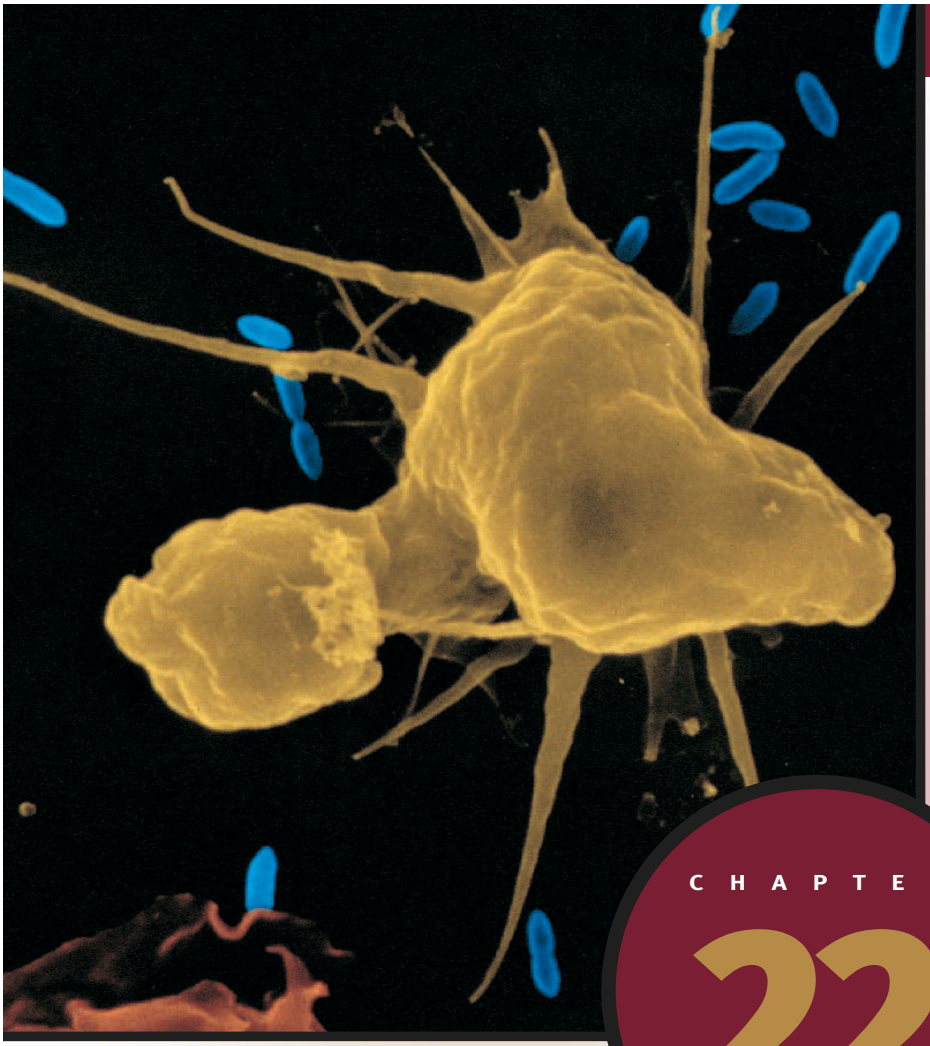


A macrophage (larger cell) is about to phagocytize a bacterial cell (E. coli).

Lymphatic System and Immunity

CHAPTER 22

One of the basic themes of life is that many organisms consume or use other organisms to survive. For example, termites feed on wood, deer graze on grasses, spiders eat termites, and wolves feed on deer. A parasite lives on or in another organism called the host. The host provides the parasite with the conditions and food necessary for survival. For example, hookworms can live in the sheltered environment of the human intestine, where they feed on blood. Humans are host to many different kinds of organisms, including microorganisms, such as bacteria, viruses, fungi, and protozoans; insects; and worms. It's often the case that parasites harm humans, causing disease and sometimes death. However, our bodies have ways to resist or destroy harmful microorganisms. This chapter considers the *lymphatic system* (772), *immunity* (779), *innate immunity* (780), *adaptive immunity* (785), *immune interactions* (800), *immunotherapy* (800), *acquired immunity* (804), and the *effects of aging on the lymphatic system and immunity* (805).

Lymphatic System

Objectives

- ***Describe the functions of the lymphatic system.***
- ***Explain the anatomy and location of the lymphatic vessels.***
- ***Describe the structures and functions of diffuse lymphatic tissue, lymphatic nodules, tonsils, lymph nodes, spleen, and thymus.***

The **lymphatic** (lim-fat′ik) **system** includes lymph, lymphatic vessels, lymphatic tissue, lymphatic nodules, lymph nodes, tonsils, the spleen, and the thymus (figure 22.1).

Functions of the Lymphatic System

The lymphatic system helps to maintain fluid balance in tissues and absorb fats from the digestive tract. It's also part of the body's defense system against microorganisms and other harmful substances.

1. *Fluid balance.* Approximately 30 L of fluid pass from the blood capillaries into the interstitial fluid each day, whereas only 27 L pass from the interstitial fluid back into the blood capillaries. If the extra 3 L of fluid were to remain in the interstitial fluid, edema would result, causing tissue damage and eventual death. Instead, the 3 L of fluid enters the lymphatic capillaries, where the fluid is called **lymph** (limf; clear spring water), and passes through the lymphatic vessels back to the blood (see chapter 21). In addition to water, lymph contains solutes derived from two sources: (1) substances in plasma, such as ions, nutrients, gases, and some proteins, pass from blood capillaries into the interstitial fluid and become part of the lymph; and (2) substances derived from cells, such as hormones, enzymes, and waste products, are also found in the lymph.

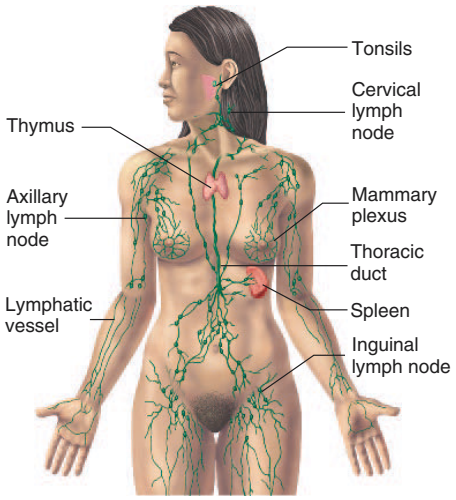


Figure 22.1 Lymphatic System
The major lymphatic organs and vessels are shown.

2. *Fat absorption.* The lymphatic system absorbs fats and other substances from the digestive tract (see chapter 24). Special lymphatic vessels called **lacteals** (lak′tē-ălz) are located in the lining of the small intestine. Fats enter the lacteals and pass through the lymphatic vessels to the venous circulation. The lymph passing through these lymphatic vessels has a milky appearance because of its fat content and is called **chyle** (kīl).
3. *Defense.* Microorganisms and other foreign substances are filtered from lymph by lymph nodes and from blood by the spleen. In addition, lymphocytes and other cells are capable of destroying microorganisms and other foreign substances.

Lymphatic Vessels

The lymphatic vessels are essential for the maintenance of fluid balance. They begin as small, dead-end tubes called **lymphatic capillaries** (figure 22.2*a*). Fluids tend to move out of blood capillaries into tissue spaces (see "Capillary Exchange and Regulation of Interstitial Fluid Volume" in chapter 21). Excess fluid passes through the tissue spaces and enters lymphatic capillaries to become lymph. Lymphatic capillaries are in almost all tissues of the body, with the exception of the central nervous system, the bone marrow, and tissues without blood vessels, such as cartilage, epidermis, and the cornea. A superficial group of lymphatic capillaries is in the dermis of the skin and the hypodermis. A deep group of lymphatic capillaries drains the muscles, joints, viscera, and other deep structures.

Lymphatic capillaries differ from blood capillaries in that they lack a basement membrane and the cells of the simple squamous epithelium slightly overlap and are attached loosely to one another (figure 22.2*b*). Two things occur as a result of this structure. First, the lymphatic capillaries are far more permeable than blood capillaries, and nothing in the interstitial fluid is excluded from the lymphatic capillaries. Second, the lymphatic capillary epithelium functions as a series of one-way valves that allow fluid to enter the capillary but prevent it from passing back into the interstitial spaces.

The lymphatic capillaries join to form larger **lymphatic vessels,** which resemble small veins. The inner layer of the lymphatic vessel consists of endothelium surrounded by an elastic membrane, the middle layer consists of smooth muscle cells and elastic fibers, and the outer layer is a thin layer of fibrous connective tissue.

Small lymphatic vessels have a beaded appearance because of the presence of one-way valves along their lengths that are similar to the valves of veins (see figure 22.2*b*). When a lymphatic vessel is compressed, backward movement of lymph is prevented by the valves; as a consequence, the lymph moves forward through the lymphatic vessel. Three factors are responsible for the compression of lymphatic vessels: (1) contraction of surrounding skeletal muscles during activity, (2) contraction of the smooth muscles in the lymphatic vessel walls, and (3) pressure changes in the thorax during respiration.

Lymph nodes are round, oval, or bean-shaped bodies distributed along the various lymphatic vessels (see "Lymph Nodes" on p. 775). They function to filter lymph, which enters and exits the

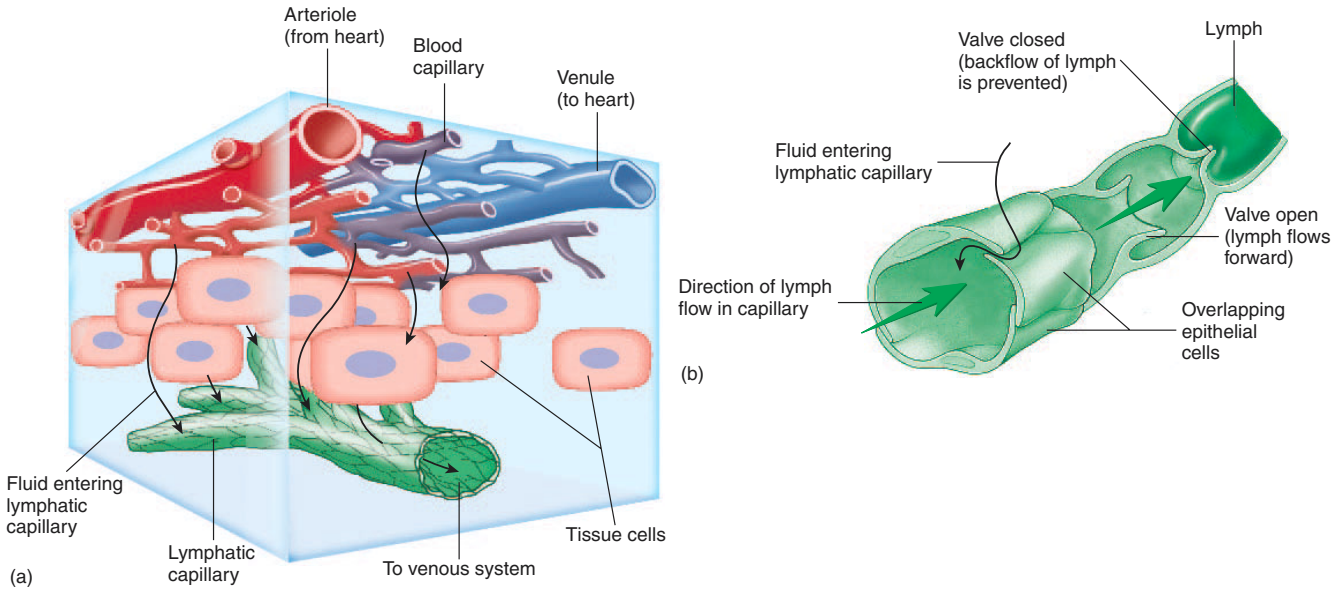


Figure 22.2 Lymph Formation and Movement

(*a*) Movement of fluid from blood capillaries into tissues and from tissues into lymphatic capillaries to form lymph. (*b*) The overlap of epithelial cells of the lymphatic capillary allows easy entry of fluid but prevents movement back into the tissue. Valves, located farther along in lymphatic vessels, also ensure one-way flow of lymph.

lymph nodes through the lymphatic vessels. The lymph nodes are connected together in a series, so that lymph leaving one lymph node is carried to another lymph node, and so on.

After passing through the lymph nodes, the lymphatic vessels converge to form larger vessels called **lymphatic trunks,** each of which drains a major portion of the body (figure 22.3*a* and *b*). The **jugular trunks** drain the head and neck; the **subclavian trunks** drain the upper limbs, superficial thoracic wall, and mammary glands; the **bronchomediastinal** (brong′kō-mē′dē-as-tī′năl) **trunks** drain thoracic organs and the deep thoracic wall; the **intestinal trunks** drain abdominal organs such as the intestines, stomach, pancreas, spleen, and liver; and the **lumbar trunks** drain the lower limbs, pelvic and abdominal walls, pelvic organs, ovaries or testes, kidneys, and adrenal glands.

The lymphatic trunks connect to large veins in the thorax or join to yet larger vessels called **lymphatic ducts,** which then connect to the large veins. The connections of the lymphatic trunks and ducts to veins are quite variable. Many connect at the junction of the internal jugular and subclavian veins, but connections on the subclavian, jugular, and even brachiocephalic vein exist.

On the right side, the jugular, subclavian, and bronchomediastinal trunks typically join a thoracic vein separately (see figure 22.3*b*). About 20% of the time, the three trunks join together to form a short duct 1 cm in length called the **right lymphatic duct** (not shown in figure 22.3*b*), which joins a thoracic vein. These trunks drain the right side of the head, right-upper limb, and right thorax (figure 22.3*c*).

The right side of the body inferior to the thorax and the entire left side of the body (see figure 22.3*c*) mostly drain through the **thoracic duct** (see figure 22.3*b*). The thoracic duct is the largest lymphatic vessel. It is approximately 38–45 cm in length, extending from the twelfth thoracic vertebra to the base of the neck (see figure 22.3*c*). The jugular and subclavian trunks join the thoracic duct. The bronchomediastinal trunk sometimes connects to the thoracic duct, but typically joins a vein. The intestinal and lumbar trunks, which drain lymph inferior to the diaphragm, supply the inferior end of the thoracic duct. They can directly join the thoracic duct or merge to form a network that connects to the thoracic duct. In a small proportion of cases, the lymphatic trunks form a sac called the **cisterna chyli** (sis-ter′nă kī′lī; a cistern or tank that contains juice).

1. *List the parts of the lymphatic system, and describe the three main functions of the lymphatic system.*
2. *How is lymph formed?*
3. *Describe the structure of a lymphatic capillary. Why is it easy for fluid and other substances to enter a lymphatic capillary?*
4. *What is the function of the valves in lymphatic vessels? Name three things that cause lymph to move through the lymphatic vessels.*
5. *What are lymphatic trunks and ducts? Name the largest lymphatic vessel. What is the cisterna chyli?*
6. *What areas of the body are drained by the right lymphatic trunks, left lymphatic trunks, and thoracic duct?*

P R E D I C T 1

During radical cancer surgery, malignant lymph nodes are often removed, and the lymphatic vessels to them are tied off to prevent metastasis, or spread, of the cancer. Predict the consequences of tying off the lymphatic vessels.

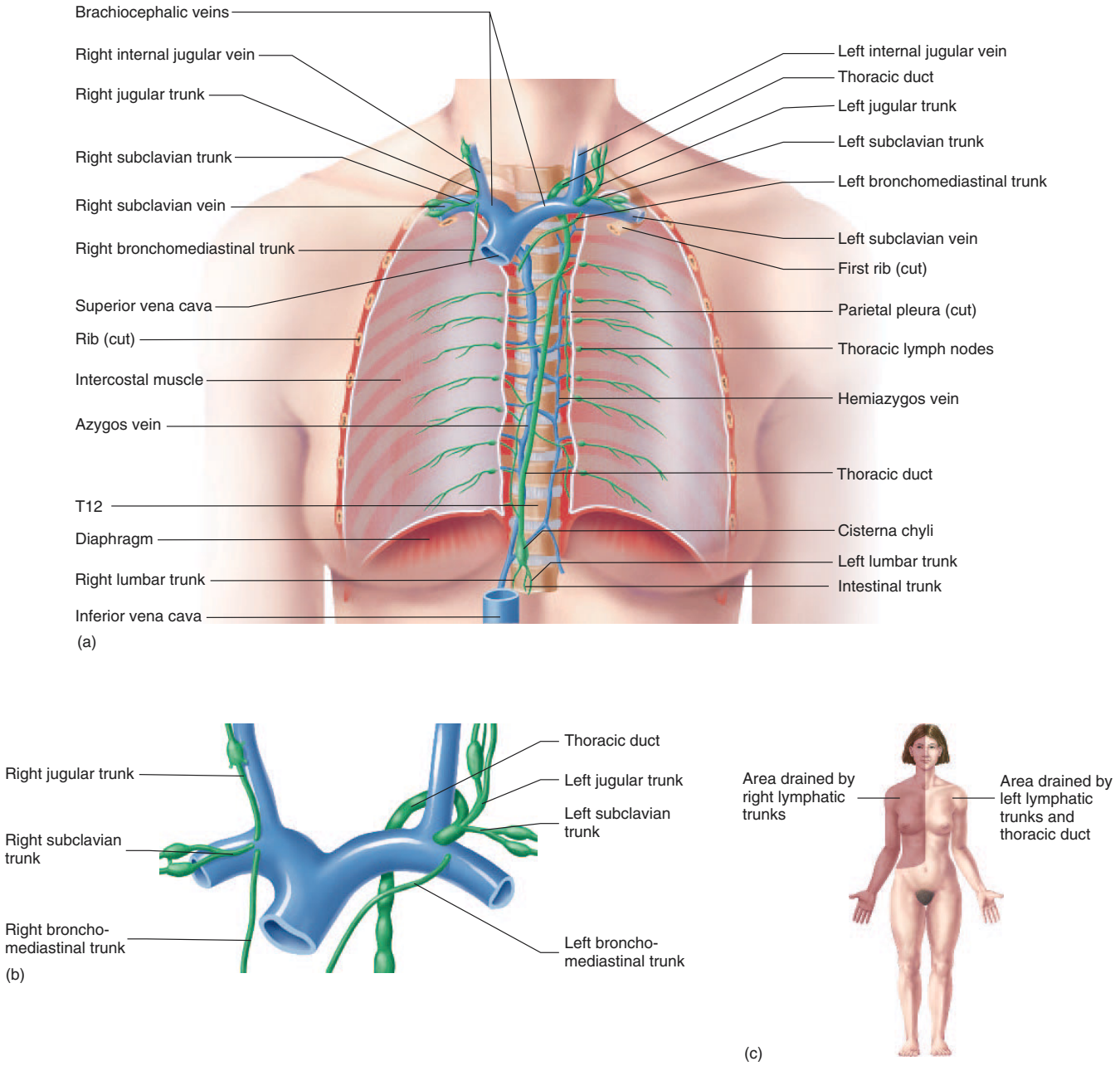


Figure 22.3 Lymph Drainage Into Veins

(*a*) Anterior view of the major lymphatic vessels in the thorax and abdomen. (*b*) Close-up view of the lymphatic vessels from which lymph enters the blood. (*c*) Regions of the body drained by the right and left lymphatic vessels.

