

With the foregoing introduction to the “actors” of the immune system, we can now discuss the “plot”—the mechanisms of immunity. Both cellular and humoral immunity occur in three stages that we can think of as recognition, attack, and memory (or “the three Rs of immunity”—recognize, react, and remember). In cellular immunity, the events of each stage are as follows.

Recognition

The recognition phase has two aspects: antigen presentation and T cell activation.

Antigen Presentation

When an antigen-presenting cell (APC) encounters and processes an antigen, it typically migrates to the nearest lymph node and displays it to T cells. Cytotoxic and helper T cells patrol the lymph nodes and other tissues as if looking for trouble. When they encounter a cell displaying an antigen on an MHC protein (MHCP), they initiate an immune response. T cells respond to two classes of MHCPs:

MHC-I proteins occur on every nucleated cell of the body (not erythrocytes). These proteins are constantly produced by the cell and transported to the plasma membrane. Along the way, they pick up small peptides in the cytoplasm and display these once they are installed in the membrane. If the peptides are normal self-antigens, they do not elicit a T cell response. If they are viral proteins or abnormal antigens made by cancer cells, however, they do. In this case, the Ag–MHCP complex is like a tag on the host cell that says, “I’m diseased; kill me.” Infected or malignant cells are then destroyed before they can do further harm to the body. *MHC-II proteins* (also called *human leukocyte antigens*, HLAs) occur only on APCs and display only foreign antigens. T_C cells respond only to MHC-I proteins and T_H cells respond only to MHC-II (table 21.3).

T Cell Activation

T cell activation is shown in figure 21.20. It begins when a T_C or T_H cell binds to an MHCP displaying an epitope

Table 21.3 Comparison of the Responses of Cytotoxic and Helper T Cells

Characteristic	T_C Cells	T_H Cells
Cells capable of stimulating a response	Any nucleated cell	Antigen-presenting cells
MHC protein	MHC-I	MHC-II

that the T cell is programmed to recognize. Before the response can go any further, the T cell must bind to another site on the target cell, a membrane protein related to interleukins that sends an activating signal to the T cell. In a sense, the T cell has to “check twice” to see if it really has bound to an antigen-presenting cell displaying a foreign antigen. This signaling process, called **costimulation**, triggers a process called **clonal selection**: the activated T cell undergoes repeated mitosis, giving rise to a clone of identical T cells programmed against the same epitope. Some cells in the clone become effector cells that carry out an immune attack, and some become memory T cells.

Attack

Helper, cytotoxic, and suppressor T cells play different roles in the attack phase.

Helper T Cells

Most immune responses require the action of helper T cells, which play a central coordinating role in both humoral and cellular immunity (fig. 21.21). When a helper T cell recognizes an Ag–MHCP complex, it secretes interleukins that attract neutrophils and natural killer cells; attract macrophages, stimulate their phagocytic activity, and inhibit them from leaving the area; and stimulate T and B cell mitosis and maturation.

Cytotoxic T Cells

Cytotoxic T cells are the only T lymphocytes that directly attack and kill other cells. They are particularly responsive to cells of transplanted tissues and organs, cancer cells, and host cells that are infected with viruses, intracellular parasites, or bacteria (fig. 21.22).

When a T_C cell recognizes a complex of antigen and MHC-I protein on a diseased or foreign cell, it “docks” on that cell, delivers a **lethal hit** of cytotoxic chemicals that will destroy it, and goes off in search of other enemy cells while the chemicals do their work. Among these chemicals are (1) perforin, which creates holes in its plasma membrane and destroys the cell in the same manner as the

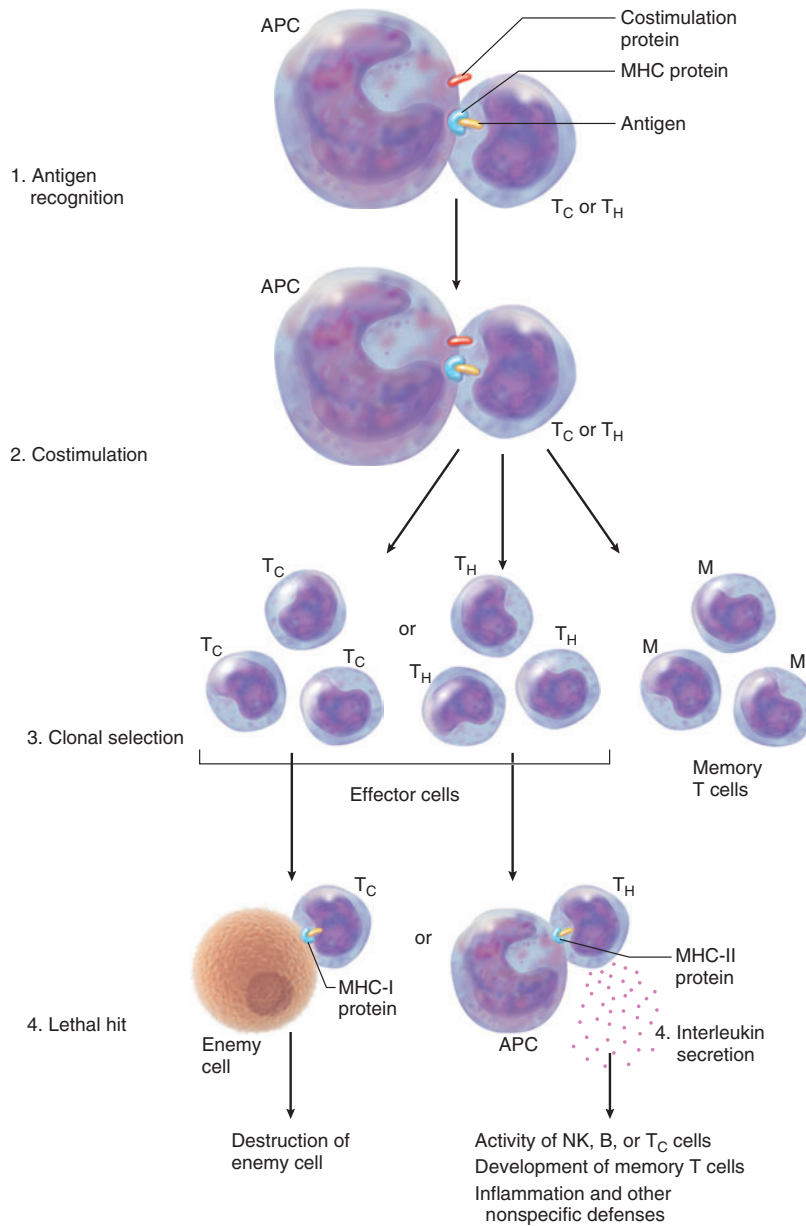


Figure 21.20 T Cell Activation.

perforin released by natural killer cells (see pp. 809–810); (2) **lymphotoxin**, which destroys the target cell's DNA; and (3) **tumor necrosis factor (TNF)**, which kills cancer cells by unknown mechanisms and stimulates fever, leukopoiesis, and eosinophil activity. T_C cells also secrete interferon, which inhibits the replication of viruses, and interleukins that regulate macrophage activity, as the interleukins of the T_H cells do.

Think About It

How is a cytotoxic T cell like a natural killer (NK) cell? How are they different?

Suppressor T Cells

As the pathogen is defeated and disappears from the tissues, suppressor T cells release interleukins that inhibit T

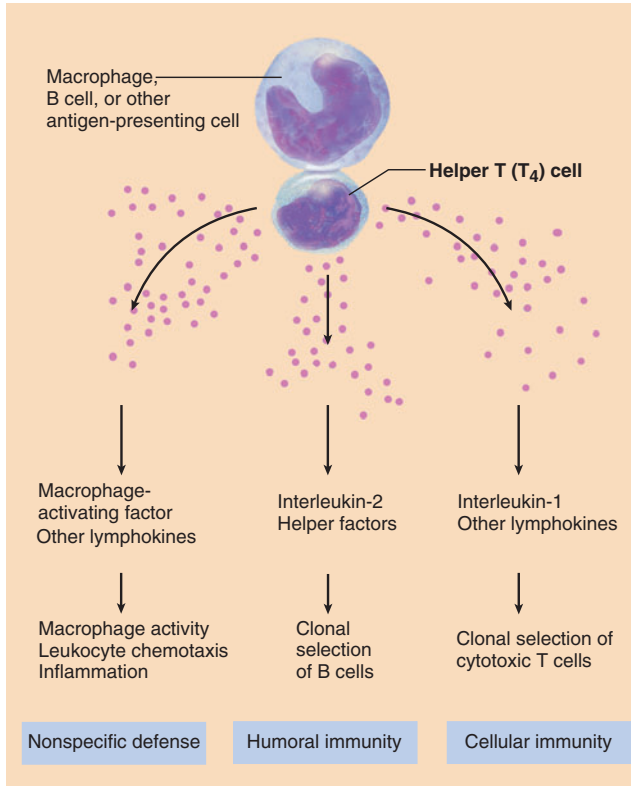


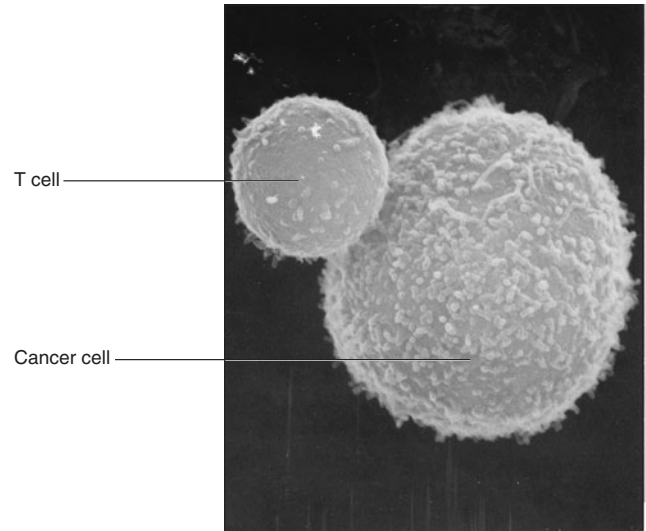
Figure 21.21 The Role of Helper T Cells in Defense and Immunity.

Why does AIDS reduce the effectiveness of all three defenses listed across the bottom?