Lymphatic Tissue and Organs

Lymphatic organs contain **lymphatic tissue,** which consists primarily of lymphocytes; but it also includes macrophages, dendritic cells, reticular cells, and other cell types. **Lymphocytes** are a type of white blood cell (see chapter 19). They originate from red bone marrow and are carried by the blood to lymphatic organs and other tissues. When the body is exposed to microorganisms or foreign substances, the lymphocytes divide, increase in number, and are part of the immune response that destroys microorganisms and foreign substances. Lymphatic tissue also has very fine collagen fibers, called **reticular fibers,** which are produced by **reticular cells.** Lymphocytes and other cells attach to these fibers. When lymph or blood filters through lymphatic organs, the fiber network traps microorganisms and other particles in the fluid.

Lymphatic tissue surrounded by a connective tissue capsule is said to be encapsulated, whereas lymphatic tissue without a capsule is called nonencapsulated. Lymphatic organs with a capsule include lymph nodes, the spleen, and the thymus. **Mucosa-associated lymphoid tissue (MALT)** is aggregates of nonencapsulated lymphatic tissue found in and beneath the mucous membranes lining the digestive, respiratory, urinary, and reproductive tracts. In these locations, the lymphatic tissue is well located to intercept microorganisms as they enter the body. Examples of MALT include diffuse lymphatic tissue, lymphatic nodules, and the tonsils.

Diffuse Lymphatic Tissue and Lymphatic Nodules

Diffuse lymphatic tissue contains dispersed lymphocytes, macrophages, and other cells; has no clear boundary; and blends with surrounding tissues (figure 22.4). It is located deep to mucous membranes, around lymphatic nodules, and within the lymph nodes and spleen.

Lymphatic nodules are denser arrangements of lymphoid tissue organized into compact, somewhat spherical structures, ranging in size from a few hundred microns to a few millimeters or more in diameter (see figure 22.4). Lymphatic nodules are numerous in the loose connective tissue of the digestive, respiratory, urinary, and reproductive systems. **Peyer's patches** are aggregations of lymphatic nodules found in the distal half of the small intestine and the appendix. In addition to MALT, lymphatic nodules are found within lymph nodes and the spleen, where they are usually referred to as **lymphatic follicles.**

Tonsils

Tonsils are large groups of lymphatic nodules and diffuse lymphatic tissue located deep to the mucous membranes within the pharynx (throat) (figure 22.5). The tonsils provide protection against bacteria and other potentially harmful material entering the pharynx from the nasal or oral cavities. In adults, the tonsils decrease in size and eventually may disappear.

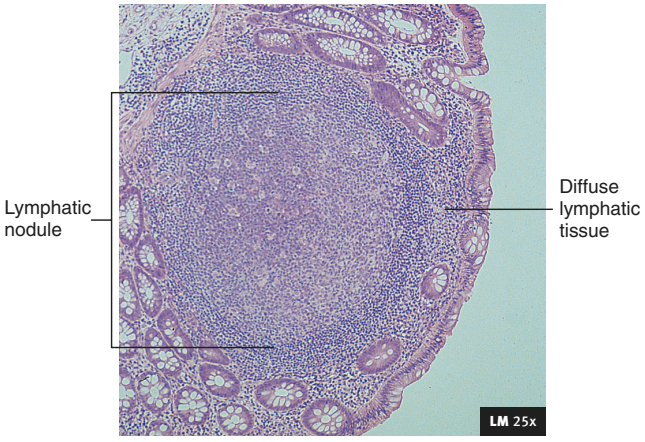


Figure 22.4 Diffuse Lymphatic Tissue and Lymphatic Nodule

Diffuse lymphatic tissue surrounding a lymphatic nodule in the small intestine (Peyer's patch).

There are three groups of tonsils, but the **palatine tonsils** usually are referred to as "the tonsils." They are relatively large, oval lymphoid masses on each side of the junction between the oral cavity and the pharynx. The **pharyngeal** (fă-rin′jē-ăl) **tonsil,** or adenoid (ad′ĕ-noyd), is a collection of somewhat closely aggregated lymphatic nodules near the junction between the nasal cavity and the pharynx. An enlarged pharyngeal tonsil can interfere with normal breathing. The **lingual tonsil** is a loosely associated collection of lymphatic nodules on the posterior surface of the tongue.

Sometimes the palatine or pharyngeal tonsils become chronically infected and must be removed. The lingual tonsil becomes infected less often than the other tonsils and is more difficult to remove.

7. *What are the functions of lymphocytes and reticular fibers in lymphatic tissue?*
8. *What is mucosa-associated lymphoid tissue (MALT)? In what way is the location of MALT beneficial?*
9. *Define diffuse lymphatic tissue, lymphatic nodule, Peyer's patches, and lymphatic follicle.*
10. *Describe the structure, function, and location of the tonsils.*

Lymph Nodes

Lymph nodes are small, round, or bean-shaped structures, ranging in size from 1–25 mm long, and are distributed along the course of the lymphatic vessels (see figures 22.1 and 22.6). They filter the lymph, removing bacteria and other materials. In addition, lymphocytes congregate, function, and proliferate within lymph nodes.

Lymph nodes are categorized as superficial or deep. **Superficial lymph nodes** are in the hypodermis beneath the skin and **deep lymph nodes** are everywhere else. Both superficial and deep lymph nodes typically are located in adipose tissue near or on blood vessels. Approximately 450 lymph nodes are found throughout the body. Cervical and head nodes (about 70) filter lymph from the head and neck, axillary nodes (about 30) filter lymph from the upper limbs and superficial thorax, thoracic nodes (about 100) filter lymph from the thoracic wall and organs, abdominopelvic nodes (about 230) filter lymph from the abdomen and pelvis, and inguinal and popliteal nodes (about 20) filter lymph from the lower limbs and superficial pelvis.

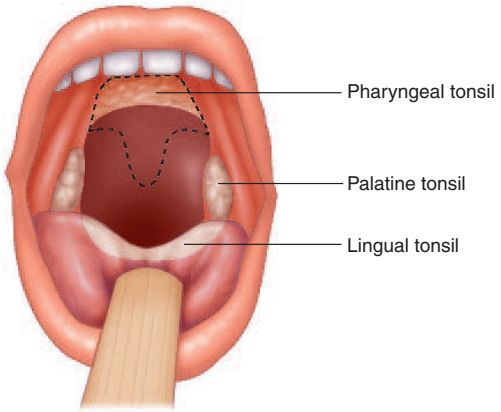


Figure 22.5 Location of the Tonsils

Anterior view of the oral cavity showing the tonsils. Part of the palate is removed (*dotted line*) to show the pharyngeal tonsil.

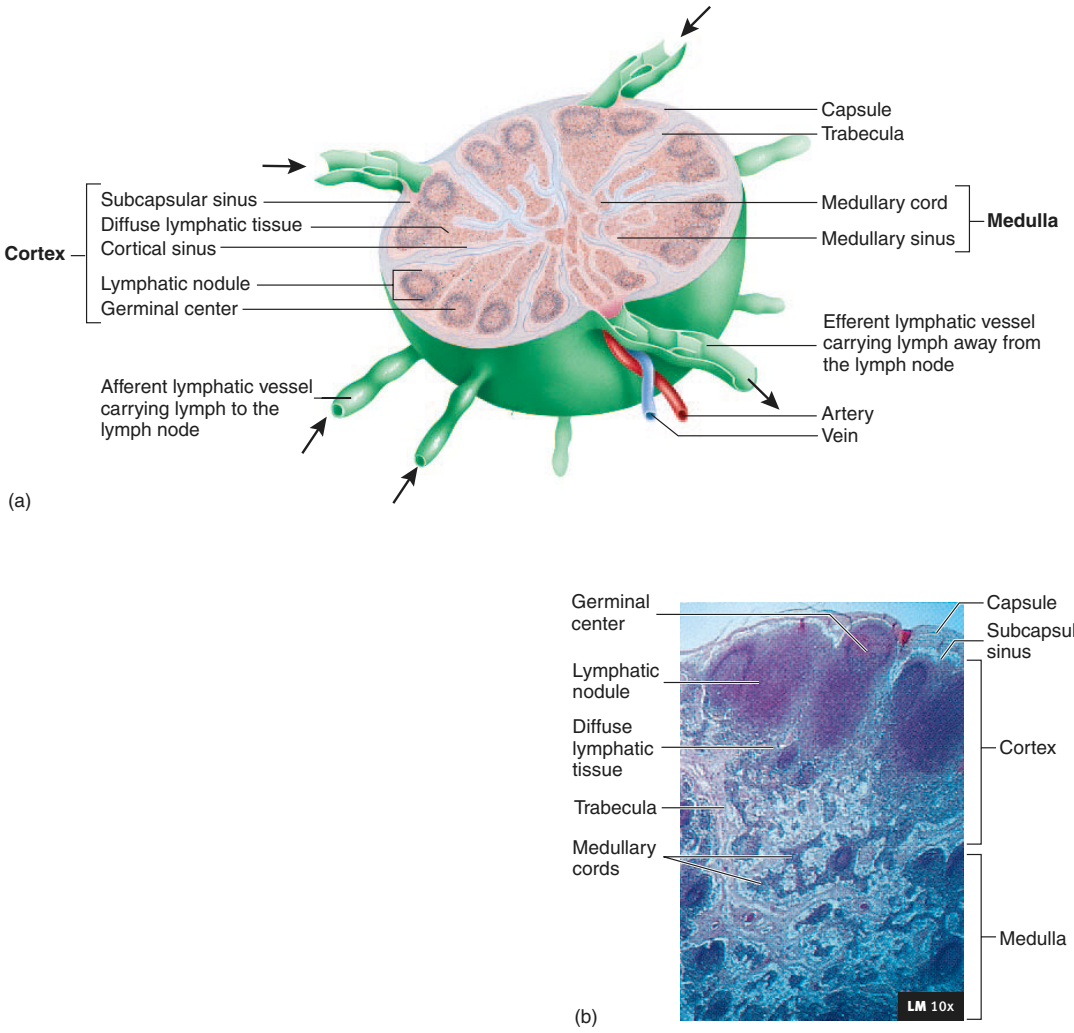


Figure 22.6 Lymph Node

(*a*) *Arrows* indicate direction of lymph flow. As lymph moves through the sinuses, phagocytic cells remove foreign substances. The germinal centers are sites of lymphocyte production. (*b*) Histology of a lymph node.

Femoral Hernia

Lymph from the lower limbs drains into the inguinal lymph nodes, which are located in the groin region. The **femoral canal** is a passageway through which lymphatic vessels from the inguinal nodes enter the abdominal cavity. A **femoral hernia** occurs when a loop of intestine pushes into, or even passes completely through, the femoral canal.

A dense connective tissue **capsule** surrounds each lymph node. Extensions of the capsule, called **trabeculae** (trăb-bek′ū-lē), form a delicate internal skeleton in the lymph node. Reticular fibers extend from the capsule and trabeculae to form a fibrous network throughout the entire node. In some areas of the lymph node, lymphocytes and macrophages are packed around the reticular fibers to form lymphatic tissue, and in other areas the reticular fibers extend across open spaces to form **lymphatic sinuses.** The lymphatic tissue and sinuses within the node are arranged into two somewhat indistinct layers, an outer cortex and an inner medulla. The **cortex** consists of a subcapsular sinus, beneath the capsule, and cortical sinuses, which are separated by diffuse lymphatic tissue, trabeculae, and lymphatic nodules. The inner **medulla** is organized into branching, irregular strands of diffuse lymphatic tissue, the **medullary cords,** separated by medullary sinuses.

Lymph nodes are the only structures to filter lymph. They have **afferent lymphatic vessels,** which carry lymph to the lymph nodes, where it is filtered, and **efferent lymphatic vessels,** which carry lymph away from the nodes. Lymph from afferent lymphatic vessels enters the subcapsular sinus and filters through the cortex to the medulla, passing through the cortical sinuses and lymphatic

tissue of the cortex. Lymph then passes through the sinuses and lymphatic tissue of the medulla and exits the lymph node through efferent lymphatic vessels. The efferent vessels of one lymph node may become the afferent vessels of another node or may converge to form lymphatic trunks, which carry lymph to the blood at thoracic blood vessels.

Macrophages line the lymphatic sinuses, and they remove bacteria and other foreign substances from the lymph as it slowly filters through the sinuses. Microorganisms or other foreign substances in the lymph can stimulate lymphocytes throughout the lymph node to undergo cell division, with proliferation especially evident in the lymphatic nodules of the cortex. These areas of rapid lymphocyte division are called **germinal centers.** The newly produced lymphocytes are released into the lymph and eventually reach the bloodstream, where they circulate. Subsequently, the lymphocytes can leave the blood and enter other lymphatic tissues.

Lymph Nodes Trap Cancer Cells

Cancer cells can spread from a tumor site, enter lymphatic capillaries, and be carried to lymph nodes where they can be trapped and where they can proliferate. If the cancer cells escape from the lymph nodes, they may pass through lymphatic vessels to the blood and eventually reach other parts of the body. During cancer surgery, malignant (cancerous) lymph nodes are often removed, and their vessels are tied off and cut to prevent the spread of the cancer.

Spleen

The **spleen,** which is roughly the size of a clenched fist, is located on the left side in the extreme, superior part of the abdominal cavity (figure 22.7). The average weight of the adult spleen is 180 g in males and 140 g in females. The size and weight of the spleen tends to decrease in older people, but in certain diseases the spleen can achieve weights of 2000 g or more.

The spleen has an outer **capsule** of dense irregular connective tissue and a small amount of smooth muscle. Bundles of connective tissue fibers from the capsule form **trabeculae,** which extend into the organ, subdividing it into small, interconnected compartments. Arteries, veins, and lymphatic vessels extend through the trabeculae to supply the compartments, which are filled with white and red pulp. **White pulp** is associated with the arterial supply and **red pulp** is associated with the veins. Approximately one-fourth of the volume of the spleen is white pulp and three-fourths is red pulp.

Branches of the **splenic** (splen′ik) **artery** enter the spleen at the **hilum,** and their branches follow the various trabeculae into the spleen (see figure 22.7*a* and *b*). From the trabeculae, arterial branches extend into the white pulp, which consists of the periarterial lymphatic sheath and lymphatic nodules (see figure 22.7*c*). The **periarterial lymphatic sheath** is diffuse lymphatic tissue surrounding arteries and arterioles extending to lymphatic nodules. Arterioles enter lymphatic nodules and give rise to capillaries supplying the red pulp, which consists of the splenic cords and venous sinuses. The **splenic cords** are a network of reticular cells which produce reticular fibers (see chapter 4). The spaces between the reticular cells are occupied by splenic macrophages and blood cells that have come from the capillaries. The **venous sinuses** are enlarged capillaries between the splenic cords. The venous sinuses typically connect to trabecular veins, which unite to form vessels that leave the spleen to form the **splenic vein.**

Blood flows through the spleen at three different rates. The fast flow takes a few seconds, intermediate flow a few minutes, and slow flow an hour or more. Most blood flows through the spleen rapidly, but about 10% moves at the intermediate rate, and 2% flows at the slow rate.

The fast flow is typical of flow through organs with a **closed circulation,** in which there is a direct capillary connection between the arterial and venous vessels (see figure 22.7*c*). In the spleen, however, direct connections only occur rarely. Most circulation in the spleen is an **open circulation,** in which there is no direct capillary connection between the arterial and venous vessels. Instead, blood empties into the boundary between the white and red pulp or into the splenic cords. In most cases, blood quickly enters into the open ends of venous sinuses, which originate near the boundary. Otherwise, the blood percolates through the splenic cords and passes through the walls of the venous sinuses, which have intercellular slits. The fast flow through the spleen results from blood moving through the closed circulation or quickly into the open ends of the venous sinuses in the open circulation. The intermediate flow is the passage of blood through the splenic cords and through the walls of the venous sinuses. The slow flow follows the same pathway as the intermediate flow, but it takes longer because of the temporary adhesion of blood cells to splenic cord cells.

The spleen destroys defective red blood cells, detects and responds to foreign substances in the blood, and acts as a blood reservoir. As red blood cells age, they lose their ability to bend and fold. Consequently, the cells can rupture as they pass through the meshwork of the splenic cords or the intercellular slits of the venous sinus walls. Splenic macrophages then phagocytize the cellular debris.