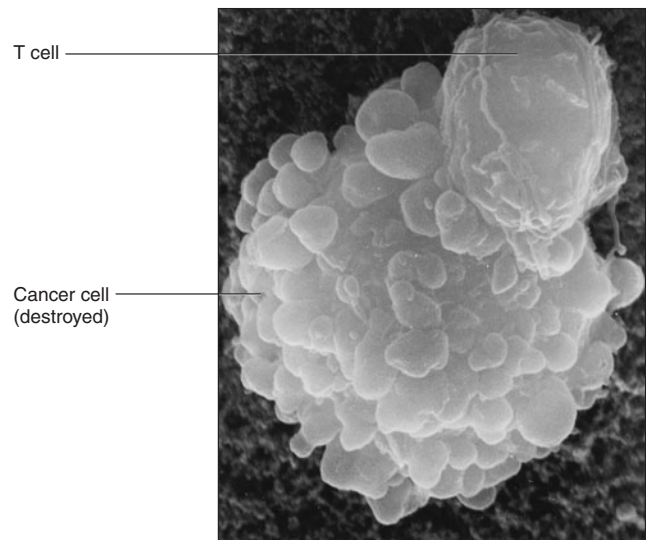
and B cell activity. This slows down the immune reaction and keeps it from running out of control. Suppressor T cells may help to prevent autoimmune diseases, discussed later.

Memory

As more and more cells are recruited by helper T cells, the immune response exerts an overwhelming force against the pathogen. The primary response, seen on first exposure to a particular pathogen, peaks in about a week and then gradually declines. It is followed by immune memory. Following clonal selection, some T_C and T_H cells become memory cells. Memory T cells are long-lived and much more numerous than the T cells of the virgin lymphocyte pool. Upon reexposure to the same pathogen later in life, memory cells mount a quick attack called the **T cell recall response**. This time-saving response destroys a pathogen so quickly that no noticeable illness occurs—that is, the person is immune to the disease.



(a)



(b)

Figure 21.22 Destruction of a Cancer Cell by a Cytotoxic T Cell. (a) T cell binding to cancer cell. (b) Death of the cancer cell due to the lethal hit by the T cell.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

- Name four types of lymphocytes that are involved in cellular immunity. Which of these is also essential to humoral immunity?
- What are the three phases of an immune response?
- Explain why cytotoxic T cells are activated by a broader range of host cells than are helper T cells.
- Describe some ways in which cytotoxic T cells destroy target cells.

Humoral Immunity

Objectives

When you have completed this section, you should be able to

- explain how B cells recognize and respond to an antigen;
- describe structure, types, and actions of antibodies;
- explain the mechanism of memory in humoral immunity; and
- compare and contrast cellular and humoral immunity.

Humoral immunity is a more indirect method of defense than cellular immunity. Instead of directly contacting enemy cells, the B lymphocytes of humoral immunity produce antibodies that bind to antigens and tag them for destruction by other means. But like cellular immunity, humoral immunity works in three stages—recognition, attack, and memory.

Recognition

An immunocompetent B cell has thousands of surface receptors for one antigen. B cell activation begins when an antigen binds to several of these receptors, links them together, and is taken into the cell by receptor-mediated endocytosis. One reason small molecules are not antigenic is that they are too small to link multiple receptors together. After endocytosis, the B cell processes (digests) the antigen, links some of the epitopes to its MHC-II proteins, and displays these on the cell surface.

Usually, the B-cell response goes no further unless a helper T cell binds to this Ag–MHCP complex. (Some B cells are directly activated by antigens without the help of a T_H cell.) When a T_H cell does bind to the complex, it secretes interleukins called *helper factors* that activate the B cell. This triggers clonal selection—B cell mitosis giving rise to a battalion of identical B cells programmed against the same antigen (fig. 21.23).

Most cells of the clone differentiate into **plasma cells**. These are larger than B cells and contain an abundance of rough endoplasmic reticulum (fig. 21.24). Plasma cells develop mainly in the germinal centers of the lymphatic follicles of the lymph nodes. About 10% of the plasma cells remain in the lymph node, but the rest leave the lymph nodes, take up residence in the bone marrow and elsewhere, and there produce antibodies until they die. A plasma cell secretes antibodies at the remarkable rate of 2,000 molecules per second over a life span of 4 to 5 days. These antibodies travel throughout the body in the blood and other body fluids. The first time you are exposed to a particular antigen, your plasma cells produce mainly an antibody class called IgM. In later exposures to the same antigen, they produce mainly IgG.

Attack

We have said much about antibodies already, and it is now time to take a closer look at what an antibody is and how it works. Also called an **immunoglobulin (Ig)**, an antibody is a defensive gamma globulin found in the blood plasma, body secretions, and some leukocyte membranes. The basic structural unit of an antibody, an **antibody monomer**, is composed of four polypeptides linked by disulfide (–S–S–) bonds (fig. 21.25). The two larger **heavy chains** are about 400 amino acids long and the two **light chains** about half that long. Each heavy chain has a hinge region where the antibody is bent, giving the monomer a T or Y shape.

All four chains have a **variable (V) region**, which gives an antibody its uniqueness. The V regions of a heavy chain and light chain combine to form an **antigen-binding site** on each arm, which attaches to the epitope of an antigen molecule. The rest of each chain is a **constant (C) region**, which has the same amino acid sequence in all antibodies of a given class (within one person). The C region determines the mechanism of an antibody's action—for example, whether it can bind complement proteins.

There are five classes of antibodies named **IgA, IgD, IgE, IgG, and IgM** (table 21.4), named for the structures of their C regions (*alpha, delta, epsilon, gamma, and mu*). IgD, IgE, and IgG are monomers. IgA has a monomeric form as well as a dimer composed of two cojoined monomers. IgM is a pentamer composed of five monomers. The surface antigen receptors synthesized by a developing B cell are IgD and IgM molecules. IgG is particularly important in the immunity of the newborn because it is the only immunoglobulin that crosses the placenta. Thus, it transfers some of the mother's immunity to her fetus. In addition, an infant acquires some maternal IgA through breast milk and colostrum (the fluid secreted for the first 2 or 3 days of breast-feeding).

The immune system is thought to produce as many as 2 million different antibodies. This is an astonishing number considering that normally each protein in the body is encoded by a different gene and we have a total of only 35,000 genes, most of which have functions unrelated to immunity. Obviously there cannot be a different gene for each antibody. Instead, the genome contains several hundred DNA segments that can be shuffled and combined in various ways to produce antibody genes unique to each antibody-producing cell line. This process is called **somatic recombination** because it forms new combinations of DNA base sequences in somatic (nonreproductive) cells. This explains how we can produce such a tremendous variety of antibodies with a limited number of genes.

Once released by a plasma cell, antibodies use four mechanisms to render antigens harmless:

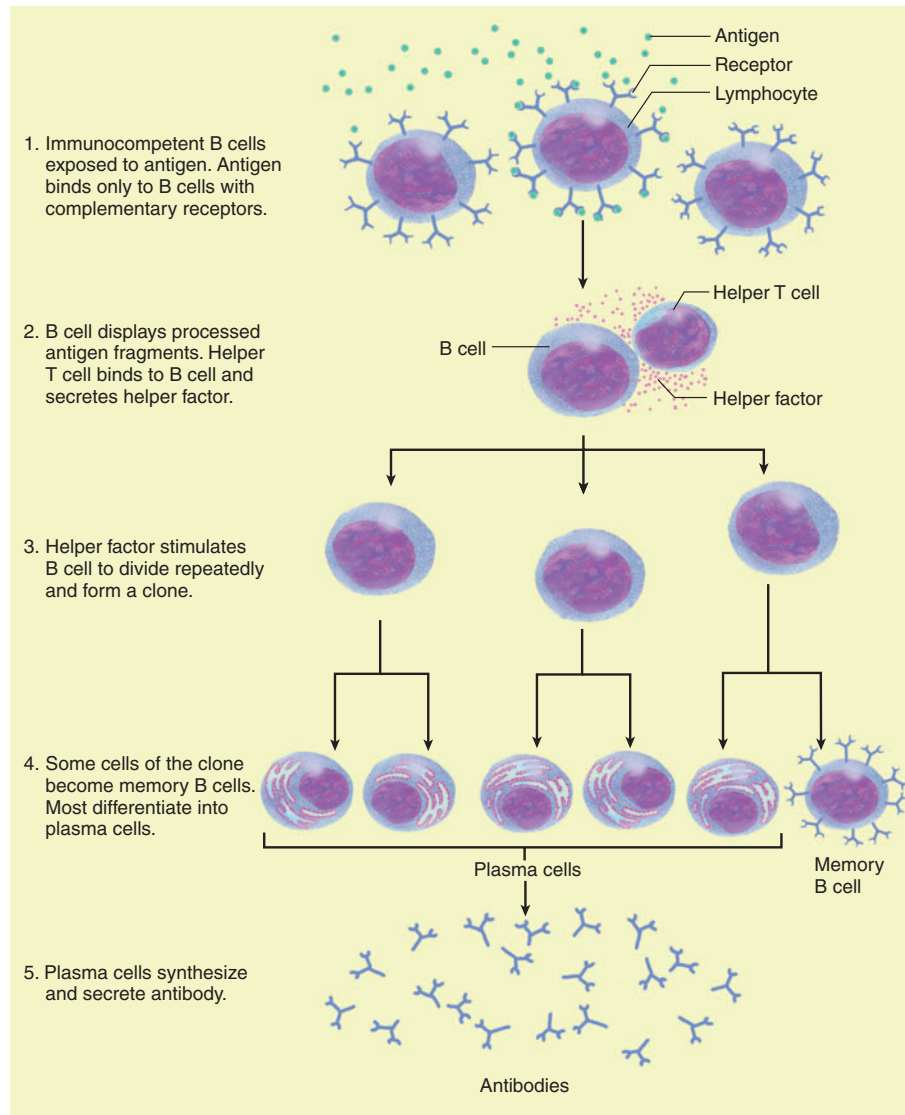


Figure 21.23 Clonal Selection and Ensuing Events of the Humoral Immune Response.

- 1. Neutralization.** Only certain regions of an antigen are pathogenic—for example, the parts of a toxin molecule or virus that enable these agents to bind to human cells. Antibodies can neutralize an antigen by binding to these active regions and masking them.
- 2. Complement fixation.** Antibodies IgM and IgG bind to enemy cells and change shape, exposing their complement-binding sites (see fig. 21.25a). This initiates the binding of complement to the enemy cell surface (see the *classical pathway*, fig. 21.14)

and leads to cytolysis, opsonization of bacteria, and enhanced inflammation, as described earlier. Complement fixation is the primary mechanism of defense against such foreign cells as bacteria and mismatched erythrocytes.