Foreign substances in the blood passing through the spleen can stimulate an immune response because of the presence in the white pulp of specialized lymphocytes, described later in this chapter. There are high concentrations of T cells in the periarterial lymphatic sheath and B cells in the lymphatic nodules.

The human spleen is a limited reservoir for blood. For example, during exercise splenic volume can be reduced by approximately 40%–50%. The resulting small increase in circulating red blood cells can promote better oxygen delivery to muscles during exercise or emergency situations. It's not presently known if in humans this reduction results from contraction of smooth muscle within the capsule, from contraction of smooth muscle (myofibroblast) within the trabeculae, or from reduced blood flow through the spleen caused by constriction of blood vessels.

Removal of the Injured Spleen

The spleen can be ruptured in traumatic abdominal injuries, even though it is protected by the ribs. A ruptured spleen can result in severe bleeding, shock, and possibly death. A **splenectomy** (splē-nek′tō-mē), removal of the spleen, can be performed to stop the bleeding. The liver and other lymphatic tissues are able to compensate for loss of the spleen's functions.

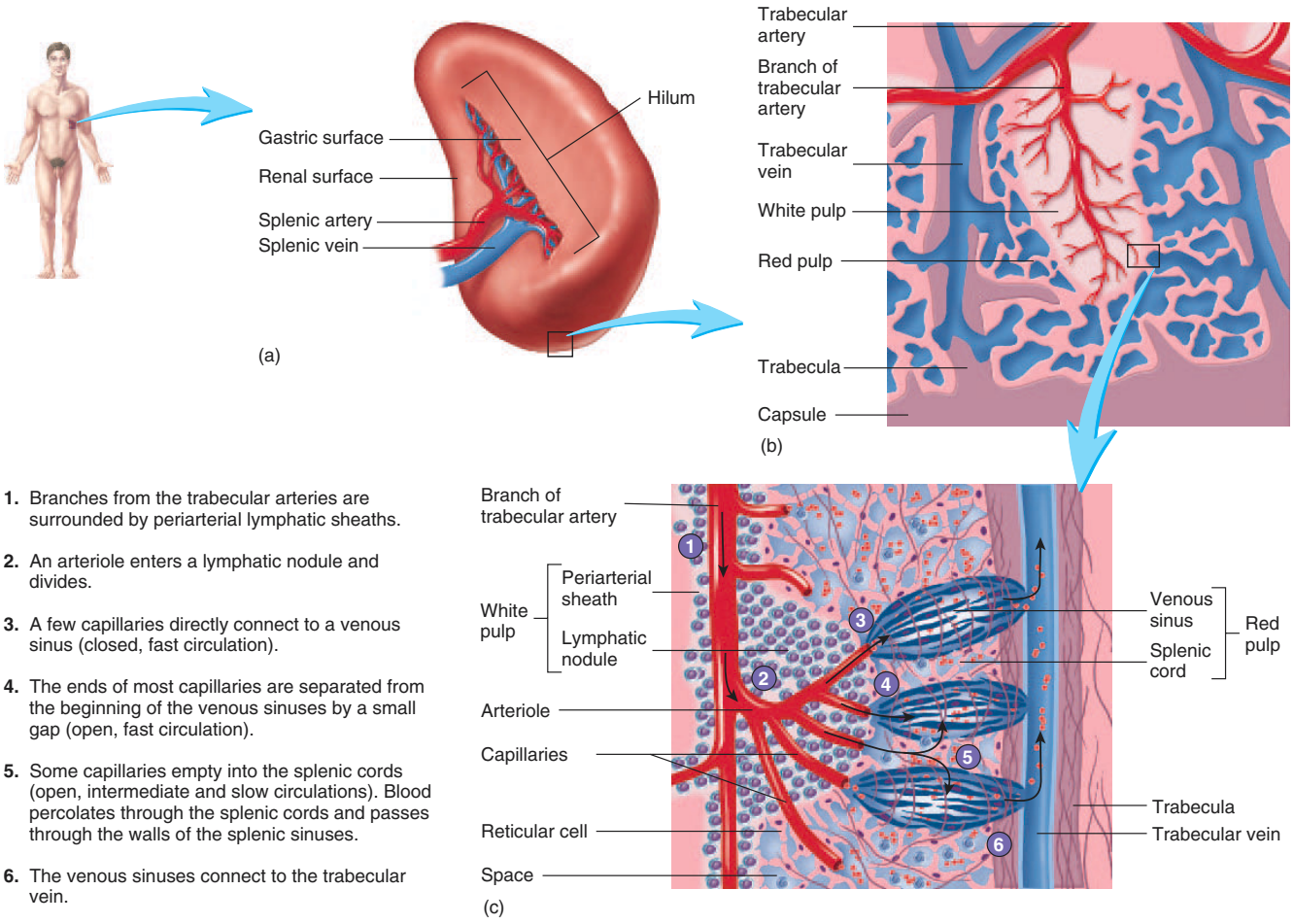


Figure 22.7 Spleen

(*a*) Inferior view of the spleen. (*b*) Section showing the arrangement of arteries, veins, white pulp, and red pulp. White pulp is associated with arteries, and red pulp is associated with veins. (*c*) Blood flow through white and red pulp. (*d*) Histology of spleen.

Thymus

The **thymus** (thī′mŭs) is a bilobed gland (figure 22.8) located in the superior mediastinum, the partition dividing the thoracic cavity into left and right parts. It was once thought that the thymus increases in size until puberty, after which it dramatically decreases in size. It's now believed that the thymus increases in size until the first year of life, after which it remains approximately the same size, even though the size of the individual increases. After 60 years of age, it decreases in size, and in older adults, the thymus may be so small that it is difficult to find during dissection. Although the size of the thymus is fairly constant throughout much of life, by 40 years of age much of the thymic lymphatic tissue has been replaced with adipose tissue.

Each lobe of the thymus is surrounded by a thin connective tissue **capsule. Trabeculae** extend from the capsule into the substance of the gland, dividing it into **lobules.** Unlike other lymphatic tissue, which has a fibrous network of reticular fibers, the framework of thymic tissue consists of epithelial cells. The

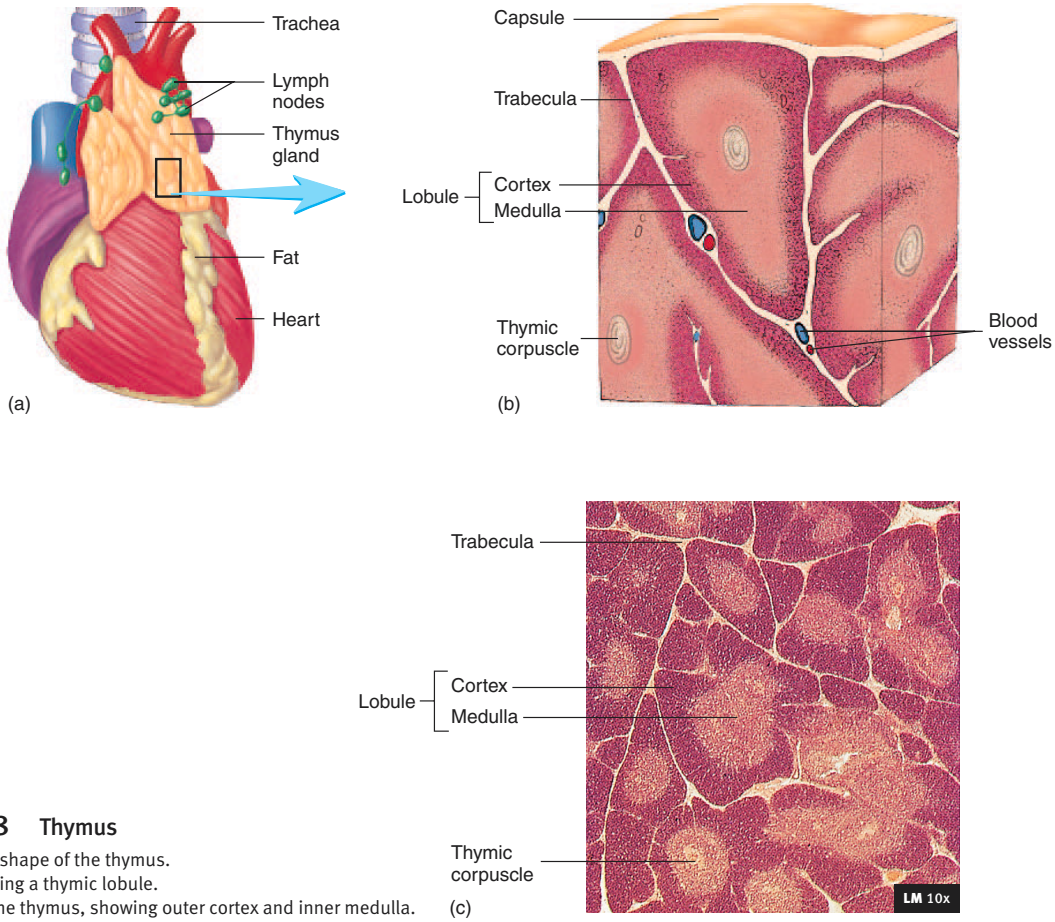


Figure 22.8 Thymus

(*a*) Location and shape of the thymus.
(*b*) Section showing a thymic lobule.
(*c*) Histology of the thymus, showing outer cortex and inner medulla.

processes of the epithelial cells are joined by desmosomes, and the cells form small, irregularly shaped compartments filled with lymphocytes. Near the capsule and trabeculae, the lymphocytes are numerous and form dark staining areas of the lobules called the **cortex.** A lighter staining central portion of the lobules, called the **medulla,** has fewer lymphocytes. The medulla also contains rounded epithelial structures, called **thymic corpuscles** (Hassall's corpuscles), whose function is unknown.

The thymus is the site of maturation of certain lymphocytes called T cells. Large numbers of lymphocytes are produced in the thymus, but most degenerate. The lymphocytes that survive the maturation process are capable of reacting to foreign substances, but they normally do not react to and destroy healthy body cells (see the "Origin and Development of Lymphocytes" on p. 786). These surviving thymic lymphocytes migrate to the medulla, enter the blood, and travel to other lymphatic tissues.

11. *Where are lymph nodes found? Describe the parts of a lymph node and explain how lymph flows through a lymph node.*
12. *What are the functions of lymph nodes? How is this accomplished? What is a germinal center?*
13. *Where is the spleen located? Name the two components of white pulp. Of red pulp.*
14. *Explain the fast, intermediate, and slow flow of blood through the spleen.*
15. *What are three functions of the spleen?*
16. *Where is the thymus located? Describe its structure. What is the blood–thymic barrier? How is it related to the function of the thymus?*

Immunity

Objective

- *Describe the two major categories of immunity.*

Immunity is the ability to resist damage from foreign substances such as microorganisms and harmful chemicals. Immunity is categorized as **innate immunity** (also called nonspecific resistance) or **adaptive immunity** (also called specific immunity). In innate immunity, the body recognizes and destroys certain foreign substances, but the response to them is the same each time the body is exposed to them. In adaptive immunity, the body recognizes and destroys foreign substances, but the response to them improves each time the foreign substance is encountered.

Clinical Focus Disorders of the Lymphatic System

It's not surprising that many infectious diseases produce symptoms associated with the lymphatic system. The lymphatic system is involved with the production of lymphocytes, which fight infectious diseases, and the lymphatic system filters blood and lymph to remove microorganisms. **Lymphadenitis** (lim-fad′ĕ-nī′tis) is an inflammation of the lymph nodes, which causes them to become enlarged and tender. This inflammation is an indication that microorganisms are being trapped and destroyed within the lymph nodes. Somtimes the lymphatic vessels become inflamed to produce **lymphangitis** (lim-fan-jī′tis). This often results in visible red streaks in the skin that extend away from the site of infection. If microorganisms pass through the lymphatic vessels and nodes to reach the blood, **septicemia** (sep-ti-sē′mē-ă), or blood poisoning, can result (see chapter 19).

Bubonic plague and elephantiasis are diseases of the lymphatic system. **Bubonic** (boo-bon′ik) **plague** is caused by bacteria *(Yersinia pestis)*, which are transferred to humans from rats by the bite of the rat flea *(Xenopsylla)*. The bacteria localize in the lymph nodes, causing them to enlarge. The term *bubonic* is derived from a Greek word referring to the groin because the disease often causes the inguinal lymph nodes of the groin to swell. Without treatment, the bacteria enter the blood, multiply, and infect tissues throughout the body, rapidly causing death in 70%–90% of those infected. In the sixth, fourteenth, and nineteenth centuries, the bubonic plague killed large numbers of people in Europe. Because of improved sanitation and the advent of antibiotics, fortunately relatively few cases occur today. **Elephantiasis** (el-ĕ-fan-tī′ă-sis) is caused by long, slender roundworms *(Wuchereria bancrofti)*. The adult worms lodge in the lymphatic vessels and block lymph flow. The resulting accumulation of fluid in the interstitial spaces and lymphatic vessels can cause permanent swelling and enlargement of a limb. The affected limb supposedly resembles an elephant's leg, providing the basis for the name of the disease. The offspring of the adult worms pass through the lymphatic system into the blood, from which they can be transferred to another human by mosquitoes.

A **lymphoma** (lim-fō′mă) is a neoplasm (tumor) of lymphatic tissue. Lymphomas are usually divided into two groups: (1) Hodgkin's disease and (2) all other lymphomas, which are called non-Hodgkin's lymphomas. Typically, lymphomas begin as an enlarged, painless mass of lymph nodes. The immune system is depressed, and the patient has an increased susceptibility to infections. Enlargement of the lymph nodes can also compress surrounding structures and produce complications. Fortunately, treatment with drugs and radiation is effective for many people who suffer from lymphoma.

Specificity and memory are characteristics of adaptive immunity but not innate immunity. **Specificity** is the ability of adaptive immunity to recognize a particular substance. For example, innate immunity can act against bacteria in general, whereas adaptive immunity can distinguish among different kinds of bacteria. **Memory** is the ability of adaptive immunity to remember previous encounters with a particular substance and, as a result, to respond to it more rapidly.

In innate immunity, each time the body is exposed to a substance, the response is the same because specificity and memory of previous encounters is not present. For example, each time a bacterial cell is introduced into the body, it is phagocytized with the same speed and efficiency. In adaptive immunity, the response during the second exposure is faster and stronger than the response to the first exposure because the immune system remembers the bacteria from the first exposure. For example, following initial exposure to the bacteria, the body can take many days to destroy them. During this time, the bacteria damage tissues and produce the symptoms of disease. After the second exposure to the same bacteria, however, the response is very rapid and effective. Bacteria are destroyed before any symptoms develop, and the person is said to be **immune.**

17. *Define the terms immunity, specificity, and memory.*
18. *What are the differences between innate and adaptive immunity?*

Innate Immunity

Objectives

- *Describe the cells and chemicals responsible for innate immunity.*
- *List the events that occur during an inflammatory response, and explain their significance.*

The main components of innate immunity include (1) mechanical mechanisms that prevent the entry of microbes into the body or that physically remove them from body surfaces; (2) chemical mediators that act directly against microorganisms or that activate other mechanisms, leading to the destruction of the microorganisms; and (3) cells involved in phagocytosis and the production of chemicals that participate in the response of the immune system.

Mechanical Mechanisms

Mechanical mechanisms, such as the skin and mucous membranes, form barriers that prevent the entry of microorganisms and chemicals into the tissues of the body. They also remove microorganisms and other substances from the surface of the body in several ways. The substances are washed from the eyes by tears, from the mouth by saliva, and from the urinary tract by urine. In the respiratory tract, ciliated mucous membranes sweep microbes trapped in the mucus to the back of the throat, where they are

swallowed. Coughing and sneezing also remove microorganisms from the respiratory tract. Microorganisms cannot cause disease if they cannot get into the body.

Chemical Mediators

Chemical mediators are molecules responsible for many aspects of innate immunity (table 22.1). Some chemical mediators found on the surface of cells, such as lysozyme, sebum, and mucus, kill microorganisms or prevent their entry into the cells. Other chemical mediators, such as histamine, complement, prostaglandins, and leukotrienes, promote inflammation by causing vasodilation, increasing vascular permeability, attracting white blood cells, and stimulating phagocytosis. In addition, interferons protect cells against viral infections.

Complement

Complement is a group of about 20 proteins that make up approximately 10% of the globulin part of serum. They include proteins named C1–C9 and factors B, D, and P (properdin). Normally, complement proteins circulate in the blood in an inactive, nonfunctional form. They become activated in the **complement cascade,** a series of reactions in which each component of the series activates the next component (figure 22.9). The complement cascade begins through either the alternative pathway or the classical pathway. The **alternative pathway** is part of innate immunity and is initiated when the complement protein C3 becomes spontaneously active. Activated C3 normally is quickly inactivated by proteins on the surface of the body's cells. Activated C3 can combine with some foreign substances, such as part of a bacterial cell or virus. It can become stabilized and cause activation of the complement cascade. The **classical pathway** is part of the adaptive immune system, discussed on p. 796.

Activated complement proteins provide protection in several ways (see figure 22.9). Five of the complement proteins come together to form a **membrane attack complex (MAC),** which forms a hole in the membrane. When membrane attack complexes form in the plasma membrane of a nucleated cell, Na^+ and water enter the cell through the hole and cause the cell to lysis. When membrane attack complexes form in the outer membrane of certain bacteria (Gram negative), an enzyme called lysozyme passes through the hole and digests the bacterial cell wall. When the wall breaks apart, the bacterial cell undergoes lysis.

Complement proteins can also attach to the surface of bacterial cells and stimulate macrophages to phagocytize the bacteria. In addition, complement proteins attract immune system cells to sites of infection and promote inflammation.