- 3. Agglutination** was described in chapter 18 in the discussion of ABO and Rh blood types. It is effective not only in mismatched blood transfusions but more importantly as a defense against bacteria. An antibody molecule has 2 to 10 binding sites; thus, it can bind to antigen molecules on two or

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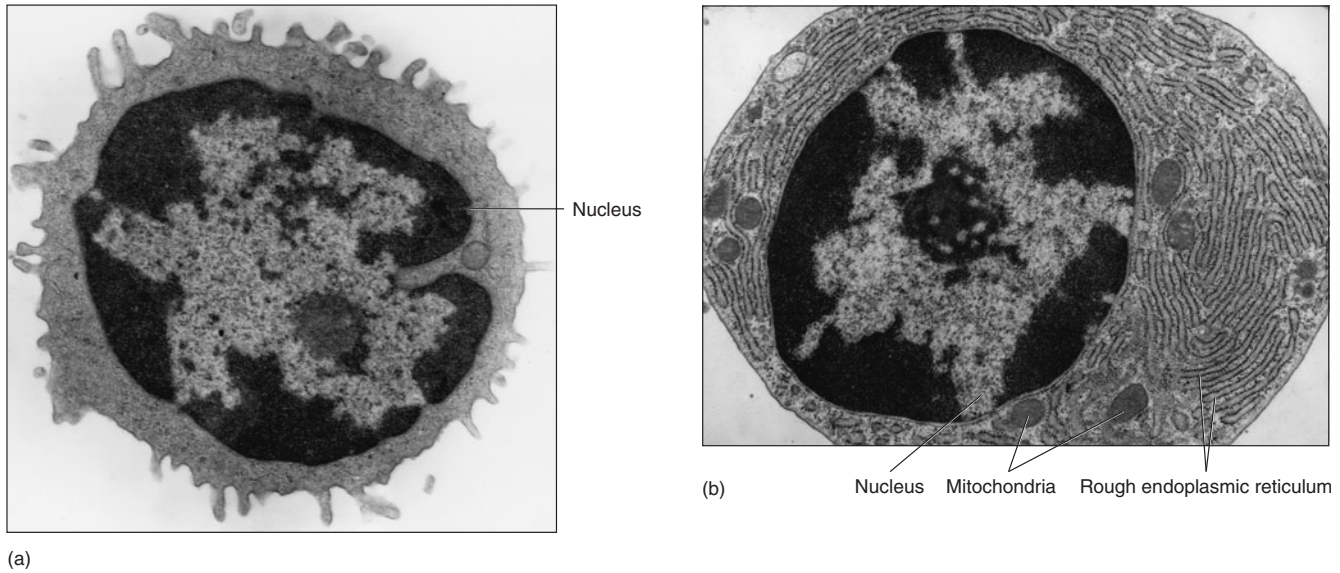


Figure 21.24 A B Cell and Plasma Cell. (a) A B cell has little cytoplasm and scanty organelles. (b) A plasma cell, which differentiates from a B cell, has an abundance of rough endoplasmic reticulum.

What does this endoplasmic reticulum do?

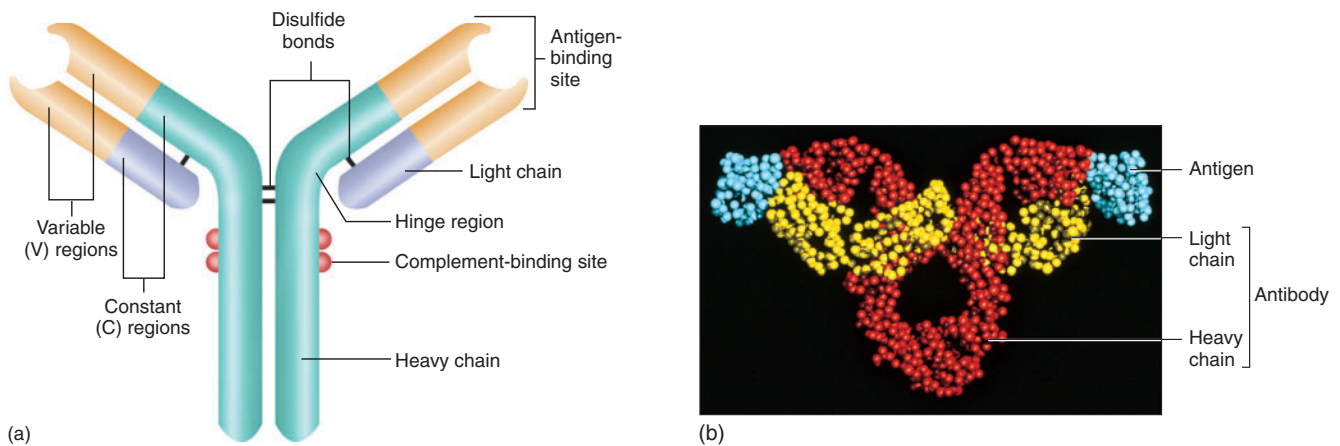


Figure 21.25 Antibody Structure. (a) A molecule of IgG, a monomer. (b) Computer-generated image of IgG bound to an antigen (lysozyme).

more enemy cells at once and stick them together (fig. 21.26a). This immobilizes microbes and antigen molecules and prevents them from spreading through the tissues.

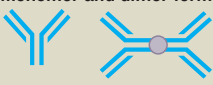


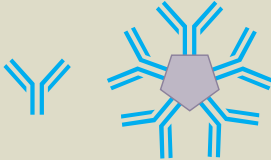
- Precipitation** begins with a similar process in which antibodies link antigen molecules (not whole cells) together. This creates an antigen-antibody complex that is too large to remain in solution (fig. 21.26b). The complex precipitates and an eosinophil may then phagocytize it.

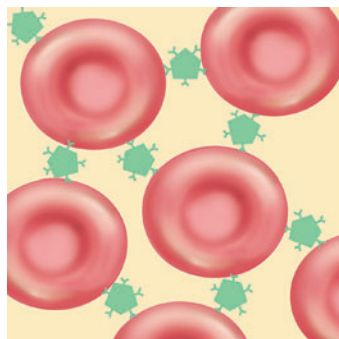
You will note that antibodies do not directly destroy an antigen in any of these mechanisms. They render it harmless by covering its pathogenic sites or agglutinating it, and they mark it for destruction by other agents such as complement, macrophages, or eosinophils.

Think About It

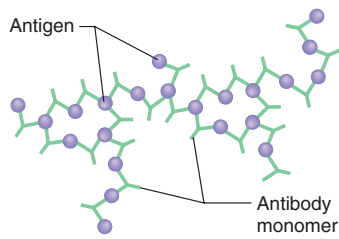
Explain why IgM has a stronger power of agglutination than antibodies of any other class.

Table 21.4 The Five Classes of Antibodies

Class	Structure	Location and Function
IgA	Monomer and dimer forms 	Plasma IgA is a monomer found in blood plasma; secretory IgA is a dimer found in mucus, saliva, tears, milk, and intestinal secretions. IgA prevents pathogens from adhering to epithelia and penetrating the underlying tissues.
IgD	Monomer	An integral protein of the B cell membrane; acts as an antigen receptor.
IgE	Monomer 	Found mainly in tonsils, skin, and mucous membranes. Stimulates mast cells and basophils to release histamine and other chemical mediators of inflammation and allergy; attracts eosinophils to sites of parasitic infection.
IgG	Monomer 	Constitutes 75% to 85% of circulating antibodies in plasma. Crosses placenta and confers temporary immunity on the fetus. Includes the anti-D antibodies of the Rh blood group. The predominant antibody secreted in the secondary immune response. IgG and IgM are the only antibodies able to bind complement.
IgM	Monomer and pentamer forms 	Monomer is an antigen receptor of the B cell membrane; pentamer occurs in blood plasma. The predominant antibody secreted in the primary immune response; very strong agglutinating ability; includes the anti-A and anti-B agglutinins of the ABO blood group.



(a)



(b)

Figure 21.26 Agglutination by Antibodies. (a) Agglutination of foreign erythrocytes by IgM. (b) An antigen-antibody complex.

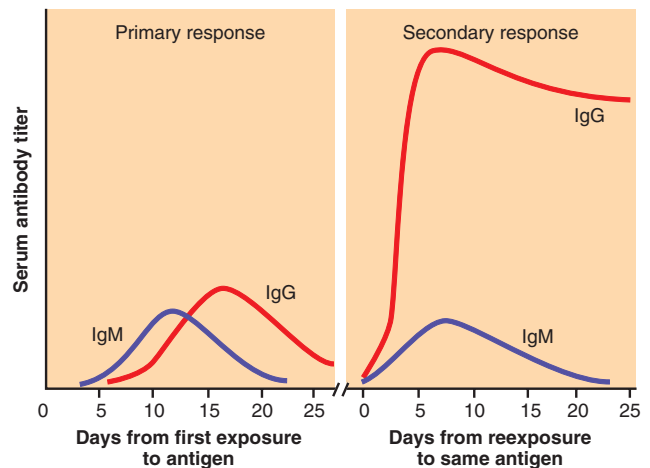


Figure 21.27 The Primary and Secondary (anamnestic) Responses in Humoral Immunity. The individual is exposed to antigen on day 0 in both cases. Note the differences in the speed of response, the height of the antibody titer, and the rate of decline in antibody titer.

Memory

When a person is exposed to a particular antigen for the first time, the immune reaction is called the **primary response**. The appearance of protective antibodies is delayed for 3 to 6 days while virgin B cells multiply and differentiate into plasma cells. As the plasma cells begin secreting antibody, the **antibody titer** (level in the blood plasma) begins to rise (fig. 21.27). IgM appears first, peaks in about 10 days, and soon declines. IgG levels rise as IgM declines, but even the IgG titer drops to a low level within a month.

The primary response, however, leaves one with an immune memory of the antigen. During clonal selection, some members of the clone become **memory B cells** rather than plasma cells (see fig. 21.23). Memory B cells, found mainly in the germinal centers of the lymph nodes, mount a very quick **secondary**, or **anamnestic**²⁰ (an-am-NESS-tic), **response** if reexposed to the same antigen. Plasma cells form within hours, so the IgG titer rises sharply and peaks within a few days. The response is so rapid that the antigen has lit-

tle chance to exert a noticeable effect on the body, and no illness results. A low level of IgM is also secreted and quickly declines, but IgG remains elevated for weeks to years, conferring lasting protection. Memory does not last as long in humoral immunity, however, as it does in cellular immunity.

Tables 21.5 and 21.6 summarize many of the cellular and chemical agents involved in humoral and cellular immunity. Table 21.7 summarizes much of what you have studied in the last two sections by comparing the features of humoral and cellular immunity. Remember that these two processes often occur simultaneously, and in conjunction with inflammation, as a three-pronged attack on the same pathogen.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

21. What is the difference between a B cell and a plasma cell?
22. Describe four ways in which an antibody reacts against an antigen.
23. Why does the secondary immune response prevent a pathogen from causing disease, while the primary immune response does not?

²⁰ana = back + mnes = remember

Table 21.5 Cellular Agents of Immunity

Cell Types	Action
Macrophages	Phagocytize bacteria, viruses, and expended or damaged host cells; act as antigen-presenting cells (APCs), which display antigen fragments to helper T cells; secrete interleukin-1 (see table 21.6)
Lymphocytes	
<i>Natural killer (NK) cells</i>	Attack bacteria, transplanted cells, and host cells that have become malignant or infected with viruses; do not depend on specific immune recognition
<i>Virgin lymphocyte pool</i>	A reserve of immunocompetent lymphocytes which are capable of responding to an antigen but have not yet encountered one
B Cells	Develop in bone marrow; as APCs, internalize and process antigens and display epitopes on cell surface; give rise to plasma cells
<i>Plasma cells</i>	Develop from B cells that have been activated by helper T cells; synthesize and secrete antibodies
<i>Memory B cells</i>	Activated B cells that do not immediately differentiate into plasma cells; act as a pool of lymphocytes that can execute a quick secondary, humoral immune response upon reexposure to the same antigen that initially induced their formation
<i>Cytotoxic T cells (Killer T, T_C, or CD8 cells)</i>	Effector cells of cellular immunity; the only lymphocytes that directly attack other cells; bind to host cells displaying antigen epitopes on MHC-I proteins; produce perforin, lymphotoxin, interferon, tumor necrosis factor, and other interleukins; produce the lethal hit that destroys target cells
<i>Helper T cells (T_H or CD4 cells)</i>	Play a central regulatory role in nonspecific defense and humoral and cellular immunity; cannot recognize free antigens but recognize antigen fragments displayed by antigen-presenting cells with MHC-II proteins; secrete interleukins that activate B, T _C , and NK cells, neutrophils, and macrophages (see actions of lymphokines in table 21.6)
<i>Suppressor T (T_S) cells (CD8 cells)</i>	Release lymphokines that inhibit B cell and T cell activity; help “wind down” the immune response as pathogen is defeated
<i>Memory T cells</i>	Activated T lymphocytes that do not immediately differentiate into effector T cells; act as a pool of lymphocytes that can execute a quick T cell recall response upon reexposure to the same antigen that activated them initially
<i>CD4 (T4) cells</i>	T lymphocytes with CD4 surface glycoproteins; primarily helper T cells
<i>CD8 (T8) cells</i>	T lymphocytes with CD8 surface glycoproteins, including cytotoxic and suppressor T cells

Table 21.6 Chemical Agents of Immunity*

Substance	Source and Action
Pathogenic Agents	
<i>Antigen (Ag)</i>	Molecule capable of triggering an immune response; usually a protein, polysaccharide, or glycolipid
<i>Hapten</i>	Small molecule unable to trigger an immune response by itself but able to bind to host molecules and produce a complex that is antigenic
Protective Agents	
<i>Antibody (Ab)</i>	An immunoglobulin (γ globulin) produced by plasma cells in response to an antigen; interferes with antigen's effects by means of complement fixation, neutralization of toxins, agglutination, and precipitation
<i>Complement</i>	Plasma proteins that help to destroy pathogens when activated by antibodies
<i>Interleukins</i>	Hormonelike messengers produced by leukocytes and macrophages to stimulate other leukocytes
Monokines	Interleukins produced by macrophages
Lymphokines	Interleukins produced by lymphocytes
Helper factors	Lymphokines produced by T_H cells that stimulate B cells to differentiate into plasma cells and synthesize antibodies
<i>Perforin</i>	A protein produced by NK and T_C cells that binds to target cells, produces a hole, and causes cytolysis
<i>Tumor necrosis factor (TNF)</i>	A factor secreted by T_C cells that kills some cancer cells by unknown means; also stimulates fever, leukopoiesis, and eosinophil activity
<i>Lymphotoxin</i>	A factor secreted by T_C cells that destroys the DNA of target cells

*Some of these chemicals have additional roles in inflammation, as described in table 21.2.

Table 21.7 Some Comparisons Between Humoral and Cellular Immunity

	Cellular Immunity	Humoral Immunity
Pathogens	Transplanted tissues and organs, cancer cells, infected cells	Bacteria, toxins, mismatched RBCs, extracellular viruses
Effector cells	Cytotoxic T cells	Plasma cells (develop from B cells)
Other cells involved in attack	Helper T cells, suppressor T cells	Helper T cells
Antigen-presenting cells	B cells, macrophages, nearly all cells	B cells
MHC proteins	MHC-I and MHC-II	MHC-II only
Chemical agents of attack	Perforins, lymphokines, lymphotoxin, tumor necrosis factor	Antibodies, complement
Mechanisms of pathogen destruction	Cytolysis (lethal hit), DNA destruction, macrophage activation, inflammation	Neutralization, complement fixation, cytolysis, opsonization, agglutination, precipitation, inflammation
Memory	T cell recall response	Secondary (anamnestic) response

Immune System Disorders

Objectives

When you have completed this section, you should be able to

- distinguish between the four classes of allergy and give an example of each;
- explain the cause of anaphylaxis and distinguish local anaphylaxis from anaphylactic shock;

- state some reasons immune self-tolerance may fail, and give examples of the resulting diseases; and
- describe the pathology of immunodeficiency diseases, especially AIDS.

Because the immune system involves complex cellular interactions controlled by numerous chemical messengers, there are many points at which things can go wrong.

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The immune response may be too vigorous, too weak, or misdirected against the wrong targets. A few disorders are summarized here to illustrate the consequences.

Hypersensitivity

Hypersensitivity is an excessive, harmful immune reaction to antigens that most people tolerate. It includes reactions to tissues transplanted from another person (*alloimmunity*), abnormal reactions to one's own tissues (*autoimmunity*), and **allergies**,²¹ which are reactions to environmental antigens. Such antigens, called **allergens**, occur in mold, dust, pollen, vaccines, bee and wasp venoms, toxins from poison ivy and other plants, and foods such as nuts, milk, eggs, and shellfish. Drugs such as penicillin, tetracycline, and insulin are allergenic to some people.

One classification system recognizes four kinds of hypersensitivity, distinguished by the types of immune agents (antibodies or T cells) involved and their methods of attack on the antigen. In this system, type I is also characterized as *acute (immediate) hypersensitivity* because the response is very rapid, while types II and III are characterized as *subacute* because they exhibit a slower onset (1–3 hours after exposure) and last longer (10–15 hours). Type IV is a delayed cell-mediated response whereas the other three are quicker antibody-mediated responses.

- **Type I (acute) hypersensitivity** includes the most common allergies. It is an IgE-mediated reaction that begins within seconds of exposure and usually subsides within 30 minutes, although it can be severe and even fatal. Allergens bind to IgE on the membranes of basophils and mast cells and stimulate them to secrete histamine and other inflammatory and vasoactive chemicals. These chemicals trigger glandular secretion, vasodilation, increased capillary permeability, smooth muscle spasms, and other effects. The effects include local edema, mucus hypersecretion and congestion, watery eyes, a runny nose, hives (red itchy skin), and sometimes cramps, diarrhea, and vomiting. Examples include food allergies and **asthma**,²² a local inflammatory reaction to inhaled allergens (see insight 21.2). **Anaphylaxis**²³ (AN-uh-fih-LAC-sis) is an immediate and severe type I reaction. Local anaphylaxis can be relieved with antihistamines.

Anaphylactic shock is a severe, widespread acute hypersensitivity that occurs when an allergen such as bee venom or penicillin is introduced to the bloodstream of an allergic individual. It is characterized by bronchoconstriction, dyspnea (labored breathing), widespread vasodilation, circulatory shock, and sometimes sudden death.

Antihistamines are inadequate to counter anaphylactic shock, but epinephrine relieves the symptoms by dilating the bronchioles, increasing cardiac output, and restoring blood pressure.

- **Type II (antibody-dependent cytotoxic) hypersensitivity** occurs when IgG or IgM attacks antigens bound to cell surfaces. The reaction leads to complement activation and either lysis or opsonization of the target cell. Macrophages phagocytize and destroy opsonized platelets, erythrocytes, or other cells. Examples of cell destruction by type II reactions are blood transfusion reactions, pemphigus vulgaris (p. 179), penicillin allergy, and some other drug reactions. In some other type II responses, an antibody binds to cell surface receptors and either interferes with their function (as in myasthenia gravis, p. 437) or overstimulates the cell (as in toxic goiter, p. 666).
- **Type III (immune complex) hypersensitivity** occurs when IgG or IgM forms antigen-antibody complexes that precipitate beneath the endothelium of the blood vessels or in other tissues. At the sites of deposition, these complexes activate complement and trigger intense inflammation, causing tissue destruction. Two examples of type III hypersensitivity are the autoimmune diseases acute glomerulonephritis (p. 907) and systemic lupus erythematosus, a widespread inflammation of the connective tissues (see table 21.8).
- **Type IV (delayed) hypersensitivity** is a cell-mediated reaction in which the signs appear about 12 to 72 hours after exposure. It begins when APCs in the lymph nodes display antigens to helper T cells, and these T cells secrete interferon and other lymphokines that activate cytotoxic T cells and macrophages. The result is a mixture of nonspecific and immune responses. Type IV reactions include allergies to haptens in cosmetics and poison ivy, graft rejection, the tuberculosis skin test, and the β cell destruction that causes insulin-dependent diabetes mellitus.