Interferons

Interferons (in-ter-fēr′onz) are proteins that protect the body against viral infection and perhaps some forms of cancer. After a virus infects a cell, viral replication can occur. Viral nucleic acids and proteins, which are produced using the cell's organelles, are assembled into new viruses. The new viruses are released from the infected cell to infect other cells. Because infected cells usually stop their normal functions or die during viral replication, viral infections are clearly harmful to the body. Fortunately, viruses and other

Table 22.1 Chemicals of Innate Immunity and Their Functions

Chemical	Description	Chemical	Description
Surface chemicals	Lysozymes (in tears, saliva, nasal secretions, and sweat) lyse cells; acid secretions (sebum in the skin and hydrochloric acid in the stomach) prevent microbial growth or kill microorganisms; mucus on the mucous membranes traps microorganisms until they can be destroyed	Complement	A group of plasma proteins that increase vascular permeability, stimulate the release of histamine, activate kinins, lyse cells, promote phagocytosis, and attract neutrophils, monocytes, macrophages, and eosinophils
Histamine	An amine released from mast cells, basophils, and platelets; histamine causes vasodilation, increases vascular permeability, stimulates gland secretions (especially mucus and tear production), causes smooth muscle contraction of airway passages (bronchioles) in the lungs, and attracts eosinophils	Prostaglandins	A group of lipids (PGEs, PGFs, thromboxanes, and prostacyclins), produced by mast cells, that cause smooth muscle relaxation and vasodilation, increase vascular permeability, and stimulate pain receptors
Kinins	Polypeptides derived from plasma proteins; kinins cause vasodilation, increase vascular permeability, stimulate pain receptors, and attract neutrophils	Leukotrienes	A group of lipids, produced primarily by mast cells and basophils, that cause prolonged smooth muscle contraction (especially in the lung bronchioles), increase vascular permeability, and attract neutrophils and eosinophils
Interferon	A protein, produced by most cells, that interferes with virus production and infection	Pyrogens	Chemicals, released by neutrophils, monocytes, and other cells, that stimulate fever production

Abbreviations: PGE = prostaglandin E; PGF = prostaglandin F.

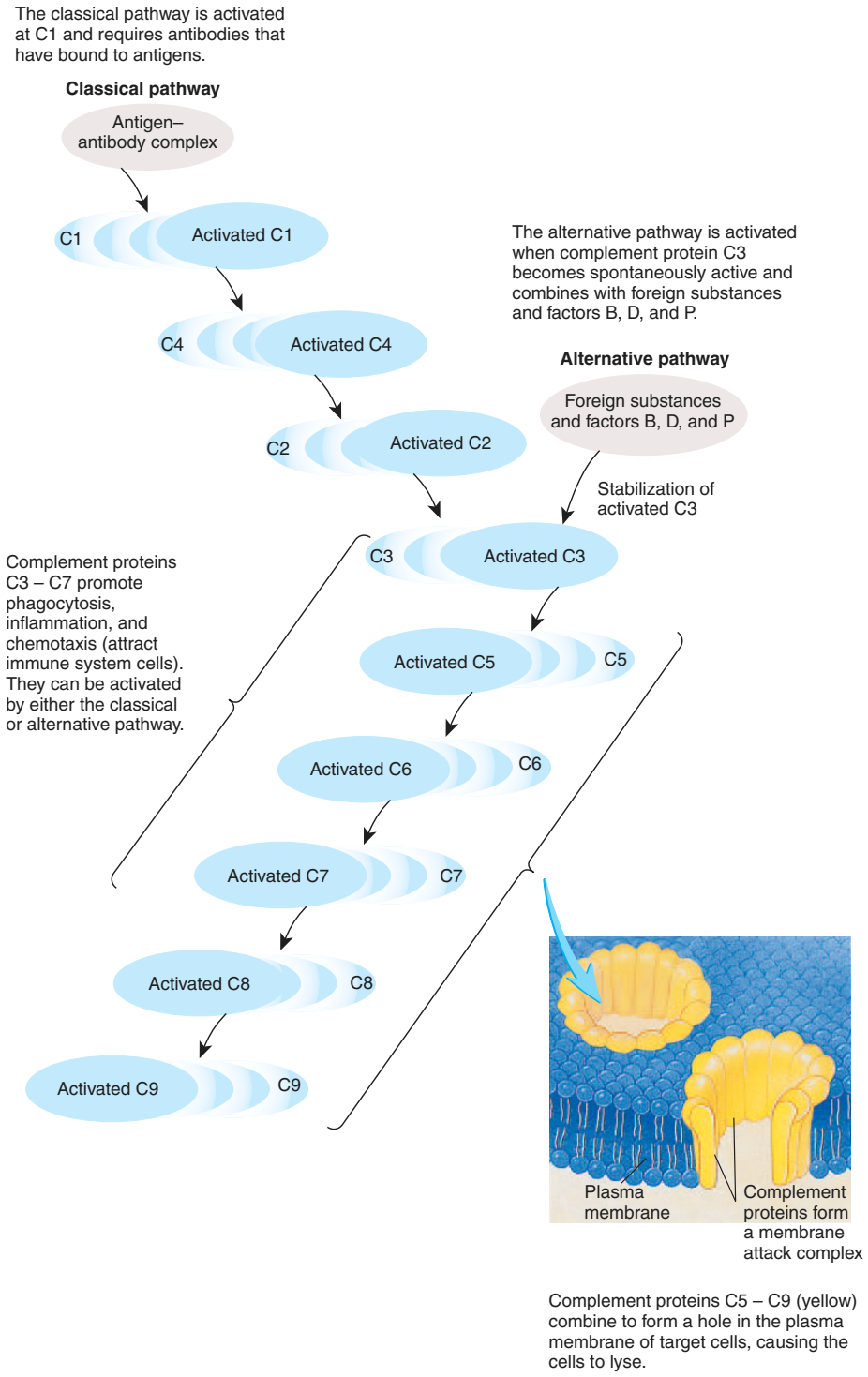


Figure 22.9 Complement Cascade

Inactive complement proteins become active complement proteins (*blue ovals*) in a cascade reaction: each activated complement protein activates the next protein in the sequence.

substances can stimulate infected cells to produce interferons. Interferons neither protect the cell that produces them nor act directly against viruses. Instead, they bind to the surface of neighboring cells, where they stimulate them to produce antiviral proteins. These antiviral proteins stop viral reproduction in the neighboring cells by preventing the production of viral nucleic acids and proteins. Interferon viral resistance is innate rather than adaptive, and the same interferons act against many different viruses. Infection by one kind of virus actually can produce protection against infection by other kinds of viruses. Some interferons also play a role in the activation of immune cells such as macrophages and natural killer cells.

Treating Viral Infections and Cancer with Interferons

Because some cancers are induced by viruses, interferons may play a role in controlling cancers. Interferons activate macrophages and natural killer cells (a type of lymphocyte), which attack tumor cells. Through genetic engineering, interferons currently are produced in sufficient quantities for clinical use and, along with other therapies, have been effective in treating certain viral infections and cancers. For example, interferons are used to treat hepatitis C, a viral disorder that can cause cirrhosis and cancer of the liver, and to treat genital warts, caused by the herpes virus. Interferons are also approved for the treatment of Kaposi's sarcoma, a cancer that can develop in AIDS patients.

19. *List the three main components of innate immunity.*
20. *Name two mechanical mechanisms that form barriers preventing the entry of microorganisms. In what ways are microorganisms removed from the surfaces of the body?*
21. *What is complement? In what two ways is it activated? How does complement provide protection?*
22. *What are interferons? How do they provide protection against viruses?*

Cells

White blood cells and the cells derived from them (see table 19.2) are the most important cellular components of the immune system (table 22.2). White blood cells are produced in red bone marrow and lymphatic tissue and are released into the blood, where they are transported throughout the body. To be effective, white blood cells must move into the tissues where they are needed. **Chemotactic** (kē-mō-tak′tik) **factors** are parts of microbes or chemicals released by tissue cells that act as chemical signals to attract white blood cells. Important chemotactic factors include complement, leukotrienes, kinins, and histamine. They diffuse from the area where they are released. White blood cells can detect small differences in chemotactic factor concentration and move from areas of lower chemotactic factor concentration to areas of higher concentration. Thus, they move toward the source of these substances, an ability called **chemotaxis.** White blood cells can move by ameboid

Table 22.2 Immune System Cells and Their Primary Functions

Cell	Primary Function	Cell	Primary Function
Innate Immunity		**Adaptive Immunity**	
Neutrophil	Phagocytosis and inflammation; usually the first cell to leave the blood and enter infected tissues	B cell	After activation, differentiates to become plasma cell or memory B cell
Monocyte	Leaves the blood and enters tissues to become a macrophage	Plasma cell	Produces antibodies that are directly or indirectly responsible for the destruction of the antigen
Macrophage	Most effective phagocyte; important in later stages of infection and in tissue repair; located throughout the body to "intercept" foreign substances; processes antigens; involved in the activation of B and T cells	Memory B cell	Quick and effective response to an antigen against which the immune system has previously reacted; responsible for immunity
Basophil	Motile cell that leaves the blood, enters tissues, and releases chemicals that promote inflammation	Cytotoxic T cell	Responsible for the destruction of cells by lysis or by the production of cytokines
Mast cell	Nonmotile cell in connective tissues that promotes inflammation through the release of chemicals	Delayed hypersensitivity T cell	Produces cytokines that promote inflammation
Eosinophil	Enters tissues from the blood and releases chemicals that inhibit inflammation	Helper T cell	Activates B and effector T cells
Natural killer cell	Lyses tumor and virus-infected cells	Suppressor T cell	Inhibits B and effector T cells
		Memory T cell	Quick and effective response to an antigen against which the immune system has previously reacted; responsible for adaptive immunity
		Dendritic cell	Processes antigen and is involved in the activation of B and T cells

movement over the surface of cells, can squeeze between cells, and sometimes pass directly through other cells.

Phagocytosis (fag-ō-sī-tō′sis) is the endocytosis and destruction of particles by cells called **phagocytes** (see figure 3.21). The particles can be microorganisms or their parts, foreign substances, or dead cells from the individual's body. The most important phagocytic cells are neutrophils and macrophages.

Neutrophils

Neutrophils are small phagocytic cells produced in large numbers in red bone marrow that are released into the blood, where they circulate for a few hours. Approximately 126 billion neutrophils per day leave the blood and pass through the wall of the gastrointestinal tract, where they provide phagocytic protection. The neutrophils are then eliminated as part of the feces. Neutrophils are usually the first cells to enter infected tissues, and they often die after a single phagocytic event.

Neutrophils also release lysosomal enzymes that kill microorganisms and also cause tissue damage and inflammation. **Pus** is an accumulation of dead neutrophils, dead microorganisms, debris from dead tissue, and fluid.

Macrophages

Macrophages are monocytes that leave the blood, enter tissues, enlarge about fivefold, and increase their number of lysosomes and mitochondria. They are large phagocytic cells that outlive neutrophils, and they can ingest more and larger phagocytic particles than neutrophils. Macrophages usually accumulate in tissues after neutrophils and are responsible for most of the phagocytic activity in the late stages of an infection, including the cleanup of dead neutrophils and other cellular debris. In addition to their phagocytic role, macrophages produce a variety of chemicals, such as interferons, prostaglandins, and complement, that enhance the immune response.

Macrophages are beneath the free surfaces of the body, such as the skin (dermis), hypodermis, mucous membranes, and serous membranes, and around blood and lymphatic vessels. In these locations, macrophages provide protection by trapping and destroying microorganisms entering the tissues.

If microbes do gain entry to the blood or lymphatic system, macrophages are waiting within enlarged spaces, called sinuses, to phagocytize them. Blood vessels in the spleen, bone marrow, and liver have sinuses, as do lymph nodes. Within the sinuses, reticular cells produce a fine network of reticular fibers that slows the flow of blood or lymph and provides a large surface area for the attachment of macrophages. In addition, macrophages are on the endothelial lining of the sinuses.

Because macrophages on the reticular fibers and endothelial lining of the sinuses were among the first macrophages studied, these cells were referred to as the **reticuloendothelial system.** It's now recognized that macrophages are derived from monocytes and are in locations other than the sinuses. Because monocytes and macrophages have a single, unlobed nucleus, they are now called the **mononuclear phagocytic system.** Sometimes macrophages are given specific names, for instance dust cells in the lungs, Kupffer cells in the liver, and microglia in the central nervous system.

Basophils, Mast Cells, and Eosinophils

Basophils, which are derived from red bone marrow, are motile white blood cells that can leave the blood and enter infected tissues. **Mast cells,** which are also derived from red bone marrow, are nonmotile cells in connective tissue, especially near capillaries. Like macrophages, mast cells are located at potential points of entry of microorganisms into the body, such as the skin, lungs, gastrointestinal tract, and urogenital tract.

Basophils and mast cells can be activated through innate immunity (e.g., by complement) or through adaptive immunity (see "Antibodies" on p. 793). When activated, they release chemicals, for example, histamine and leukotrienes, that produce an inflammatory response or activate other mechanisms, for example, smooth muscle contraction in the lungs.

Eosinophils are produced in red bone marrow, enter the blood, and within a few minutes enter tissues. Enzymes released by eosinophils break down chemicals released by basophils and mast cells. Thus, at the same time that inflammation is initiated, mechanisms are activated that contain and reduce the inflammatory response. This process is similar to the blood clotting system in which clot prevention and removal mechanisms are activated while the clot is being formed (see chapter 19). In patients with parasitic infections or allergic reactions with much inflammation, eosinophil numbers greatly increase. Eosinophils also secrete enzymes that effectively kill some parasites.

Natural Killer Cells

Natural killer (NK) cells are a type of lymphocyte produced in red bone marrow, and they account for up to 15% of lymphocytes. NK cells recognize classes of cells, such as tumor cells or virus-infected cells in general, rather than specific tumor cells or cells infected by a specific virus. For this reason and because NK cells don't exhibit a memory response, they are classified as part of innate immunity. NK cells use a variety of methods to kill their target cells, including the release of chemicals that damage plasma membranes, causing the cells to lyse.

23. *Define the terms chemotactic factor, chemotaxis, and phagocytosis.*
24. *What are the functions of neutrophils and macrophages? What is pus?*
25. *What effects are produced by the chemicals released from basophils, mast cells, and eosinophils?*
26. *Describe the function of NK cells.*

Inflammatory Response

The **inflammatory response** is a complex sequence of events involving many of the chemical mediators and cells of innate immunity. Tissue injury, regardless of the type, can cause inflammation. Trauma, burns, chemicals, or infections can damage tissues, resulting in inflammation. A bacterial infection is used here to illustrate an inflammatory response (figure 22.10). The bacteria, or damage to tissues, cause the release or activation of chemical mediators, such as histamine, prostaglandins, leukotrienes, complement, kinins, and others. The chemical mediators produce several effects: (1) vasodilation, which increases blood flow and brings phagocytes and other white blood cells to the area; (2) chemotactic attraction

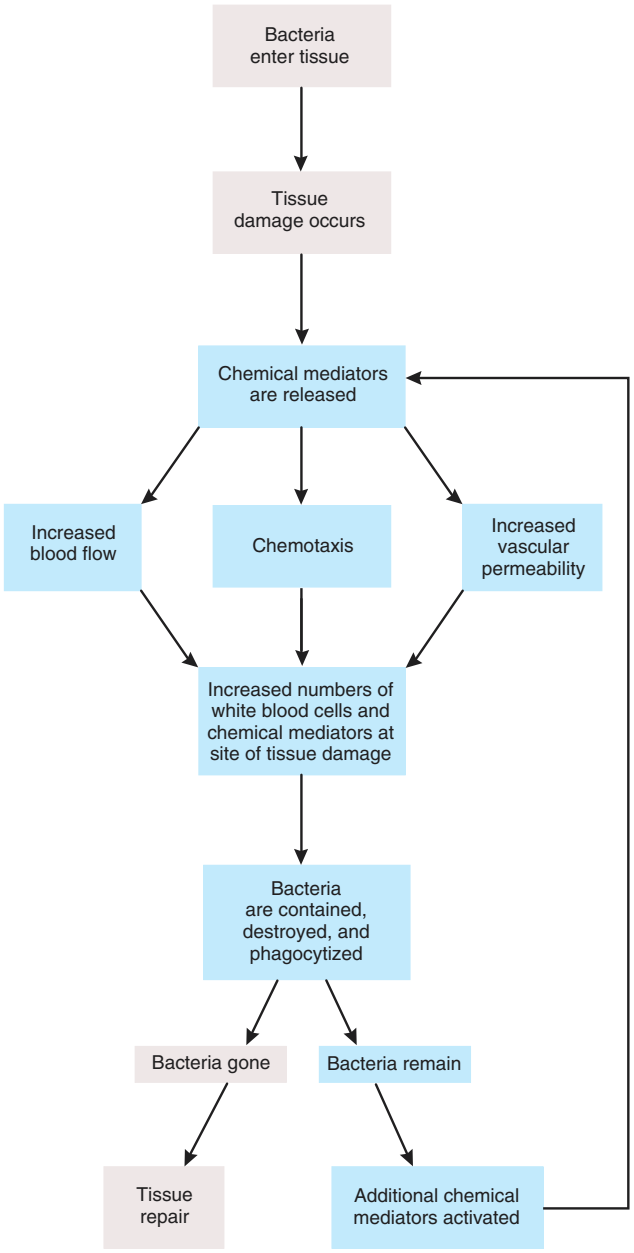


Figure 22.10 Inflammatory Response

Flow diagram of the inflammatory response. Bacteria cause tissue damage and release of chemical mediators that initiate inflammation, resulting in the destruction of the bacteria.

of phagocytes, which leave the blood and enter the tissue; and (3) increased vascular permeability, which allows fibrinogen and complement to enter the tissue from the blood. Fibrinogen is converted to fibrin, which prevents the spread of infection by walling off the infected area. Complement further enhances the inflammatory response and attracts additional phagocytes. The process of releasing chemical mediators and attracting phagocytes and other white blood cells continues until the bacteria are destroyed. Phagocytes (mainly macrophages) remove microorganisms and dead tissue, and the damaged tissues are repaired.

Inflammation can be localized or systemic. **Local inflammation** is an inflammatory response confined to a specific area of the body (see chapter 4). Symptoms of local inflammation include redness, heat, swelling, pain, and loss of function. Redness, heat, and swelling result from increased blood flow and increased vascular permeability. Pain is caused by swelling and by chemicals acting on pain receptors. Loss of function results from tissue destruction, swelling, and pain.

Systemic inflammation is an inflammatory response that occurs in many parts of the body. In addition to the local symptoms at the sites of inflammation, three additional features can be present. First, red bone marrow produces and releases large numbers of neutrophils, which promote phagocytosis. Second, **pyrogens** (pī′rō-jenz, fire producing), chemicals released by microorganisms, macrophages, neutrophils, and other cells, stimulate fever production. Pyrogens affect the body's temperature-regulating mechanism in the hypothalamus, heat is conserved, and body temperature increases. Fever promotes the activities of the immune system, such as phagocytosis, and inhibits the growth of some microorganisms. Third, in severe cases of systemic inflammation, increased vascular permeability is so widespread that large amounts of fluid are lost from the blood into the tissues. The decreased blood volume can cause shock and death.

27. *Describe the events that take place during an inflammatory response.*
28. *What are the symptoms of local and systemic inflammations?*

Adaptive Immunity

Objectives

- *Explain the origin, development, activation, and inhibition of lymphocytes.*
- *Describe antibody-mediated immunity, including the structure, types, and effects of antibodies.*
- *Describe cell-mediated immunity and the functions of T cells.*

Adaptive immunity involves the ability to recognize, respond to, and remember a particular substance. Substances that stimulate adaptive immunity are called **antigens** (an′ti-jenz). They usually are large molecules with a molecular weight of 10,000 or more. **Haptens** (hap′tenz) are small molecules (low molecular weight) capable of combining with larger molecules like blood proteins to stimulate an adaptive immune system response.

Allergic Reactions to Penicillin

Penicillin is an example of a hapten of clinical importance. It's a small molecule that doesn't evoke an immune system response. Penicillin can, however, break down and bind to serum proteins to form a combined molecule that can produce an allergic reaction. Most commonly, the reaction produces a rash and fever, but rarely a severe reaction can cause death.

Antigens are divided into two groups: foreign antigens and self-antigens. **Foreign antigens** are not produced by the body but are introduced from outside it. Components of bacteria, viruses, and other microorganisms are examples of foreign antigens that cause disease. Pollen, animal dander (scaly, dried skin), feces of house dust mites, foods, and drugs are also foreign antigens and can trigger an overreaction of the immune system in some people, called an **allergic reaction.** Transplanted tissues and organs that contain foreign antigens result in the rejection of the transplant. **Self-antigens** are molecules produced by the body that stimulate an adaptive immune system response. The response to self-antigens can be beneficial or harmful. For example, the recognition of tumor antigens can result in tumor destruction, whereas **autoimmune disease** can result when self-antigens stimulate unwanted tissue destruction.

Adaptive immunity historically has been divided into two types: **humoral** (hū′mōr-ăl) and **cell-mediated immunity.** Early investigators of the immune system found that, when plasma from an immune animal was injected into the blood of a nonimmune animal, the nonimmune animal became immune. Because this process involved body fluids (humors), it was called humoral immunity. It was also discovered that blood cells transferred from an immune animal could be responsible for immunity, and this process was called cell-mediated immunity.

It's now known that immunity results from the activities of lymphocytes called B and T cells (see table 22.2). **B cells** give rise to cells that produce proteins called **antibodies,** which are found in the plasma. Humoral immunity is now called **antibody-mediated immunity** because antibodies are responsible.

T cells are responsible for cell-mediated immunity. Several subpopulations of T cells exist, each of which is responsible for a particular aspect of cell-mediated immunity. For example, **effector T cells,** such as **cytotoxic T cells** and **delayed hypersensitivity T cells,** are responsible for producing the effects of cell-mediated immunity; whereas **regulatory T cells,** such as **helper T cells** and **suppressor T cells,** can promote or inhibit the activities of both antibody-mediated immunity and cell-mediated immunity.

Table 22.3 summarizes and contrasts the main features of innate, antibody-mediated, and cell-mediated immunity.

29. *Define the terms antigen and hapten. Distinguish between a foreign antigen and a self-antigen.*
30. *What are allergic reactions and autoimmune diseases?*

Origin and Development of Lymphocytes

All blood cells, including lymphocytes, are derived from stem cells in the red bone marrow (see chapter 19). The process of blood cell formation begins during embryonic development and continues throughout life. Some stem cells give rise to pre-T cells that migrate through the blood to the thymus, where they divide and are processed into T cells. The thymus produces hormones such as thymosin, which stimulates T-cell maturation. Other stem cells produce pre-B cells, which are processed in the red bone marrow into B cells (figure 22.11). A **positive selection** process results in the survival of pre-B and pre-T cells that are capable of an immune response. Cells that are incapable of an immune response die.

The B and T cells that can respond to antigens are composed of small groups of identical lymphocytes called **clones.** Although

Table 22.3 Comparison of Innate Immunity, Antibody-Mediated Immunity, and Cell-Mediated Immunity

Characteristics	Innate Immunity	Antibody-Mediated Immunity	Cell-Mediated Immunity
Primary cells	Neutrophils, eosinophils, basophils, mast cells, monocytes, and macrophages	B cells	T cells
Origin of cells	Red bone marrow	Red bone marrow	Red bone marrow
Site of maturation	Red bone marrow (neutrophils, eosinophils, basophils, monocytes) and tissues (mast cells and macrophages)	Red bone marrow	Thymus
Location of mature cells	Blood, connective tissue, and lymphatic tissue	Blood and lymphatic tissue	Blood and lymphatic tissue
Primary secretory products	Histamine, kinins, complement, prostaglandins, leukotrienes, and interferon	Antibodies	Cytokines
Primary actions	Inflammatory response and phagocytosis	Protection against extracellular antigens (bacteria, toxins, parasites, and viruses outside of cells)	Protection against intracellular antigens (viruses, intracellular bacteria, and intracellular fungi) and tumors: regulates antibody-mediated immunity and cell-mediated immunity responses (helper T and suppressor T cells)
Hypersensitivity reactions	None	Immediate hypersensitivity (atopy, anaphylaxis, cytotoxic reactions, and immune complex disease)	Delayed hypersensitivity (allergy of infection and contact hypersensitivity)

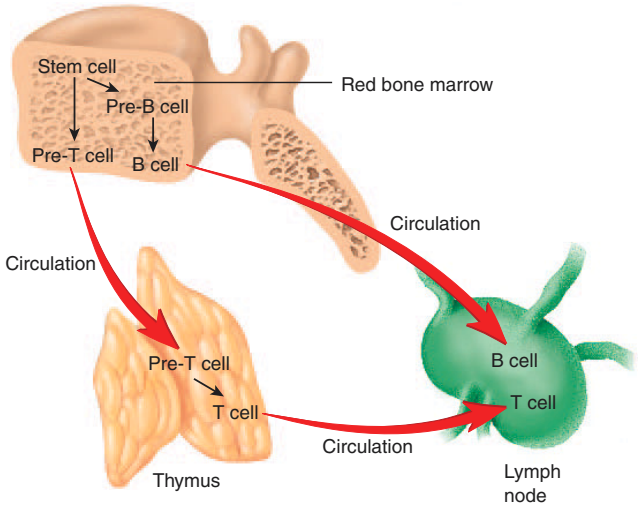


Figure 22.11 Origin and Processing of B and T Cells

Both B and T cells originate in red bone marrow. B cells are processed in the red marrow, whereas T cells are processed in the thymus. Both cell types circulate to other lymphatic tissues, where they can divide and increase in number in response to antigens.

each clone can respond only to a particular antigen, such a large number of clones exist that the immune system can react to most molecules. Some of the clones can also respond to self-antigens. A **negative selection** process eliminates or suppresses clones acting against self-antigens, thereby preventing the destruction of self-cells. Although the negative selection process mostly occurs during prenatal development, it continues throughout life (see section on "Inhibition of Lymphocytes" on p. 792).

B cells are released from red bone marrow, T cells are released from the thymus, and both types of cells move through the blood to lymphatic tissue. There are approximately five T cells for every B cell in the blood. These lymphocytes live for a few months to many years and continually circulate between the blood and the lymphatic tissues. Antigens can come into contact with and activate lymphocytes, resulting in cell divisions that increase the number of lymphocytes that can recognize the antigen. These lymphocytes can circulate in blood and lymph to reach antigens in tissues throughout the body.

The **primary lymphatic organs** are the sites where lymphocytes mature into functional cells. These organs are the red bone marrow and thymus. The **secondary lymphatic organs and tissues** are the sites where lymphocytes interact with each other, antigen-presenting cells, and antigens to produce an immune response. The secondary lymphatic organs and tissues include diffuse lymphatic tissue, lymphatic nodules, tonsils, lymph nodes, and the spleen.

31. *Describe the origin and development of B and T cells.*
32. *What are lymphocyte clones? Distinguish between positive and negative lymphocyte selection.*
33. *What are primary and secondary lymphatic organs and tissues?*

Activation of Lymphocytes

Antigens activate lymphocytes in different ways, depending on the type of lymphocyte and the type of antigen involved. Despite these differences, however, two general principles of lymphocyte activation exist: (1) lymphocytes must be able to recognize the antigen, and (2) after recognition, the lymphocytes must increase in number to effectively destroy the antigen.

Antigenic Determinants and Antigen Receptors

If an adaptive immune system response is to occur, lymphocytes must recognize an antigen. Lymphocytes don't interact with an entire antigen, however. Instead, **antigenic determinants,** or **epitopes** (ep′i-tōpz), are specific regions of a given antigen recognized by a lymphocyte, and each antigen has many different antigenic determinants (figure 22.12). All the lymphocytes of a given clone have on their surfaces identical proteins called **antigen receptors,** which combine with a specific antigenic determinant. The immune system response to an antigen with a particular antigenic determinant is similar to the lock-and-key model for enzymes (see chapter 2), and any given antigenic determinant can combine only with a specific antigen receptor. The **T-cell receptor** consists of two polypeptide chains, which are subdivided into a variable and a constant region (figure 22.13). The variable region can bind to an antigen. The many different types of T-cell receptors respond to different antigens because they have different variable regions. The **B-cell receptor** consists of four polypeptide chains with two identical variable regions. It is a type of antibody and is considered in greater detail on p. 793.

Major Histocompatibility Complex Molecules

Although some antigens bind to their receptors and directly activate B cells and some T cells, most lymphocyte activation involves glycoproteins on the surfaces of cells called **major histocompatibility complex (MHC) molecules.** MHC molecules are attached to plasma membranes, and they have a variable region that can bind to foreign and self-antigens.

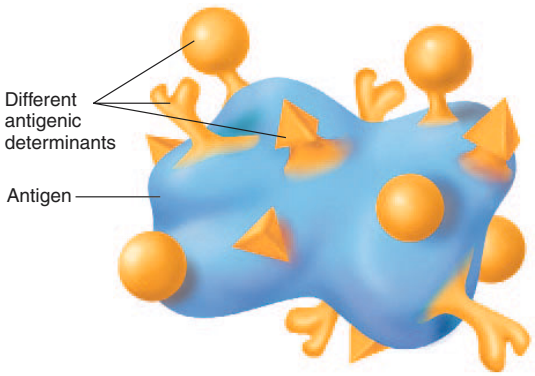


Figure 22.12 Antigenic Determinants

An antigen has many antigenic determinants to which lymphocytes can respond.

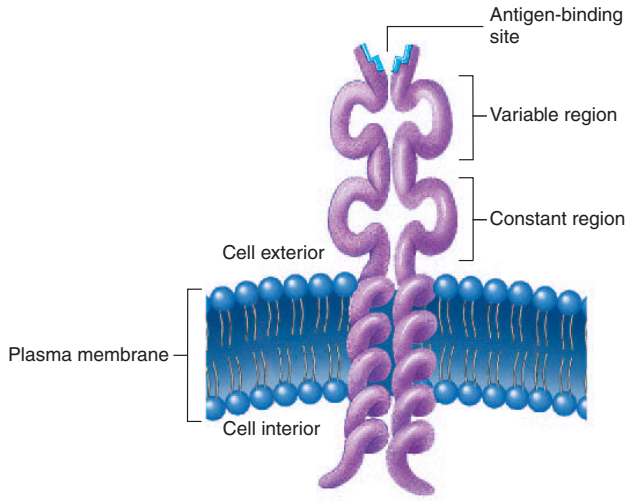


Figure 22.13 The T-Cell Receptor

The T-cell receptor consists of two polypeptide chains. The variable region of each type of T-cell receptor is specific for a given antigen. The constant region attaches the T-cell receptor to the plasma membrane.

MHC class I molecules are found on nucleated cells and function to display antigens produced inside the cells on their surfaces (figure 22.14*a*). This is necessary because the immune system cannot directly respond to an antigen inside a cell. For example, viruses reproduce inside cells, forming viral proteins that are foreign antigens. Some of these viral proteins are broken down in the cytoplasm. The protein fragments enter the rough endoplasmic reticulum and combine with MHC class I molecules to form complexes that move through the Golgi apparatus to be distributed on the surface of the cell (see chapter 3).

MHC class I/antigen complexes on the surface of cells can bind to T-cell receptors on the surface of T cells. This combination is a signal that activates T cells. As described later in this chapter, activated T cells can destroy infected cells, which effectively stops viral replication. Thus, the MHC class I/antigen complex functions as a signal, or "red flag," that prompts the immune system to destroy the displaying cell. In essence, the cell is displaying a sign that says, "Kill me!" This process is said to be **MHC-restricted,** because both the antigen and the individual organism's own MHC molecule are required.

P R E D I C T 2

In mouse A, T cells can respond to virus X. If these T cells are transferred to mouse B, which is infected with virus X, will the T cells respond to the virus? Explain.

The same process that moves foreign protein fragments to the surface of cells can also inadvertently transport self-protein fragments (see figure 22.14*a*). As part of normal protein metabolism, cells continually break down old proteins and synthesize new ones. Some self-protein fragments that result from protein breakdown can combine with MHC class I molecules and be displayed on the surface of the cell, thus becoming self-antigens. Normally, the immune system doesn't respond to self-antigens in combination with MHC molecules because the lymphocytes that could respond have been eliminated or inactivated (see section on "Inhibition of Lymphocytes" on p. 792).

MHC class II molecules are found on **antigen-presenting cells,** which include B cells, macrophages, monocytes, and dendritic cells. **Dendritic** (den-drit′ik) **cells** are large, motile cells with long cytoplasmic extensions, and they are scattered throughout most tissues (except the brain), with their highest concentrations in lymphatic tissues and the skin. Dendritic cells in the skin are often called **Langerhans' cells.**

Antigen-presenting cells are specialized to take in foreign antigens, to process the antigens, and to use MHC class II molecules to display the foreign antigens to other immune system cells (figure 22.14*b*). For example, the MHC class II/antigen complex can bind with a T-cell receptor. Because both the antigen and the individual's own MHC class II molecule are required, this process is said to be MHC-restricted. Unlike MHC class I molecules, however, this display does not result in the destruction of the antigen-presenting cell. Instead the MHC class II/antigen complex is a "rally around the flag" signal that stimulates other immune system cells to respond to the antigen. The displaying cell is like Paul Revere, who spread the alarm for the militia to arm and organize. The militia then went out and killed the enemy. For example, when the lymphocytes of the B-cell clone that can recognize the antigen come into contact with the MHC class II/antigen complex, they are stimulated to divide. The activities of these lymphocytes, such as the production of antibodies, then result in the destruction of the antigen.

34. *Define the terms antigenic determinant and antigen receptor. How are they related to each other?*
35. *What type of antigens are displayed by MHC class I and II molecules?*
36. *What type of cells display MHC class I and II antigen complexes, and what happens as a result?*
37. *Define MHC-restricted.*

P R E D I C T 3

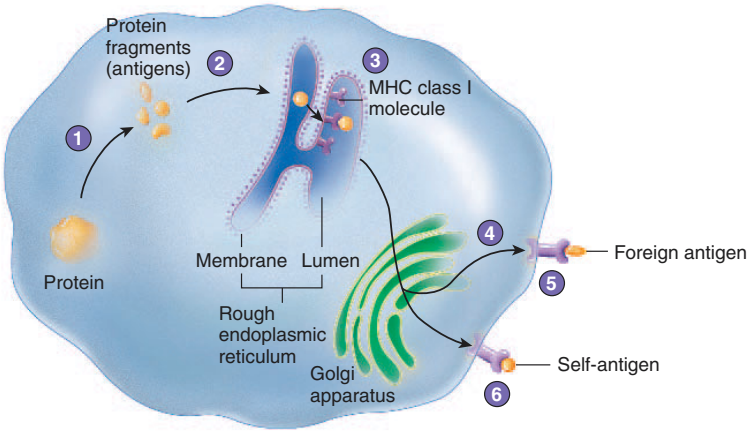
How does elimination of the antigen stop the production of antibodies?

Costimulation

The combination of an MHC class II/antigen complex with an antigen receptor is usually only the first signal necessary to produce a response from a B or T cell. In many cases, **costimulation** by additional signals is also required. Costimulation is accomplished by molecules released from cells and by molecules attached to the surface of cells. **Cytokines** (sī′tō-kīnz), which are proteins or peptides secreted by one cell as a regulator of neighboring cells, promote costimulation (figure 22.15*a*). Cytokines produced by lymphocytes are often called **lymphokines** (lim′fō-kīnz). Cytokines are involved in the regulation of immunity, inflammation, tissue repair, cell growth, and other processes. Table 22.4 lists important cytokines and their functions.