Insight 21.2 Clinical Application

Asthma

Asthma is the most common chronic illness of children, especially boys. It is the leading cause of school absenteeism and childhood hospitalization in the United States. About half of all cases develop before age 10 and only 15% after age 40. In the United States, it affects about 5% of adults and up to 10% of children, and takes about 5,000 lives per year. Moreover, asthma is on the rise; there are about twice as many cases and deaths now as there were 20 years ago.

In *allergic (extrinsic) asthma*, the most common form, the respiratory crisis is triggered by allergies in pollen, mold, animal dander, food, dust mites, or cockroaches. The allergens stimulate plasma cells to

²¹ *allo* = altered + *erg* = action, reaction

²² *asthma* = panting

²³ *ana* = against + *phylax* = protection

secrete IgE, which binds to mast cells of the respiratory mucosa. Reexposure to the allergen causes the mast cells to release a complex mixture of histamine, interleukins, and several other inflammatory chemicals, which trigger intense airway inflammation. *Nonallergic (intrinsic) asthma* is not caused by allergens but can be triggered by infections, drugs, air pollutants, cold dry air, exercise, or emotions. This form is more common in adults over age 35 than in children. The effects, however, are much the same.

Within minutes, the bronchioles constrict spasmodically (*bronchospasm*), and a person exhibits severe coughing, wheezing, and sometimes fatal suffocation. A second respiratory crisis often occurs 6 to 8 hours later. Interleukins attract eosinophils to the bronchial tissue, where they secrete proteins that paralyze the respiratory cilia, severely damage the epithelium, and lead to scarring and extensive long-term damage to the lungs. The bronchioles also become edematous and plugged with thick, sticky mucus. People who die of asthmatic suffocation typically show airways so plugged with gelatinous mucus that they could not exhale. The lungs remain hyperinflated even at autopsy.

Asthma is treated with epinephrine and other β -adrenergic stimulants used to dilate the airway and restore breathing, and inhaled corticosteroids or nonsteroidal antiinflammatory drugs to minimize airway inflammation and long-term damage. The treatment regimen can be very complicated, often requiring more than eight different medications daily, and compliance is therefore difficult for children and patients with low income or educational attainment.

Asthma runs in families and seems to result from a combination of hereditary factors and environmental irritants. In the United States, asthma is most common, paradoxically, in two groups: (1) inner-city children who are exposed to crowding, poor sanitation and ventilation, and who do not go outside very much or get enough exercise; and (2) children from extremely clean homes, perhaps because they have had too little opportunity to develop normal immunities. Asthma is also more common in countries where vaccines and antibiotics are widely used. It is less common in developing countries and in farm children of the United States.

Autoimmune Diseases

Autoimmune diseases are failures of self-tolerance—the immune system fails to distinguish self-antigens from foreign antigens and produces **autoantibodies** that attack the body's own tissues. There are at least three reasons why self-tolerance may fail:

1. **Cross-reactivity.** Some antibodies against foreign antigens react to similar self-antigens. In rheumatic fever, for example, a streptococcus infection stimulates production of antibodies that react not only against the bacteria but also against antigens of the heart tissue. It often results in scarring and stenosis (narrowing) of the mitral and aortic valves.
2. **Abnormal exposure of self-antigens to the blood.** Some of our native antigens are normally not exposed to the blood. For example, a blood-testis barrier (BTB) normally isolates sperm cells from the blood. Breakdown of the BTB can cause sterility when sperm first form in adolescence and activate the production of autoantibodies.

3. **Change in the structure of self-antigens.** Viruses and drugs may change the structure of self-antigens and cause the immune system to perceive them as foreign. One theory of the cause of type I diabetes mellitus is that a viral infection alters the antigens of β cells of the pancreatic islets, which leads to an autoimmune attack on the β cells.

Immunodeficiency Diseases

In the foregoing diseases, the immune system reacts too vigorously or directs its attack against the wrong targets. In immunodeficiency diseases, by contrast, the immune system fails to respond vigorously enough.

Severe Combined Immunodeficiency Disease (SCID)

Severe combined immunodeficiency disease is a group of disorders caused by recessive alleles that result in a scarcity or absence of both T and B cells. Children with SCID are highly vulnerable to opportunistic infections and must live in protective enclosures. Perhaps the most publicized case was David, who spent his life in sterile plastic chambers (fig. 21.28), finally succumbing at age 12 to cancer triggered by a viral infection. Children with SCID are sometimes helped by transplants of bone marrow or fetal thymus, but in some cases the transplanted cells fail to survive and multiply, or transplanted T cells attack the patient's tissues (the *graft-versus-host response*). David contracted a fatal virus from his sister through a bone marrow transplant.

Acquired Immunodeficiency Syndrome (AIDS)

Acquired immunodeficiency diseases are nonhereditary diseases contracted after birth. The best-known example is **acquired immunodeficiency syndrome (AIDS)**, a group of conditions that involve a severely depressed immune response resulting from infection with the **human immunodeficiency virus (HIV)**.

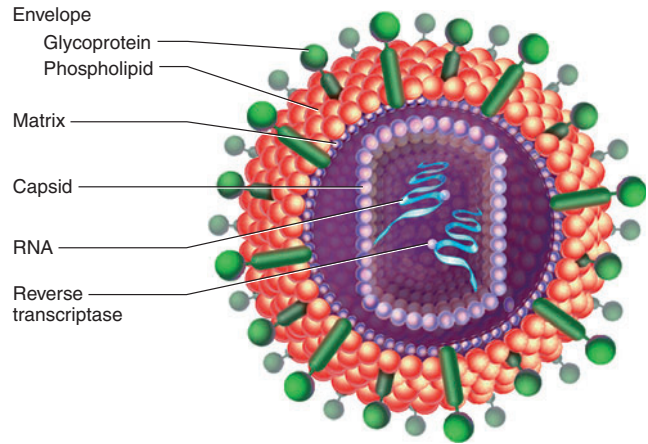
The structure of HIV is shown in figure 21.29a. Its inner core consists of a protein *capsid* enclosing two molecules of RNA, two molecules of an enzyme called *reverse transcriptase*, and a few other enzyme molecules. The capsid is enclosed in another layer of viral protein, the *matrix*. External to this is a *viral envelope* composed of phospholipids and glycoproteins derived from the host cell. Like other viruses, HIV can only be replicated by a living host cell. It invades helper T (CD4) cells, dendritic cells, and macrophages. HIV adheres to a target cell by means of one of its envelope glycoproteins and “tricks” the target cell into internalizing it by receptor-mediated endocytosis. Within the host cell, reverse transcriptase uses the viral RNA as a template to synthesize DNA—the opposite of the usual process of genetic transcription. Viruses that carry



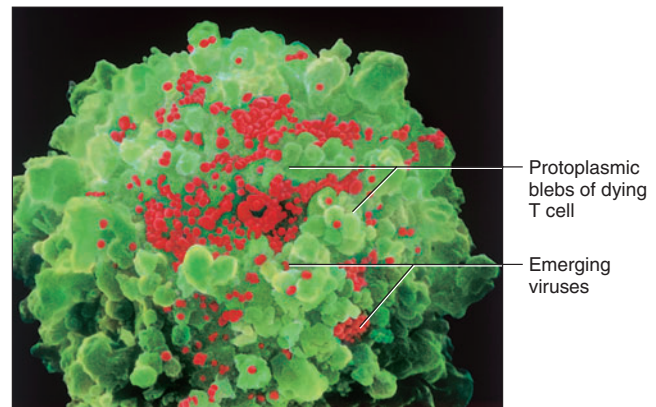
Figure 21.28 Severe Combined Immunodeficiency Disease. David Vetter lived with SCID from 1971 to 1984. At the age of six, he received a portable sterile enclosure designed by NASA that allowed him to leave the hospital for the first time.

out this RNA→DNA reverse transcription are called *retroviruses*.²⁴ The new DNA is inserted into the host cell's DNA, where it may lie dormant for months to years. When activated, however, it induces the host cell to produce new

²⁴*retr* = an acronym from *reverse transcription*



(a)



(b)

Figure 21.29 The Human Immunodeficiency Virus (HIV). (a) Structure of the virus. (b) Viruses emerging from a dying helper T cell. Each virus can now invade a new helper T cell and produce a similar number of descendants.

Which of the molecules in figure a is the target of the drug azidothymidine (AZT)? Why does AZT inhibit the spread of HIV?

viral RNA, capsid proteins, and matrix proteins. As the new viruses emerge from the host cell (fig. 21.29b), they are coated with bits of the cell's plasma membrane, forming the new viral envelope. The new viruses then adhere to more host cells and repeat the process.

By destroying T_H cells, HIV strikes at a central coordinating agent of nonspecific defense, humoral immunity, and cellular immunity (see fig. 21.21). The incubation period—from the time of infection to the time of the first symptoms—can range from a few months to 12 years. Flu-like episodes of chills and fever occur as HIV attacks T_H cells. At first, antibodies against HIV are produced and the T_H count returns nearly to normal. As the virus destroys more and more cells, however, the signs and symptoms

become more pronounced: night sweats, fatigue, headache, extreme weight loss, and lymphadenitis.

Normally, the T_H count is 600 to 1,200 cells/ μ L of blood, but a criterion of AIDS is a T_H count less than 200 cells/ μ L. With such severe depletion of T_H cells, a person succumbs to opportunistic infections with *Toxoplasma* (a protozoan previously known mainly for causing birth defects), *Pneumocystis* (a group of respiratory fungi), herpes simplex virus, cytomegalovirus (which can cause blindness), or tuberculosis bacteria. White patches may appear in the mouth, caused by *Candida* (thrush) or Epstein-Barr²⁵ virus (leukoplakia). A form of cancer called Kaposi²⁶ sarcoma, common in AIDS patients, originates in the endothelial cells of the blood vessels and causes bruise-like purple lesions visible in the skin (fig. 21.30).

Patients with full-blown AIDS show no response to standard skin tests for delayed hypersensitivity. Slurred speech, loss of motor and cognitive functions, and dementia may occur as HIV invades the brain by way of infected macrophages and induces them to release toxins that destroy neurons and astrocytes. Death from cancer or infection is inevitable, usually within a few months but sometimes as long as 8 years after diagnosis. Some people, however, have been diagnosed as HIV-positive and yet have survived for 10 years or longer without developing AIDS.