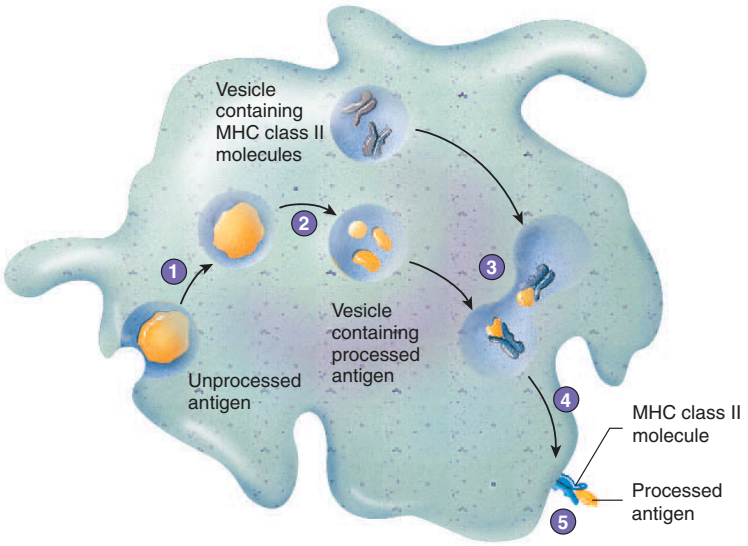
1. Foreign proteins or self-proteins within the cytosol are broken down into fragments that are antigens.
2. Antigens are transported into the rough endoplasmic reticulum.
3. Antigens combine with MHC class I molecules.
4. The MHC class I/antigen complex is transported to the Golgi apparatus, packaged into a vesicle, and transported to the plasma membrane.
5. Foreign antigens combined with MHC class I molecules stimulate cell destruction.
6. Self-antigens combined with MHC class I molecules do not stimulate cell destruction.

(a)



1. The unprocessed extracellular antigen is ingested by endocytosis and is within a vesicle.
2. The antigen is broken down into fragments to form processed antigens.
3. The vesicle containing the processed antigen fuses with vesicles produced by the Golgi apparatus that contain MHC class II molecules. The processed antigen and the MHC class II molecule combine.
4. The MHC class II/antigen complex is transported to the plasma membrane.
5. The displayed MHC class II/antigen complex can stimulate immune cells.

(b)



Process Figure 22.14 Antigen Processing

(*a*) Foreign proteins, such as viral proteins, or self-proteins in the cytosol, are processed and presented at the cell surface by MHC class I molecules. (*b*) Extracellular antigens are taken into an antigen-presenting cell, processed, and presented at the cell surface by MHC class II molecules.

Certain pairs of surface molecules can also be involved in costimulation (figure 22.15*b*). When the surface molecule on one cell combines with the surface molecule on another, the combination can act as a signal that stimulates a response from one of the cells, or the combination can hold the cells together. Typically, several different kinds of surface molecules are necessary to produce a response. For example, a molecule called B7 on macrophages must bind with a molecule called CD28 on helper T cells before the helper T cells can respond to the antigen presented by the macrophage. In addition, helper T cells have a glycoprotein called CD4, which helps to connect helper T cells to the macrophage by binding to MHC class II molecules. For this reason, helper T cells are sometimes referred to as **CD4, or T4, cells.** In a similar fashion, cytotoxic T cells are sometimes called **CD8, or T8, cells** because they have a glycoprotein called CD8, which helps to connect cytotoxic T cells to cells displaying MHC class I molecules. The CD designation stands for "cluster of differentiation," which is a system used to classify many surface molecules.

Lymphocyte Proliferation

Before exposure to an antigen, the number of lymphocytes in a clone is too small to produce an effective response against the antigen. Exposure to an antigen results in an increase in lymphocyte number. First, there is an increase in the number of helper T cells. This is important because the increased number of helper T cells

Figure 22.15 Costimulation

The first signal required for activation of a helper T cell is the binding of the MHC class II/antigen complex to the T-cell receptor. (*a*) One costimulatory signal is the release by the macrophage of a cytokine that binds to a receptor on the helper T cell. (*b*) Another costimulatory signal is the binding of a B7 molecule of the macrophage with a CD28 molecule of the helper T cell. The CD4 molecule of the helper T cell binds to the macrophage's MHC class II molecule and helps to hold the cells together.

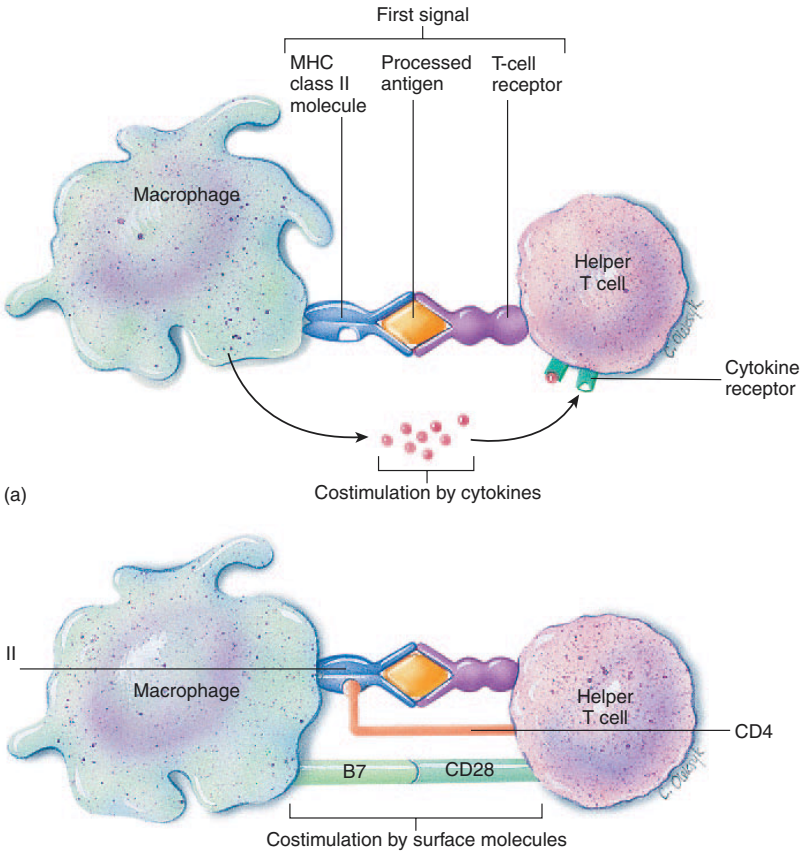


Table 22.4 Cytokines and Their Functions

Cytokine*	Description
Interferon alpha (IFNα)	Prevents viral replication and inhibits cell growth; secreted by virus-infected cells
Interferon beta (IFNβ)	Prevents viral replication, inhibits cell growth, and decreases the expression of major histocompatibility complex (MHC) class I and II molecules; secreted by virus-infected fibroblasts
Interferon gamma (IFNγ)	About 20 different proteins that activate macrophages and natural killer (NK) cells, stimulate adaptive immunity by increasing the expression of MHC class I and II molecules, and prevent viral replication; secreted by helper T, cytotoxic T, and NK cells
Interleukin-1 (IL-1)	Costimulation of B and T cells, promotes inflammation through prostaglandin production, and induces fever acting through the hypothalamus (pyrogen); secreted by macrophages, B cells, and fibroblasts
Interleukin-2 (IL-2)	Costimulation of B and T cells, activation of macrophages and NK cells; secreted by helper T cells
Interleukin-4 (IL-4)	Plays a role in allergic reactions by activation of B cells, resulting in the production of immunoglobulin E (IgE); secreted by helper T cells
Interleukin-5 (IL-5)	Part of the response against parasites by stimulating eosinophil production; secreted by helper T cells
Interleukin-8 (IL-8)	Chemotactic factor that promotes inflammation by attracting neutrophils and basophils; secreted by macrophages
Interleukin-10 (IL-10)	Inhibits the secretion of interferon gamma and interleukins; secreted by suppressor T cells
Lymphotoxin	Kills target cells; secreted by cytotoxic T cells
Perforin	Makes a hole in the membrane of target cells, resulting in lysis of the cell; secreted by cytotoxic T cells
Tumor necrosis factor (TNF)	Activates macrophages and promotes fever (pyrogen); secreted by macrophages

*Some cytokines were named according to the laboratory test first used to identify them; however, these names rarely are a good description of the actual function of the cytokine.

responding to the antigen can find and stimulate B or effector T cells. Second, the number of B or effector T cells increases. This is important because it is these cells that are responsible for the immune response that destroys the antigen.

1. *Proliferation of helper T cells* (figure 22.16). Antigen-presenting cells use MHC class II molecules to present processed antigens to helper T cells. Only the helper T cells with the T-cell receptors that can bind to the antigen respond. These helper T cells respond to the MHC class II/antigen complex and costimulation by dividing. As a result, the number of helper T cells that recognize the antigen increases.
2. *Proliferation and activation of B or effector T cells.* Typically, the proliferation and activation of B or effector T cells involves helper T cells. This process is illustrated in figure 22.17 for B cells, but a similar set of events occurs for effector T cells. The clone of B cells that can recognize a particular antigen have B-cell receptors that can bind to that antigen. B cells use MHC class II/antigen complexes to present antigens to the helper T cells produced in *step 1*. These helper T cells stimulate the B cells to divide and produce antibodies. The increased number of cells, each producing antibodies, can produce an immune response that destroys the antigens (see "Effects of Antibodies" on p. 796).

1. Antigen-presenting cells such as macrophages take in, process, and display antigens on the cell's surface.

2. The antigens are bound to MHC class II molecules, which function to present the processed antigen to the T-cell receptor of the helper T cell for recognition.

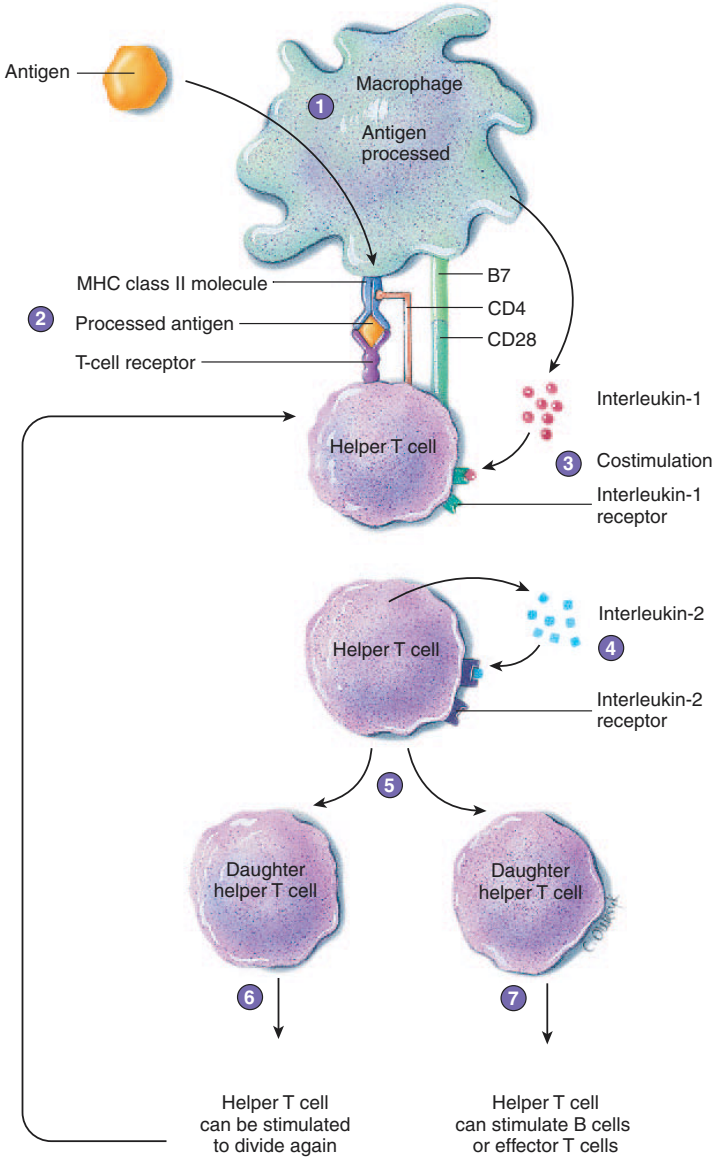
3. Costimulation occurs by the CD4 glycoprotein of the helper T cell or by cytokines. The macrophage secretes a cytokine called interleukin-1.

4. Interleukin-1 stimulates the helper T cell to secrete the cytokine interleukin-2 and to produce interleukin-2 receptors.

5. The helper T cell stimulates itself to divide when interleukin-2 binds to interleukin-2 receptors.

6. The "daughter" helper T cells resulting from this division can be stimulated to divide again if they are exposed to the same antigen that stimulated the "parent" helper T cell. This greatly increases the number of helper T cells.

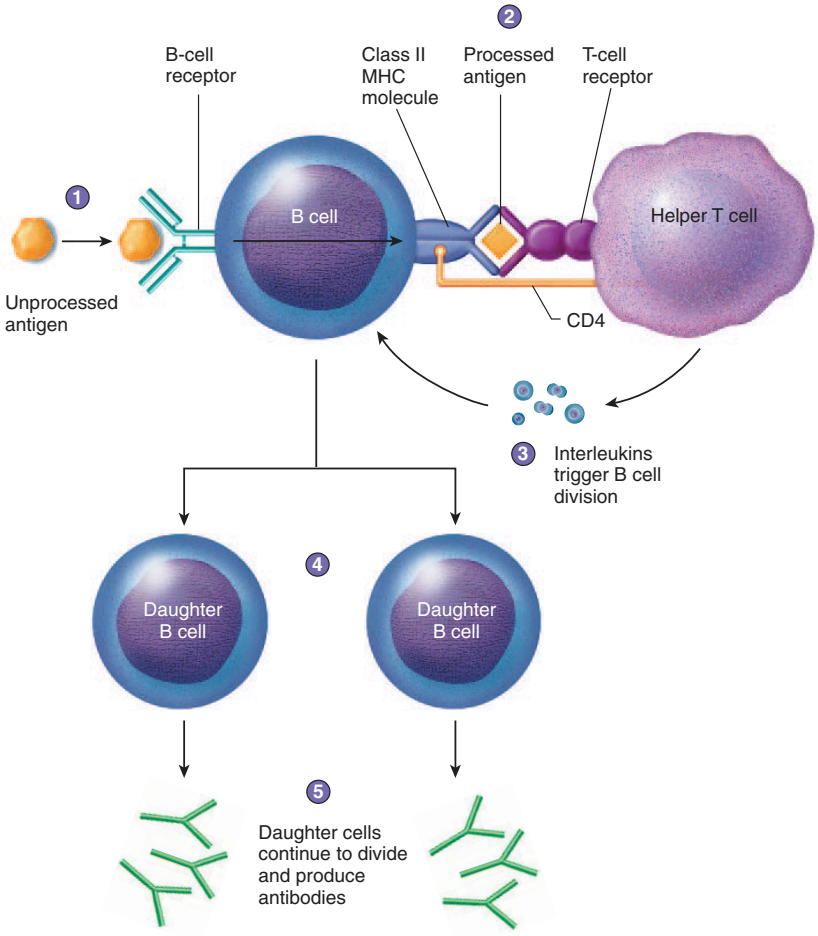
7. The increased number of helper T cells can facilitate the activation of B cells or effector T cells.



Process Figure 22.16 Proliferation of Helper T Cells

An antigen-presenting cell (macrophage) stimulates helper T cells to divide.

1. Before a B cell can be activated by a helper T cell, the B cell must process the same antigen that activated the helper T cell. The antigen binds to a B-cell receptor, and both the receptor and antigen are taken into the cell by endocytosis.
2. The B cell uses an MHC class II molecule to present the processed antigen to the helper T cell.
3. The helper T cell responds by releasing various interleukins that stimulate the B cell to divide.
4. The B cell divides, and the resulting daughter cells divide, and so on, eventually producing many cells (only two are shown here).
5. The increased number of cells produce antibodies, which are part of the antibody-mediated immune system response that eliminates the antigen.



Process Figure 22.17 Proliferation of B Cells

A helper T cell stimulates a B cell to divide.

38. ***What is costimulation? State two ways in which it can happen.***
39. ***Why are helper T cells sometimes called CD4, or T4, cells? Why are cytotoxic T cells sometimes called CD8, or T8, cells?***
40. ***Describe how antigen-presenting cells stimulate an increase in the number of helper T cells. Why is this important?***
41. ***Describe how helper T cells stimulate an increase in the number of B or T cells. Why is this important?***

Inhibition of Lymphocytes

Tolerance is a state of unresponsiveness of lymphocytes to a specific antigen. Although foreign antigens can induce tolerance, the most important function of tolerance is to prevent the immune system from responding to self-antigens. The need to maintain tolerance and to avoid the development of autoimmune disease is obvious. Tolerance can be induced in many ways.

1. *Deletion of self-reactive lymphocytes.* During prenatal development and after birth, stem cells in red bone marrow and the thymus give rise to immature lymphocytes that develop into mature lymphocytes capable of an immune response. When immature lymphocytes are exposed to antigens, instead of responding in ways that result in the elimination of the antigen, they respond by dying. Because immature lymphocytes are exposed to self-antigens, this process eliminates self-reactive lymphocytes. In addition, immature lymphocytes that escape deletion during their development and become mature, self-reacting lymphocytes can still be deleted in ways that are not clearly understood.

2. *Preventing activation of lymphocytes.* For activation of lymphocytes to take place, two signals are usually required: (1) the MHC/antigen complex binding with an antigen receptor and (2) costimulation. Preventing either of these events stops lymphocyte activation. For example, blocking, altering, or deleting an antigen receptor prevents activation. **Anergy** (an′er-jē), which means "without working," is a condition of inactivity in which a B or T cell does not respond to an antigen. Anergy develops when an MHC/antigen complex binds to an antigen receptor, and no costimulation occurs. For example, if a T cell encounters a self-antigen on a cell that cannot provide costimulation, the T cell is turned off. It's likely that only antigen-presenting cells can provide costimulation.

Inhibiting and Stimulating Immunity

Decreasing the production or activity of cytokines can suppress the immune system. For example, cyclosporine, a drug used to prevent the rejection of transplanted organs, inhibits the production of interleukin-2. Conversely, genetically engineered interleukins can be used to stimulate the immune system. Administering interleukin-2 has promoted the destruction of cancer cells in some cases by increasing the activities of effector T cells.

3. *Activation of suppressor T cells.* **Suppressor T cells** are a poorly understood group of T cells that are defined by their ability to suppress immune responses. It's likely that suppressor T cells are subpopulations of helper T cells and cytotoxic T cells. The suppressor (helper) T cells release suppressive cytokines, or the suppressor (cytotoxic) T cells kill antigen-presenting cells.

42. What is tolerance? List three ways it is accomplished.

Antibody-Mediated Immunity

Exposure of the body to an antigen can lead to activation of B cells and to production of antibodies, which are responsible for destruction of the antigen. Because antibodies occur in body fluids, **antibody-mediated immunity** is effective against extracellular antigens. These include bacteria, viruses, protozoans, fungi, parasites, and toxins when they are outside cells. Antibody-mediated immunity can also cause immediate hypersensitivity reactions (see "Clinical Focus: Immune System Problems of Clinical Significance" on p. 794).

Antibodies

Antibodies are proteins produced in response to an antigen. Large amounts of antibodies occur in plasma, although plasma also contains other proteins. On the basis of protein type and associated lipids, plasma proteins are separated into albumin and alpha-(α), beta-(β), and gamma-(γ)globulin parts. As a group, antibodies are sometimes called **gamma globulins** because they are mostly found in the γ-globulin part of plasma. They are also called **immunoglobulins (Ig)** because they are globulin proteins involved in immunity.

The five general classes of immunoglobulins are denoted IgG, IgM, IgA, IgE, and IgD (table 22.5). All classes of antibodies have a similar structure, consisting of four polypeptide chains (figure 22.18): two identical heavy chains and two identical light chains. Each light chain is attached to a heavy chain, and the ends of the combined heavy and light chains form the **variable region** of the antibody, which is the part that combines with the antigenic determinant of the antigen. Different antibodies have different variable regions, and they are specific for different antigens. The rest of the antibody is the **constant region,** which is responsible for activities of antibodies like the ability to activate complement or to attach the antibody to such cells as macrophages, basophils, mast cells, and eosinophils. All the antibodies of a particular class have nearly the same constant regions.

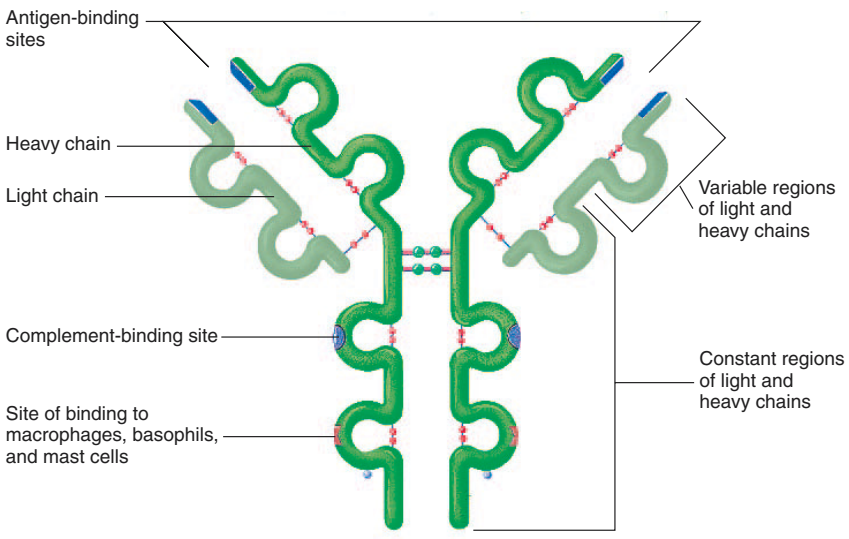


Figure 22.18 Structure of an Antibody

Antibodies consist of two heavy and two light polypeptide chains. The variable region of the antibody binds to the antigen. The constant region of the antibody can activate the classical pathway of the complement cascade. The constant region can also attach the antibody to the plasma membrane of cells such as macrophages, basophils, or mast cells.

Clinical Focus Immune System Problems of Clinical Significance

Hypersensitivity Reactions

Immune and hypersensitivity (allergy) reactions involve the same mechanisms, but the differences between them are unclear. Both require exposure to an antigen and subsequent stimulation of antibody-mediated immunity or cell-mediated immunity (or both). If immunity to an antigen is established, later exposure to the antigen results in an immune system response that eliminates the antigen, and no symptoms appear. In **hypersensitivity reactions,** the antigen is called an **allergen,** and later exposure to the allergen stimulates much the same process that occurs during the normal immune system response. The processes that eliminate the allergen, however, also produce undesirable side effects, such as a very strong inflammatory reaction. This immune system response can be more harmful than beneficial and can produce many unpleasant symptoms. Hypersensitivity reactions are categorized as immediate or delayed.

Immediate Hypersensitivities

An **immediate hypersensitivity reaction** occurs when antibodies interact with allergens and cause symptoms to appear within a few minutes of exposure to the allergens. Immediate hypersensitivity reactions include atopy, anaphylaxis, cytotoxic reactions, and immune complex disease.

Atopy (at′ō-pē) is a localized IgE-mediated hypersensitivity reaction. For example, plant pollens can be allergens that cause hay fever when they are inhaled and absorbed through the respiratory mucosa. The resulting localized inflammatory response produces swelling of the mucosa and excess mucus production. In asthma patients, allergens can stimulate the release of leukotrienes and histamine in the bronchioles of the lung, causing constriction of the smooth muscles of the bronchioles and difficulty in breathing. Hives (urticaria) is an allergic reaction that results in a skin rash or localized swellings and is usually caused by an ingested allergen.

Anaphylaxis (an′ă-fi-lak′sis) is a systemic IgE-mediated reaction and can be life-threatening. Introduction of allergens, such as drugs (e.g., penicillin) and insect stings, is the most common cause. The chemicals released from mast cells and basophils cause systemic vasodilation, a drop in blood pressure, and cardiac failure. Symptoms of hay fever, asthma, and hives may also be observed.

In **cytotoxic reactions,** IgG or IgM combines with the antigen on the surface of a cell, resulting in the activation of complement and subsequent lysis of the cell. A cytotoxic reaction against a bacterial cell can be protective, but against a human cell it can be harmful. Transfusion reactions caused by incompatible blood types, hemolytic disease of the newborn (see chapter 19), and some types of autoimmune disease are examples of harmful cytotoxic reactions.

Immune complex disease occurs when too many immune complexes are formed. Immune complexes are combinations of soluble antigens and IgG or IgM. When too many immune complexes are present, too much complement is activated, and an acute inflammatory response develops. Complement attracts neutrophils to the area of inflammation and stimulates the release of lysosomal enzymes. This release causes tissue damage, especially in small blood vessels, where the immune complexes tend to lodge; and lack of blood supply causes tissue necrosis. Arthus reactions, serum sickness, some autoimmune diseases, and chronic graft rejection are examples of immune complex diseases.

An **Arthus reaction** is a localized immune complex reaction. For example, suppose an individual has been sensitized to antigens in the tetanus toxoid vaccine because of repeated vaccinations. If that individual were vaccinated again, large amounts of antigen in the vaccine would be present at the injection site. Antibodies could complex with the antigens, causing a localized inflammatory response, neutrophil infiltration, and tissue necrosis.

Serum sickness is a systemic Arthus reaction in which the antibody–antigen complexes circulate and lodge in many different tissues. Serum sickness can develop from prolonged exposure to an antigen, which provides enough time for an antibody response and the formation of many immune complexes. Examples of antigens include long-lasting drugs and proteins found in the serum used for achieving passive artificial immunity. Symptoms include fever, swollen lymph nodes and spleen, and arthritis. Symptoms of anaphylaxis, such as hives, may also be present because IgE involvement is a part of serum sickness. If large numbers of the circulating antibody–antigen complexes are removed from the blood by the kidney, immune complex glomerulonephritis can develop, in which kidney blood vessels are destroyed and the kidneys fail to function.

Delayed Hypersensitivity

Delayed hypersensitivity is mediated by T cells, and symptoms usually take several hours or days to develop. Like immediate hypersensitivity, delayed hypersensitivity is an acute extension of the normal operation of the immune system. Exposure to the allergen causes activation of T cells and the production of cytokines. The cytokines attract basophils and monocytes, which differentiate into macrophages. The activities of these cells result in progressive tissue destruction, loss of function, and scarring.

Delayed hypersensitivity can develop as allergy of infection and contact hypersensitivity. **Allergy of infection** is a side effect of cell-mediated efforts to eliminate intracellular microorganisms, and the amount of tissue destroyed is determined by the persistence and distribution of the antigen. The minor rash of measles results from tissue damage as cell-mediated immunity destroys virus-infected cells.

In patients with chronic infections with long-term antigenic stimulation, the allergy-of-infection response can cause extensive tissue damage. The destruction of lung tissue in tuberculosis is an example.

Contact hypersensitivity is a delayed hypersensitivity reaction to allergens that contact the skin or mucous membranes. Poison ivy, poison oak, soaps, cosmetics, drugs, and a variety of chemicals can

induce contact hypersensitivity, usually after prolonged exposure. The allergen is absorbed by epithelial cells, and T cells invade the affected area, causing inflammation and tissue destruction. Although itching can be intense, scratching is harmful because it damages tissues and causes additional inflammation.

Autoimmune Diseases

In **autoimmune disease,** the immune system fails to differentiate between self-antigens and foreign antigens. Consequently, an immune system response is produced against some self-antigens, resulting in tissue destruction. In many instances, autoimmunity probably results from a breakdown of tolerance, which normally prevents an immune system response to self-antigens. In a situation called molecular mimicry, a foreign antigen that is very similar to a self-antigen stimulates an immune system response. After the foreign antigen is eliminated, the immune system continues to act against the self-antigen. It's hypothesized that type I diabetes (see chapter 18) develops in this fashion. In susceptible people, a foreign antigen can stimulate adaptive immunity, especially cell-mediated immunity, which destroys the insulin-producing beta cells of the pancreas. Other autoimmune diseases that involve antibodies are rheumatoid arthritis, rheumatic fever, Graves' disease, systemic lupus erythematosus, and myasthenia gravis.

Immunodeficiencies

Immunodeficiency is a failure of some part of the immune system to function properly. A deficient immune system is not uncommon because it can have many causes. Inadequate protein in the diet inhibits protein synthesis, thereby allowing antibody levels to decrease. Stress can depress the immune system, and fighting an infection can deplete lymphocyte and granulocyte reserves and make a person more susceptible to further infection. Diseases that cause proliferation of lymphocytes, such as mononucleosis, leukemias, and myelomas, can result in an abundance of lymphocytes that don't function properly. Finally, the immune system can purposefully be suppressed by drugs to prevent graft rejection.

Congenital (present at birth) immunodeficiencies can involve inadequate B-cell formation, inadequate T-cell formation, or both. **Severe combined immunodeficiency disease (SCID)** in which both B and T cells fail to differentiate, although rare, is probably the best known. Unless the person suffering from SCID is kept in a sterile environment or is provided with a compatible bone marrow transplant, death from infection results.

Tumor Control

Tumor cells have tumor antigens that distinguish them from normal cells. According to the concept of **immune surveillance,** the immune system detects tumor cells and destroys them before a tumor can form. T cells, natural killer cells, and macrophages are involved in the destruction of tumor cells. Immune surveillance may exist for some forms of cancer caused by viruses. The immune response appears to be directed more against the viruses, however, than against tumors in general. Only a few cancers are known to be caused by viruses in humans. For most tumors, the response of the immune system may be ineffective and too late.

Transplantation

Genes that code for the production of MHC molecules are generally called major histocompatibility complex genes. Histocompatibility refers to the ability of tissues (Greek, *histo*) to get along (compatibility) when tissues are transplanted from one individual to another. In humans, the major histocompatibility complex genes are often referred to as **human leukocyte antigen (HLA) genes** because they were first identified in leukocytes. The HLA genes control the production of HLAs, also called MHC antigens, which are inserted onto the surface of cells. The immune system can distinguish between self-cells and foreign cells because they are both marked with HLAs. Rejection of a transplanted tissue is caused by a normal immune system response to the foreign HLAs. Millions of possible combinations of the HLA genes exist, and it's very rare for two individuals (except identical twins) to have the same set of HLA genes. Because they are genetically determined, however, the closer the relationship between two individuals, the greater the likelihood of sharing the same HLA genes.

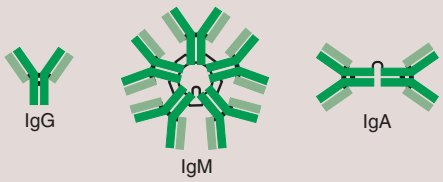
Acute rejection of a graft occurs several weeks after transplantation and results from a delayed hypersensitivity reaction and cell lysis. Lymphocytes and macrophages infiltrate the area, a strong inflammatory response occurs, and the foreign tissue is destroyed. If acute rejection doesn't develop, **chronic rejection** may occur at a later time. In chronic rejection, immune complexes form in the arteries supplying the graft, blood supply fails, and the graft is rejected.

Graft rejection can occur in two different directions. In **host-versus-graft rejection,** the recipient's immune system recognizes the donor's tissue as foreign and rejects the transplant. In a **graft-versus-host rejection,** the donor tissue recognizes the recipient's tissue as foreign, and the transplant rejects the recipient, causing destruction of the recipient's tissues, and death.

To reduce graft rejection, a tissue match is performed. Only tissues with HLAs similar to the recipient's have a chance of acceptance. Even when the match is close, immunosuppressive drugs must be administered throughout the person's life to prevent rejection. Unfortunately, the person then has a drug-produced immunodeficiency and is more susceptible to infections. An exact match is possible only for a graft from one part to another part of the same person's body or between identical twins.

HLAs are important in ways in addition to organ transplants. Because they are genetically determined, characterization of HLAs can help resolve paternity suits. In forensic medicine, the HLAs in blood, semen, and other tissues help identify the person from whom the tissue came.

Table 22.5 Classes of Antibodies and Their Functions

Antibody	Total Serum Antibody (%)	Structure	Description
IgG	80–85		Activates complement and functions as an opsonin to increase phagocytosis; can cross the placenta and provide immune protection to the fetus and newborn; responsible for Rh reactions, such as hemolytic disease of the newborn
IgM	5–10		Activates complement and acts as an antigen-binding receptor on the surface of B cells; responsible for transfusion reactions in the ABO blood system; often the first antibody produced in response to an antigen
IgA	15		Secreted into saliva, tears, and onto mucous membranes to provide protection on body surfaces; found in colostrum and milk to provide immune protection to the newborn
IgE	0.002		Binds to mast cells and basophils and stimulates the inflammatory response
IgD	0.2		Functions as antigen-binding receptors on B cells

Uses of Monoclonal Antibodies

Each type of **monoclonal antibody** is a pure antibody preparation that is specific for only one antigen. When the antigen is injected into a laboratory animal, it activates a B-cell clone against the antigen. The B cells are removed from the animal and fused with tumor cells. The resulting hybridoma cells have two ideal characteristics: they divide to form large numbers of cells, and the cells of a given clone produce only one kind of antibody.

Monoclonal antibodies are used for determining pregnancy and for diagnosing diseases like gonorrhea, syphilis, hepatitis, rabies, and cancer. These tests are specific and rapid because the monoclonal antibodies bind only to the antigen being tested. Monoclonal antibodies may someday be used to effectively treat cancer by delivering drugs to cancer cells (see "Immunotherapy" on p. 800).

Effects of Antibodies

Antibodies can directly affect antigens in two ways. The antibody can bind to the antigenic determinant and interfere with the ability of the antigen to function (figure 22.19*a*). Alternatively, the antibody can combine with an antigenic determinant on two different antigens, rendering the antigens ineffective (figure 22.19*b*). The ability of antibodies to join antigens together is the basis for many clinical tests, such as blood typing, because, when enough antigens are bound together, they become visible as a clump or a precipitate.

Although antibodies can directly affect antigens, most of their effectiveness results from other mechanisms. When an antibody (IgG or IgM) combines with an antigen through the variable region, the constant region can activate the complement cascade through the classical pathway (figure 22.9*c*). Activated complement stimulates inflammation; attracts neutrophils, monocytes, macrophages, and eosinophils to sites of infection; and kills bacteria by lysis.

Antibodies (IgE) can initiate an inflammatory response (figure 22.9*d*). The antibodies attach to mast cells or basophils through their constant region. When antigens combine with the variable region of the antibodies, the mast cells or basophils release chemicals through exocytosis, and inflammation results.

Opsonins (op′sŏ-ninz) are substances that make an antigen more susceptible to phagocytosis. An antibody (IgG) acts as an opsonin by connecting to an antigen through the variable region of the antibody and to a macrophage through the constant region of the antibody. The macrophage then phagocytizes the antigen and the antibody (figure 22.19*e*).

Antibody Production

The production of antibodies after the first exposure to an antigen is different from that after a second or subsequent exposure. The **primary response** results from the first exposure of a B cell to an antigen for which it is specific and includes a series of cell divisions, cell differentiation, and antibody production. The B-cell receptors on the surface of B cells are antibodies, usually IgM and IgD. The receptors have the same variable region as the antibodies that are eventually produced by the B cell. Before stimulation by an antigen, B cells are small lymphocytes. After activation, the B cells undergo a series of divisions to produce large lymphocytes. Some of these enlarged cells become **plasma cells,** which produce antibodies, and others revert back to small lymphocytes and become **memory B**

(a) **Inactivates the antigen.** An antibody binds to an antigen and inactivates it.