HIV is transmitted through blood, semen, vaginal secretions, and breast milk. It can be transmitted from mother to fetus through the placenta or from mother to infant during childbirth or nursing. HIV occurs in saliva and tears, but is not believed to be transmitted by those fluids. The most common means of transmission are sexual intercourse (vaginal, anal, or oral), contaminated

blood products, and drug injections with contaminated needles. Worldwide, about 75% of HIV infections are acquired through heterosexual, predominantly vaginal intercourse. In the United States, most cases occur in men who have sex with other men, but adolescents are the fastest rising group of AIDS patients because of the increasing exchange of unprotected sexual intercourse for drugs. The sharing of needles for drug use remains the chief means of transmission in urban ghettos. Many hemophiliacs became infected with HIV through blood transfusions before preventive measures were implemented in 1984, but all donated blood is now tested for HIV and the risk of infection is less than 1%. HIV cannot be contracted by donating blood, but irrational fear has resulted in an alarming drop in blood donors.

AIDS is not known to be transmitted through casual contact—for example, to family members, friends, coworkers, classmates, or medical personnel in charge of AIDS patients. It is not transmitted by kissing. Despite some speculation and fear, it has not been found to be transmitted by mosquitoes or other blood-sucking arthropods.

HIV survives poorly outside the human body. It is destroyed by laundering, dishwashing, exposure to heat (50°C [135°F] for at least 10 minutes), chlorination of swimming pools and hot tubs, and disinfectants such as bleach, Lysol, hydrogen peroxide, rubbing alcohol, and germicidal skin cleansers (Betadine and Hibiclens, for example). A properly used, undamaged latex condom is an effective barrier to HIV, especially if augmented with the spermicide nonoxynol-9. Animal membrane condoms are not effective at blocking HIV transmission because the viruses are smaller than the gaps in the membrane.

The AIDS epidemic has triggered an effort of unprecedented intensity to find a vaccine or cure. The strategies against HIV include efforts to prevent its binding to the CD4 proteins of T_H cells, disrupting the action of reverse transcriptase, or inhibiting the assembly of new viruses or their release from host cells. HIV is a difficult pathogen to attack. Since it “hides” within host cells, it usually escapes recognition by the immune system. In the brain, it is protected by the blood-brain barrier.

About 1% of HIV's genes mutate every year. This rapid rate of mutation is a barrier to both natural immunity and development of a vaccine. Even when immune cells do become sensitized to HIV, the virus soon mutates and produces new surface antigens that escape recognition. The high mutation rate also would quickly make today's vaccine ineffective against tomorrow's strain of the virus. Another obstacle to treatment and prevention is the lack of animal models for vaccine and drug research and development. Most animals are not susceptible to HIV. The chimpanzee is an exception, but chimpanzees are difficult to maintain, and there are economic barriers and ethical controversies surrounding their use.

Until recently, the only anti-HIV drug approved by the Food and Drug Administration (FDA) was azi-

²⁵M. A. Epstein (1921–), British physician; Y. M. Barr (1932–), British virologist

²⁶Moritz Kaposi (1837–1902), Austrian physician



Figure 21.30 Kaposi Sarcoma. Typical lesions on the arm and chest of a patient with AIDS.

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dothymidine (AZT, or Retrovir), which inhibits reverse transcriptase and prolongs the lives of some HIV-positive individuals. AZT is now recommended for any patient with a CD4 count below 500 cells/ μ L, but it has undesirable side effects including bone marrow toxicity and anemia. The FDA has approved other drugs, including dideoxyinosine (ddI) and dideoxycytidine (ddC) for patients who do not respond to AZT, but these drugs can also have severe side effects.

Another class of drugs—protease inhibitors—inhibit enzymes (proteases) that HIV needs in order to replicate. In 1995, a “triple cocktail” of two reverse transcriptase inhibitors and a protease inhibitor was proving to be highly effective at inhibiting viral replication, but by 1997, HIV had evolved a resistance to these drugs and this treatment was failing in more than half of all patients. Alpha interferon has shown some success in inhibiting HIV replication and slowing the progress of Kaposi sarcoma.

There remain not only these vexing clinical problems but also a number of unanswered questions about the basic biology of HIV. It remains unknown, for example, why there are such strikingly different patterns of heterosexual versus homosexual transmission in different countries and why some people succumb so rapidly to infection, while others can be HIV-positive for years without developing

AIDS. AIDS remains a stubborn problem sure to challenge virologists and epidemiologists for many years to come.

We have surveyed the major classes of immune system disorders and a few particularly notorious immune diseases. A few additional lymphatic and immune system disorders are described in table 21.8. The effects of aging on the lymphatic and immune systems are described on page 1111.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

24. How does subacute hypersensitivity differ from acute hypersensitivity? Give an example of each.
25. Aside from the time required for a reaction to appear, how does delayed hypersensitivity differ from the acute and subacute types?
26. State some reasons why antibodies may begin attacking self-antigens that they did not previously respond to. What are these self-reactive antibodies called?
27. What is the distinction between a person who has an HIV infection and a person who has AIDS?
28. How does a reverse transcriptase inhibitor such as AZT slow the progress of AIDS?

Table 21.8 Some Disorders of the Lymphatic and Immune Systems

Contact dermatitis	A form of delayed hypersensitivity that produces skin lesions limited to the site of contact with an allergen or haptens; includes responses to poison ivy, cosmetics, latex, detergents, industrial chemicals, and some topical medicines.	
Hives (urticaria) ²⁷	An allergic skin reaction characterized by a “wheal and flare” reaction: white blisters (wheals) surrounded by reddened areas (flares), usually with itching. Caused by local histamine release in response to allergens. Can be triggered by food or drugs, but sometimes by nonimmunological factors such as cold, friction, or emotional stress.	
Hodgkin ²⁸ disease	A lymph node malignancy, with early symptoms including enlarged painful lymph nodes, especially in the neck, and fever of unknown origin; often progresses to neighboring lymph nodes. Radiation and chemotherapy cure about three out of four patients.	
Splenomegaly ²⁹	Enlargement of the spleen, sometimes without underlying disease but often indicating infections, autoimmune diseases, heart failure, cirrhosis, Hodgkin disease, and other cancers. The enlarged spleen may “hoard” erythrocytes, causing anemia, and may become fragile and subject to rupture.	
Systemic lupus erythematosus	Formation of autoantibodies against DNA and other nuclear antigens, resulting in accumulation of antigen-antibody complexes in blood vessels and other organs, where they trigger widespread connective tissue inflammation. Named for skin lesions once likened to a wolf bite. ³⁰ Causes fever, fatigue, joint pain, weight loss, intolerance of bright light, and a “butterfly rash” across the nose and cheeks. Death may result from renal failure.	
<i>Disorders described elsewhere</i>		
Acute glomerulonephritis 907	Diabetes mellitus 668	Rheumatic fever 723
AIDS 829	Elephantiasis 801	Rheumatoid arthritis 320
Allergy 828	Lymphadenitis 806	SCID 829
Anaphylaxis 828	Myasthenia gravis 437	Toxic goiter 666
Asthma 828	Pemphigus vulgaris 179	

²⁷urtica = nettle

²⁸Thomas Hodgkin (1798–1866), British physician

²⁹megaly = enlargement

³⁰lupus = wolf + erythema = redness

Insight 21.3 Clinical Application

Neuroimmunology— The Mind-Body Connection

Neuroimmunology is a relatively new branch of medicine concerned with the relationship between mind and body in health and disease. It is attempting especially to understand how a person's state of mind influences health and illness through a three-way communication between the nervous, endocrine, and immune systems.

The sympathetic nervous system issues nerve fibers to the spleen, thymus, lymph nodes, and Peyer patches, where nerve fibers contact thymocytes, B cells, and macrophages. These immune cells have adrenergic receptors for norepinephrine and many other neurotransmitters such as neuropeptide Y, substance P, and vasoactive intestinal peptide (VIP). These neurotransmitters have been shown to influence immune cell activity in various ways. Epinephrine, for example, reduces the lymphocyte count and inhibits NK cell activity, thus suppressing immunity. Cortisol, another stress hormone, inhibits T cell and macrophage activity, antibody production, and the secretion of inflammatory chemicals. It also promotes atrophy of the thymus, spleen, and lymph nodes and reduces the number of circulating lymphocytes, macrophages, and eosinophils. Thus, it is not surprising that prolonged stress increases susceptibility to illnesses such as infections and cancer.

The immune system also sends messages to the nervous and endocrine systems. Immune cells synthesize numerous hormones and neurotransmitters that we normally associate with endocrine and nerve cells. B lymphocytes produce adrenocorticotropic hormone (ACTH)

and enkephalins; T lymphocytes produce growth hormone, thyroid-stimulating hormone, luteinizing hormone, and follicle-stimulating hormone. Monocytes secrete prolactin, VIP, and somatostatin. The interleukins and tumor-necrosis factor (TNF) produced by immune cells produce feelings of fatigue and lethargy when we are sick, and stimulate the hypothalamus to secrete corticotropin-releasing hormone, thus leading to ACTH and cortisol secretion. It remains uncertain and controversial whether the quantities of some of these substances produced by immune cells are enough to have far-reaching effects on the body, but it seems increasingly possible that immune cells may have wide-ranging effects on nervous and endocrine functions that affect recovery from illness.

Although neuroimmunology has met with some skepticism among physicians, there is less and less room for doubt about the importance of a person's state of mind to immune function. People under stress, such as medical students during examination periods and people caring for relatives with Alzheimer disease, show more respiratory infections than other people and respond less effectively to hepatitis and flu vaccines. The attitudes, coping abilities, and social support systems of patients significantly influence survival time even in such serious diseases as AIDS and breast cancer. Women with breast cancer die at markedly higher rates if their husbands cope poorly with stress. Attitudes such as optimism, cheer, depression, resignation, or despair in the face of disease significantly affect immune function. Religious beliefs can also influence the prospect of recovery. Indeed, ardent believers in voodoo sometimes die just from the belief that someone has cast a spell on them. The stress of hospitalization can counteract the treatment one gives to a patient, and neuroimmunology has obvious implications for treating patients in ways that minimize their stress and thereby promote recovery.

Connective Issues

Interactions Between the LYMPHATIC and IMMUNE SYSTEMS and Other Organ Systems

- ← indicates ways in which these systems affect other organ systems
- ➔ indicates ways in which other organ systems affect these systems

Nearly All Systems

Lymphatic system drains excess tissue fluid and removes cellular debris and pathogens. Immune system provides defense against pathogens and immune surveillance against cancer.

Integumentary System

- ➔ Skin provides mechanical and chemical barriers to pathogens; has antigen-presenting cells in epidermis and dermis; and is a common site of inflammation

Skeletal System

- ➔ Lymphocytes and macrophages arise from bone marrow cells; skeleton protects thymus and spleen

Muscular System

- ➔ Skeletal muscle pump moves lymph through lymphatic vessels

Nervous System

- ➔ Neuropeptides and emotional states affect immune function; blood-brain barrier prevents antibodies and immune cells from entering brain tissue

Endocrine System

- ← Lymph transports some hormones
- ➔ Hormones from thymus stimulate development of lymphatic organs and T cells; stress hormones depress immunity and increase susceptibility to infection and cancer

Circulatory System

- ← Cardiovascular system would soon fail without return of fluid and protein by lymphatic system; spleen disposes of expired erythrocytes and recycles iron; lymphatic organs prevent accumulation of debris and pathogens in blood
- ➔ Lymphatic vessels develop from embryonic veins; arterial pulsation aids flow of lymph in neighboring lymphatic vessels; leukocytes serve in nonspecific and specific defense; blood transports immune cells, antibodies, complement, interferon, and other immune chemicals; capillary endothelial cells signal areas of tissue injury and stimulate margination and diapedesis of leukocytes; blood clotting restricts spread of pathogens

Respiratory System

- ← Alveolar macrophages remove debris from lungs
- ➔ Provides immune system with O₂; disposes of CO₂; thoracic pump aids lymph flow; pharynx houses tonsils



Urinary System

- ← Absorbs fluid and proteins in kidneys, which is essential to enabling kidneys to concentrate the urine and conserve water
- ➔ Eliminates waste and maintains fluid and electrolyte balance important to lymphatic and immune function; urine flushes some pathogens from body; acidic pH of urine protects against urinary tract infection

Digestive System

- ← Lymph absorbs and transports digested lipids
- ➔ Nourishes lymphatic system and affects lymph composition; stomach acid destroys ingested pathogens

Reproductive System

- ← Immune system requires that the testes have a blood-testis barrier to prevent autoimmune destruction of sperm
- ➔ Vaginal acidity inhibits growth of pathogens

Chapter Review

Review of Key Concepts

The Lymphatic System (p. 800)

1. The lymphatic system consists of the lymph nodes, spleen, thymus, and tonsils; lymphatic tissue in other organs; a system of *lymphatic vessels*; and the *lymph* transported in these vessels. It serves for fluid recovery, immunity, and dietary lipid absorption.
2. Lymph is usually a colorless liquid similar to blood plasma, but is milky when absorbing digested lipids.
3. Lymph originates in blind *lymphatic capillaries* that pick up tissue fluid throughout the body.
4. Lymphatic capillaries converge to form larger lymphatic vessels with a histology similar to blood vessels. The largest vessels—the right lymphatic duct and thoracic duct—empty lymph into the subclavian veins.
5. There is no heartlike pump to move the lymph; lymph flows under forces similar to those that drive venous return, and like some veins, lymphatic vessels have valves to ensure a one-way flow.
6. The cells of lymphatic tissue are T lymphocytes, B lymphocytes, macrophages, dendritic cells, and reticular cells.
7. *Diffuse lymphatic tissue* is an aggregation of these cells in the walls of other organs, especially in the respiratory, digestive, urinary, and reproductive tracts. In some places, these cells become especially densely aggregated into *lymphatic nodules*, such as the *Peyer patches* of the ileum.
8. Lymphatic organs have well defined anatomical locations and have a fibrous capsule that at least partially separates them from adjacent organs and tissues. They are the lymph nodes, tonsils, thymus, and spleen.
9. Lymph nodes number in the hundreds and are small, encapsulated, elongated or bean-shaped organs found along the course of the lymphatic vessels. They

- receive afferent lymphatic vessels and give rise to efferent ones.
10. The parenchyma of a lymph node exhibits an outer *cortex* composed mainly of lymphatic follicles, and a deeper *medulla* with a network of *medullary cords*.
 11. Lymph nodes filter the lymph, remove impurities before it returns to the bloodstream, contribute lymphocytes to the lymph and blood, and initiate immune responses to foreign antigens in the body fluids.
 12. The *tonsils* encircle the pharynx and include a medial *pharyngeal tonsil* in the nasopharynx, a pair of *palatine tonsils* at the rear of the oral cavity, and numerous *lingual tonsils* clustered in the root of the tongue. Their superficial surface is covered with epithelium and their deep surface with a fibrous partial capsule. The lymphatic follicles are aligned along pits called *tonsillar crypts*.
 13. The *thymus* is located in the mediastinum above the heart. It is a site of T lymphocyte development and a source of hormones that regulate lymphocyte activity.
 14. The *spleen* lies in the left hypochondriac region between the diaphragm and kidney. Its parenchyma is composed of *red pulp* containing concentrated RBCs and *white pulp* composed of lymphocytes and macrophages.
 15. The spleen monitors the blood for foreign antigens, activates immune responses to them, disposes of old RBCs, and helps to regulate blood volume.

Nonspecific Resistance (p. 808)

1. Our defenses against pathogens include external barriers to infection; attacks on pathogens by antimicrobial proteins, inflammation, fever, and other means; and the immune system.
2. The first two mechanisms are called *nonspecific resistance* because they guard equally against a broad range of pathogens and do not require prior

- exposure to them. Immunity is a *specific defense* limited to one pathogen or a few closely related ones.
3. The skin acts as a barrier to pathogens because of its tough keratinized surface, its relative dryness, and antimicrobial chemicals such as lactic acid and *defensins*.
 4. Mucous membranes prevent most pathogens from entering the body because of the stickiness of the mucus, the antimicrobial action of *lysozyme*, and the viscosity of *hyaluronic acid*.
 5. *Neutrophils*, the most abundant leukocytes, destroy bacteria by phagocytizing and digesting them and by a *respiratory burst* that produces a chemical *killing zone* of oxidizing agents.
 6. *Eosinophils* phagocytize antigen-antibody complexes, allergens, and inflammatory chemicals, and produce antiparasitic enzymes.
 7. *Basophils* aid in defense by secreting *histamine* and *heparin*.
 8. *Lymphocytes* are of several kinds. Only one type, the natural killer (NK) cells, are involved in nonspecific defense. NK cells secrete *perforins* that destroy bacteria, transplanted cells, and host cells that are virus-infected or cancerous.
 9. *Monocytes* develop into macrophages, which have voracious phagocytic activity and act as antigen-presenting cells. Macrophages include *histiocytes*, *dendritic cells*, *microglia*, and *alveolar* and *hepatic macrophages*.
 10. *Interferons* are polypeptides secreted by cells in response to viral infection. They alert neighboring cells to synthesize antiviral proteins before they become infected, and they activate NK cells and macrophages.
 11. The *complement system* is a group of 20 or more β globulins that are activated by pathogens and combat them by enhancing inflammation, *opsonizing* bacteria, and causing *cytolysis* of foreign cells.

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12. *Inflammation* is a defensive response to infection and trauma, characterized by redness, swelling, heat, and pain (the four *cardinal signs*).
13. Inflammation begins with a mobilization of defenses by vasoactive inflammatory chemicals such as histamine, bradykinin, and leukotrienes. These chemicals dilate blood vessels, increase blood flow, and make capillary walls more permeable, thus hastening the delivery of defensive cells and chemicals to the site of injury.
14. Leukocytes adhere to the vessel wall (*margination*), crawl between the endothelial cells into the connective tissues (*diapedesis*), and migrate toward sources of inflammatory chemicals (*chemotaxis*).
15. Inflammation continues with containment and destruction of the pathogens. This is achieved by clotting of the tissue fluid and attack by macrophages, leukocytes, and antibodies.
16. Inflammation concludes with tissue cleanup and repair, including phagocytosis of tissue debris and pathogens by macrophages, edema and lymphatic drainage of the inflamed tissue, and tissue repair stimulated by platelet-derived growth factor.
17. *Fever (pyrexia)* is induced by chemical *pyrogens* secreted by neutrophils and macrophages. The elevated body temperature inhibits the reproduction of pathogens and the spread of infection.

General Aspects of Specific Immunity (p. 815)

1. The *immune system* is a group of widely distributed cells that populate most body tissues and help to destroy pathogens.
2. Immunity is characterized by its *specificity* and *memory*.
3. The two basic forms of immunity are *cellular* (cell-mediated) and *humoral* (antibody-mediated).
4. Immunity can also be characterized as *active* (production of the body's own antibodies or immune cells) or *passive* (conferred by antibodies or lymphocytes donated by another individual), and as *natural* (caused by natural exposure to a pathogen) or *artificial* (induced by vaccination or

injection of immune serum). Only active immunity results in immune memory and lasting protection.

5. *Antigens* are any molecules that induce immune responses. They are relatively large, complex, genetically unique molecules (proteins, polysaccharides, glycoproteins, and glycolipids).
6. The antigenicity of a molecule is due to a specific region of it called the *epitope*.
7. *Haptens* are small molecules that become antigenic by binding to larger host molecules.
8. *T cells* are lymphocytes that mature in the thymus, survive the process of *negative selection*, and go on to populate other lymphatic tissues and organs.
9. *B cells* are lymphocytes that mature in the bone marrow, survive negative selection, and then populate the same organs as T cells.
10. *Antigen-presenting cells (APCs)* are B cells, macrophages, reticular cells, and dendritic cells that process antigens, display the epitopes on their surface MHC proteins, and alert the immune system to the presence of a pathogen.
11. *Interleukins* are chemical signals by which immune cells communicate with each other.

Cellular Immunity (p. 818)

1. Cellular immunity employs four classes of T lymphocytes: *cytotoxic (T_C)*, *helper (T_H)*, *suppressor (T_S)*, and *memory T cells*.
2. Cellular immunity takes place in three stages: recognition, attack, and memory.
3. *Recognition*: APCs that detect foreign antigens typically migrate to the lymph nodes and display the epitopes there. T_H and T_C cells respond only to epitopes attached to MHC proteins (MHCPs).
4. MHC-I proteins occur on every nucleated cell of the body and display viral and cancer-related proteins from the host cell. T_C cells respond only to antigens bound to MHC-I proteins.
5. MHC-II proteins occur only on APCs and display only foreign antigens. T_H cells respond only to antigens bound to MHC-II proteins.
6. When a T_C or T_H cell recognizes an antigen-MHCP complex, it binds to a

second site on the target cell.

Costimulation by this site triggers *clonal selection*, multiplication of the T cell. Some daughter T cells carry out the attack on the invader and some become memory T cells.

7. *Attack*: Activated T_H cells secrete interleukins that attract neutrophils, NK cells, and macrophages and stimulate T and B cell mitosis and maturation. Activated T_C cells directly attack and destroy target cells, especially infected host cells, transplanted cells, and cancer cells. They employ a "lethal hit" of cytotoxic chemicals including *perforin*, *lymphotoxins*, and *tumor necrosis factor*. They also secrete interferons and interleukins. T_S cells suppress T and B cell activity as the pathogen is defeated and removed from the tissues.
8. *Memory*: The primary response to first exposure to a pathogen is followed by immune memory. Upon later reexposure, memory T cells respond so quickly (the *T cell recall response*) that no noticeable illness occurs.

Humoral Immunity (p. 822)

1. Humoral immunity is based on the production of antibodies rather than on lymphocytes directly contacting and attacking enemy cells. It also occurs in recognition, attack, and memory stages.
2. *Recognition*: An immunocompetent B cell binds and internalizes an antigen, processes it, and displays its epitopes on its surface MHC-II proteins. A T_H cell binds to the antigen-MHCP complex and secretes *helper factors* that activate the B cell.
3. The B cell divides repeatedly. Some daughter cells become memory B cells while others become antibody-synthesizing *plasma cells*.
4. *Attack*: Attack is carried out by antibodies (immunoglobulins). The basic *antibody monomer* is a Y-shaped complex of four polypeptide chains (two heavy and two light chains). Each has a *constant (C) region* that is identical in all antibodies of a given class, and a *variable (V) region* that gives each antibody its uniqueness. Each has an *antigen-binding site* at the tip of each V region and can therefore bind two antigen molecules.

- There are five classes of antibodies—IgA, IgD, IgE, IgG, and IgM—that differ in the number of antibody monomers (from one to five), structure of the C region, and immune function (table 21.4).
- Antibodies inactivate antigens by *neutralization*, *complement fixation*, *agglutination*, and *precipitation*.
- Memory*: Upon reexposure to the same antigen, memory B cells mount a *secondary (anamnestic) response* so quickly that no illness results.

Immune System Disorders (p. 827)

- There are three principal dysfunctions of the immune system: too vigorous or too weak a response, or a response that is misdirected against the wrong target.
- Hypersensitivity* is an excessive reaction against antigens that most people tolerate. *Allergy* is the most common form of hypersensitivity.
- Type I (acute) hypersensitivity* is an IgE-mediated response that begins within seconds of exposure and subsides within about 30 minutes. Examples include asthma, anaphylaxis, and anaphylactic shock.
- Type II (antibody-dependent cytotoxic) hypersensitivity* occurs when IgG or IgM attacks antigens bound to a target cell membrane, as in a transfusion reaction.
- Type III (immune complex) hypersensitivity* results from widespread deposition of antigen-antibody complexes in various tissues, triggering intense inflammation, as in acute glomerulonephritis and systemic lupus erythematosus.
- Type IV (delayed) hypersensitivity* is a cell-mediated reaction (types I–III are antibody-mediated) that appears 12–72 hours after exposure, as in the reaction to poison ivy and the TB skin test.
- Autoimmune diseases* are disorders in which the immune system fails to distinguish self-antigens from foreign antigens and attacks the body's own tissues. They can occur because of cross-reactivity of antibodies, as in rheumatic fever; abnormal exposure of some self-antigens to the blood, as in one form of sterility resulting from sperm destruction; or changes in self-antigen structure, as in type I diabetes mellitus.
- Immunodeficiency diseases* are failures of the immune system to respond strongly enough to defend the body from pathogens. These include *severe combined immunodeficiency disease (SCID)*, present at birth, and *acquired immunodeficiency disease (AIDS)*, resulting from HIV infection.
- HIV is a retrovirus that destroys T_H cells. Since T_H cells play a central coordinating role in cellular and humoral immunity and nonspecific defense, HIV knocks out the central control over multiple forms of defense and leaves a person vulnerable to *opportunistic infections* and certain forms of cancer.

Selected Vocabulary

lymphatic system 800	antigen-presenting cell 804	complement system 810	hypersensitivity 828
lymph 800	lymph node 804	inflammation 810	anaphylaxis 828
T lymphocyte 804	tonsil 806	cellular immunity 816	autoimmune disease 829
B lymphocyte 804	thymus 806	humoral immunity 816	acquired immunodeficiency syndrome (AIDS) 830
antibody 804	spleen 806	vaccination 816	human immunodeficiency virus (HIV) 830
macrophage 804	pathogen 808	MHC protein 817	
antigen 804	interferon 810	interleukin 817	

Testing Your Recall

- The only lymphatic organ with both afferent and efferent lymphatic vessels is
 - the spleen.
 - a lymph node.
 - a tonsil.
 - a Peyer patch.
 - the thymus.
- Which of the following cells are involved in nonspecific resistance but not in specific defense?
 - helper T cells
 - cytotoxic T cells
 - natural killer cells
 - B cells
 - plasma cells
- The respiratory burst is used by _____ to kill bacteria.
 - neutrophils
 - basophils
 - mast cells
 - NK cells
 - cytotoxic T cells
- Which of these is a macrophage?
 - microglia
 - a plasma cell
 - a reticular cell
 - a helper T cell
 - a mast cell
- The cytolytic action of the complement system is most similar to the action of
 - interleukin-1.
 - platelet-derived growth factor.
 - lymphotoxin.
 - perforin.
 - IgE.
- _____ become antigenic by binding to larger host molecules.
 - Epitopes
 - Haptens
 - Lymphokines
 - Pyrogens
 - Cell-adhesion molecules

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7. Which of the following correctly states the order of events in humoral immunity? Let 1 = antigen display, 2 = antibody secretion, 3 = secretion of helper factor, 4 = clonal selection, and 5 = endocytosis of an antigen.
 - a. 3-4-1-5-2
 - b. 5-3-1-2-4
 - c. 3-5-1-4-2
 - d. 5-3-1-4-2
 - e. 5-1-3-4-2
8. The cardinal signs of inflammation include all of the following *except*
 - a. redness.
 - b. swelling.
 - c. heat.
 - d. fever.
 - e. pain.
9. A helper T cell can bind only to another cell that has
 - a. MHC-II proteins.
 - b. an epitope.
 - c. an antigen-binding site.
 - d. a complement-binding site.
 - e. a CD4 protein.
10. Which of the following results from a lack of self-tolerance?
 - a. SCID
 - b. AIDS
 - c. systemic lupus erythematosus
 - d. anaphylaxis
 - e. asthma
11. Any organism or substance capable of causing disease is called a/an _____.
12. Mucous membranes contain an antibacterial enzyme called _____.
13. _____ is a condition in which one or more lymph nodes are swollen and painful to the touch.
14. The movement of leukocytes through the capillary wall is called _____.
15. In the process of _____, complement proteins coat bacteria and serve as binding sites for phagocytes.
16. Any substance that triggers a fever is called a/an _____.
17. The chemical signals produced by leukocytes to stimulate other leukocytes are called _____.
18. Part of an antibody called the _____ binds to part of an antigen called the _____.
19. Self-tolerance results from a process called _____, in which lymphocytes programmed to react against self-antigens die.
20. Any disease in which antibodies attack one's own tissues is called a/an _____ disease.

Answers in Appendix B

True or False

Determine which five of the following statements are false, and briefly explain why.

1. Some bacteria employ lysozyme to liquify the tissue gel and make it easier for them to get around.
2. T lymphocytes undergo clonal deletion and anergy in the thymus.
3. Interferons help to reduce inflammation.
4. T lymphocytes are involved only in cell-mediated immunity.
5. The white pulp of the spleen gets its color mainly from lymphocytes and macrophages.
6. Perforins are employed in both nonspecific resistance and cellular immunity.
7. Histamine and heparin are secreted by basophils and mast cells.
8. A person who is HIV-positive and has a T_H (CD4) count of 1,000 cells/ μ L does not have AIDS.
9. Anergy is often a cause of autoimmune diseases.
10. Interferons kill pathogenic bacteria by making holes in their cell walls.

Answers in Appendix B

Testing Your Comprehension

1. Anti-D antibodies of an Rh⁻ woman sometimes cross the placenta and hemolyze the RBCs of an Rh⁺ fetus (see p. 697). Yet the anti-B antibodies of a type A mother seldom affect the RBCs of a type B fetus. Explain this difference based on your knowledge of the five immunoglobulin classes.
2. In treating a woman for malignancy in the right breast, the surgeon removes some of her axillary lymph nodes. Following surgery, the patient experiences edema of her right arm. Explain why.
3. A girl with a defective heart receives a new heart transplanted from another child who was killed in an accident. The patient is given an antilymphocyte serum containing antibodies against her lymphocytes. The transplanted heart is not rejected, but the patient dies of an overwhelming bacterial infection. Explain why the antilymphocyte serum was given and why the patient was so vulnerable to infection.
4. A burn research center uses mice for studies of skin grafting. To prevent graft rejection, the mice are thymectomized at birth. Even though B cells do not develop in the thymus, these mice show no humoral immune response and are very susceptible to infection. Explain why the removal of the thymus would improve the success of skin grafts but adversely affect humoral immunity.
5. Contrast the structure of a B cell with that of a plasma cell, and explain how their structural difference relates to their functional difference.

Answers At the Online Learning Center

Answers to Figure Legend Questions

- 21.4 There would be no consistent one-way flow of lymph. Lymph and tissue fluid would accumulate, especially in the lower regions of the body.
- 21.15 Both of these produce a ring of proteins in the target cell plasma membrane, opening a hole in the membrane through which the cell contents escape.
- 21.21 All three defenses depend on the action of helper T cells, which are destroyed by HIV.
- 21.24 The ER is the site of antibody synthesis.
- 21.29 AZT targets reverse transcriptase. If this enzyme is unable to function, HIV cannot produce viral DNA and insert it into the host cell DNA, and the virus therefore cannot be replicated.

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