(b) **Binds antigens together.** Antibodies bind several antigens together.

(c) **Activates the complement cascade.** An antigen binds to an antibody. As a result, the antibody can activate complement proteins, which can produce inflammation, chemotaxis, and lysis.

(d) **Initiates the release of inflammatory chemicals.** An antibody binds to a mast cell or basophil. When an antigen binds to the antibody, it triggers a release of chemicals that cause inflammation.

(e) **Facilitates phagocytosis.** An antibody binds to an antigen and then to a macrophage, which phagocytizes the antibody and antigen.

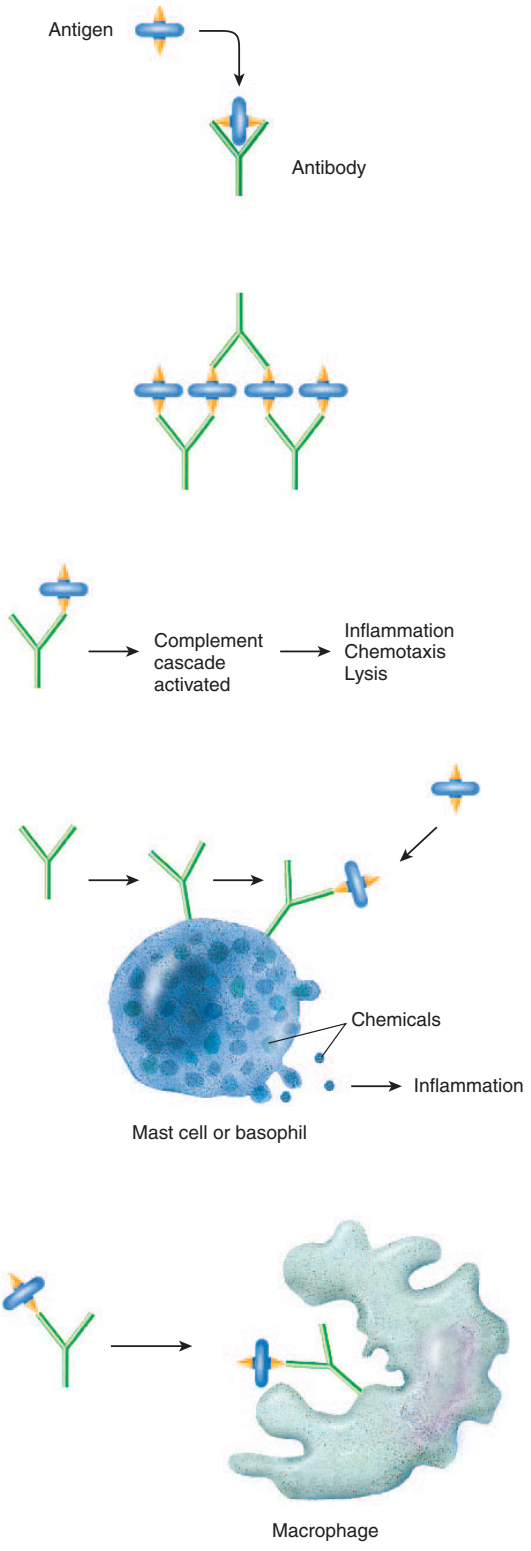


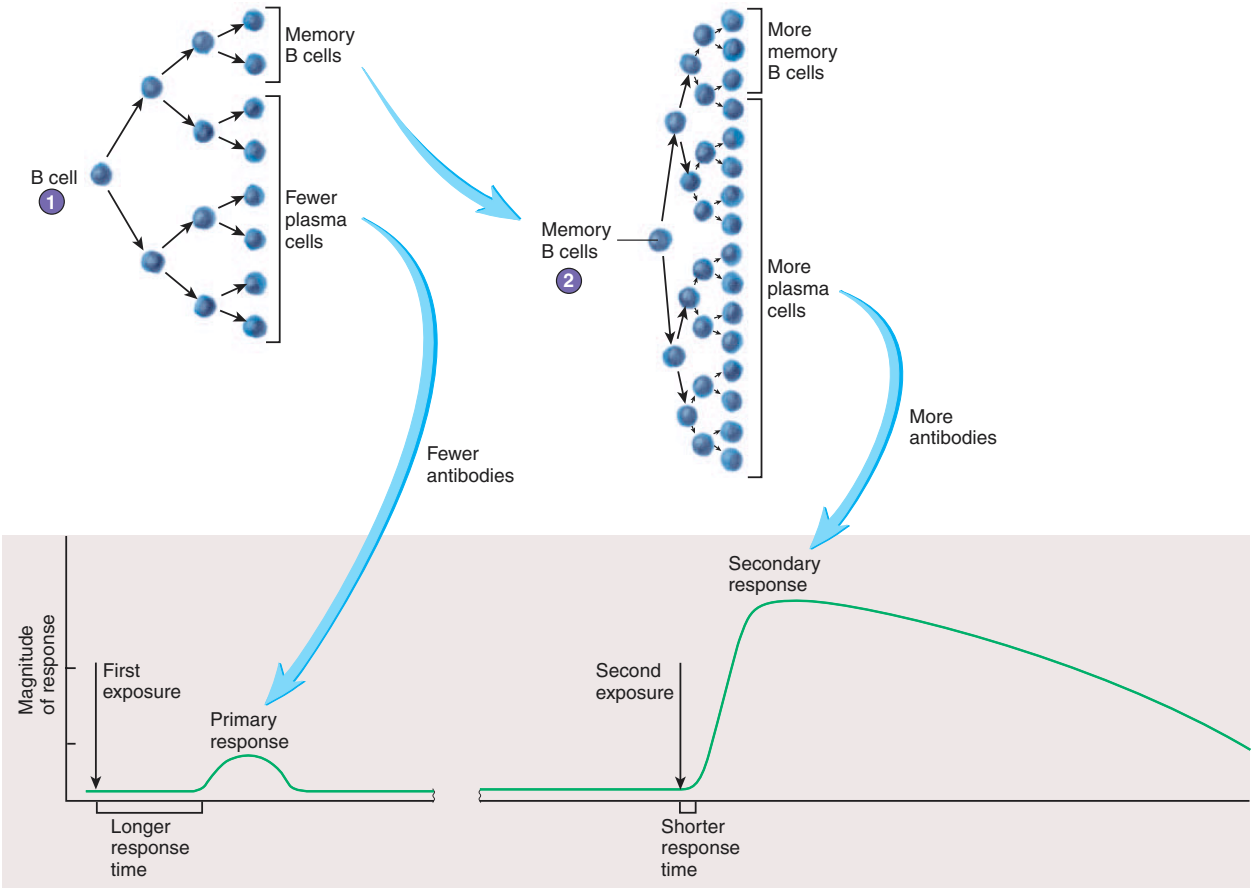
Figure 22.19 Actions of Antibodies

Antibodies can inactivate antigens, promote phagocytosis (binding antigens together or opsonization), and cause inflammation (release of chemicals from mast cells or basophils and activation of the complement cascade).

cells (figure 22.20). Usually, IgM is the first antibody produced in response to an antigen, but later other classes of antibodies are produced as well. The primary response normally takes 3–14 days to produce enough antibodies to be effective against the antigen. In the meantime, the individual usually develops disease symptoms because the antigen has had time to cause tissue damage.

The **secondary,** or **memory, response** occurs when the immune system is exposed to an antigen against which it has already produced a primary response. The secondary response results from memory B cells, which rapidly divide to produce plasma cells and large amounts of antibody when exposed to the antigen. The secondary response provides better protection than the primary response for two reasons. First, the time required to start producing antibodies is less (hours to a few days); and second, the amount of antibody produced is much larger. As a consequence, the antigen is quickly destroyed, no disease symptoms develop, and the person is immune.

The memory response also includes the formation of new memory B cells, which provide protection against additional exposures to the antigen. Memory B cells are the basis for adaptive immunity. After destruction of the antigen, plasma cells die, the antibodies they released are degraded, and antibody levels decline to the point at which they can no longer provide adequate protection. Memory B cells may persist for many years and probably for life in some cases. If memory cell production is not stimulated, however, or if the memory B cells produced are short-lived, repeated infections of the same disease are possible. For example, the same cold virus can cause the common cold more than once in the same person.



1. **Primary response.** The primary response occurs when a B cell is first activated by an antigen. The B cell proliferates to form plasma cells and memory cells. The plasma cells produce antibodies.

2. **Secondary response.** The secondary response occurs when another exposure to the same antigen causes the memory cells to rapidly form plasma cells and additional memory cells. The secondary response is faster and produces more antibodies than the primary response.

Process Figure 22.20 Antibody Production

43. *What type of lymphocyte is responsible for antibody-mediated immunity? What are the functions of antibody-mediated immunity?*
44. *What are the functions of the constant and variable regions of an antibody? List the five classes of antibodies, and state their functions.*
45. *Describe the different ways that antibodies participate in the destruction of antigens.*
46. *What are plasma cells and memory cells, and what are their functions?*
47. *What are the primary and secondary antibody responses? Why doesn't the primary response prevent illness but the secondary response does?*

P R E D I C T 4

One theory for long-lasting immunity assumes that humans are continually exposed to the disease-causing agent. Explain how this exposure could produce lifelong immunity.

Cell-Mediated Immunity

Cell-mediated immunity is a function of T cells and is most effective against intracellular microorganisms, such as viruses, fungi, intracellular bacteria, and parasites. Delayed hypersensitivity reactions and control of tumors also involve cell-mediated immunity (see "Clinical Focus: Immune System Problems of Clinical Significance" on p. 794).

Activation of T cells to antigens is regulated by antigen-presenting cells and helper T cells. Once activated, T cells undergo a series of divisions and produce effector T cells, such as cytotoxic T cells, and memory T cells (figure 22.21). Effector T cells are responsible for the cell-mediated immunity response. Memory T cells can provide a secondary response and long-lasting immunity in the same fashion as memory B cells.

Cytotoxic T Cells

Cytotoxic T cells have two main effects: they lyse cells and they produce cytokines. Cytotoxic T cells can come into contact with other cells and cause them to lyse. Virus-infected cells have viral antigens, tumor cells have tumor antigens, and tissue transplants have foreign antigens on their surfaces that can stimulate cytotoxic T-cell activity. A cytotoxic T cell binds to a target cell and releases chemicals that cause the target cell to lyse. The major method of lysis involves a protein called **perforin,** which forms a pore in the membrane of the target cell. The cytotoxic T cell then moves on to destroy additional target cells.

In addition to lysing cells, cytotoxic T cells release cytokines that activate additional components of the immune system. For example, one important function of cytokines is the recruitment of cells like macrophages. These cells are then responsible for phagocytosis and inflammation.

P R E D I C T 5

In patients with acquired immunodeficiency syndrome (AIDS), helper T cells are destroyed by a viral infection. The patients can die of pneumonia caused by an intracellular fungus *(Pneumocystis carinii)* or from Kaposi's sarcoma, which consists of tumorous growths in the skin and lymph nodes. Explain what is happening.

Delayed Hypersensitivity T Cells

Delayed hypersensitivity T cells respond to antigens by releasing cytokines. Consequently, they promote phagocytosis and inflammation, especially in allergic reactions (see "Clinical Focus: Immune System Problems of Clinical Significance" on p. 794). For example, poison ivy antigens can be processed by Langerhans' cells in the skin, which present the antigen to delayed hypersensitivity T cells, resulting in an intense inflammatory response.

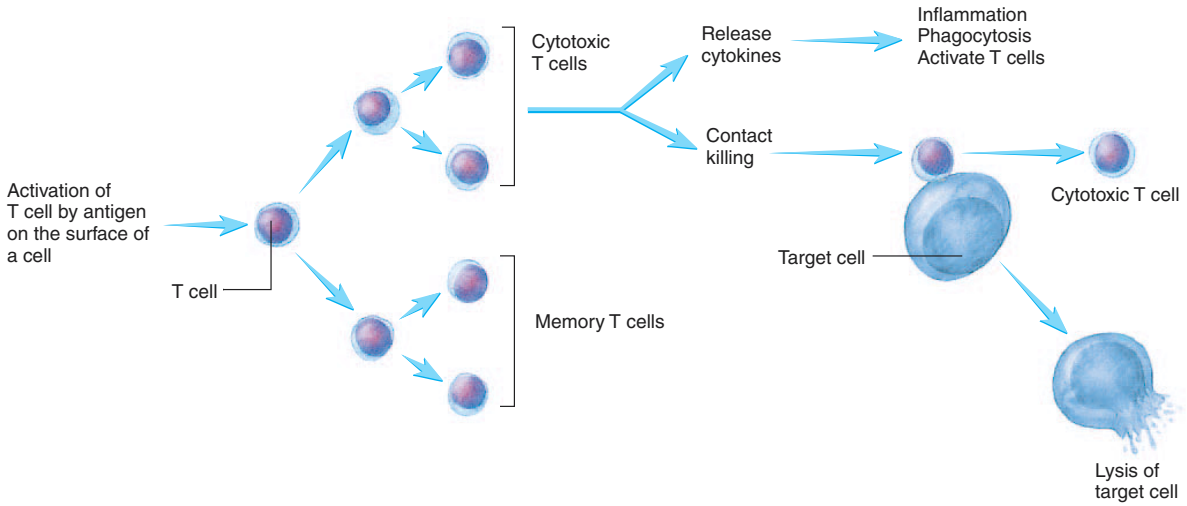


Figure 22.21 Stimulation and Effects of T Cells

When T cells are presented with a processed antigen, they can form memory T and cytotoxic T cells. Memory T cells are responsible for the secondary response, and cytotoxic T cells cause contact killing or release cytokines that promote the destruction of the antigen.

48. *What type of lymphocyte is responsible for cell-mediated immunity? What are the functions of cell-mediated immunity?*
49. *State the two main responses of cytotoxic T cells.*
50. *What kind of immune response is produce by delayed hypersensitivity T cells?*
51. *How is long-lasting immunity achieved in cell-mediated immunity?*

Immune Interactions

Objective

- *Describe immune interactions.*

Although the immune system can be described in terms of innate, antibody-mediated, and cell-mediated immunity, only one immune system really exists. These categories are an artificial division that is used to emphasize particular aspects of immunity. Actually, immune system responses often involve components of more than one type of immunity (figure 22.22). For example, although adaptive immunity can recognize and remember specific antigens, once recognition has occurred, many of the events that lead to the destruction of the antigen are innate immunity activities, such as inflammation and phagocytosis.

52. *Describe how interactions between innate, antibody-mediated, and cell-mediated immunity can eliminate an antigen.*

Immunotherapy

Objective

- *Define and give examples of immunotherapy.*

Knowledge of the basic ways that the immune system operates has produced two fundamental benefits: (1) an understanding of the cause and progression of many diseases, and (2) the development or proposed development of effective methods to prevent, stop, or even reverse diseases.

Immunotherapy treats disease by altering immune system function or by directly attacking harmful cells. Some approaches attempt to boost immune system function in general. For example, administering cytokines or other agents can promote inflammation and the activation of immune cells, which can help in the destruction of tumor cells. On the other hand, sometimes inhibiting the immune system is helpful. For example, multiple sclerosis is an autoimmune disease in which the immune system treats self-antigens as foreign antigens, thereby destroying the myelin that covers axons. Interferon beta (IFNβ) blocks the expression of MHC molecules that display self-antigens and is now being used to treat multiple sclerosis.

Some immunotherapy takes a more specific approach. For example, vaccination can prevent many diseases (see section on "Acquired Immunity" on p. 804). The ability to produce monoclonal antibodies may result in therapies that are effective for treating tumors. If an antigen unique to tumor cells can be found, then monoclonal antibodies could be used to deliver radioactive isotopes, drugs, toxins, enzymes, or cytokines that can kill the tumor cell or can activate the immune system to kill the cell. Unfortunately, no antigen on tumor cells has been found that is not also found on normal cells. Nonetheless, this approach may be useful if damage to normal cells is minimal. For example, tumor cells may have more surface antigens of a particular type than normal cells, resulting in greater treatment delivery. Tumor cells may also be more susceptible to damage, or normal cells may be better able to recover from the treatment.

One problem with monoclonal antibody delivery systems is that the immune system recognizes the monoclonal antibody as a foreign antigen. After the first exposure, a memory response quickly destroys the monoclonal antibodies, rendering the treatment ineffective. In a process called **humanization,** the monoclonal antibodies are modified to resemble human antibodies. This approach has allowed monoclonal antibodies to sneak past the immune system.

The use of monoclonal antibodies to treat tumors is mostly in the research stage of development, but a few clinical trials are now yielding promising results. For example, monoclonal antibodies with radioactive iodine (^{131}I) have caused regression of B-cell lymphomas and produced few side effects. Herceptin is a monclonal antibody that binds to a growth factor that is overexpressed in 25%–30% of primary breast cancers. The antibodies serve to "tag" cancer cells, which are then lysed by natural killer cells. Herceptin slows disease progression and increases survival time, but it's not a cure for breast cancer.

Many other approaches for immunotherapy are being studied, and the development of treatments that use the immune system are certain to increase in the future. Your knowledge of the immune system will enable you to understand and appreciate these therapies.

53. *What is immunotherapy? Give examples.*

Neuroendocrine Regulation of Immunity

An intriguing possibility for reducing the severity of diseases or even curing them is to use neuroendocrine regulation of immunity. The nervous system regulates the secretion of hormones, such as cortisol, epinephrine, endorphins, and enkephalins, for which lymphocytes have receptors. For example, cortisol released during times of stress inhibits the immune system. In addition, most lymphatic tissues, including some individual lymphocytes, receive sympathetic innervation. That a neuroendocrine connection exists with the immune system is clear. The question we need to answer is: Can we use this connection to control our own immunotherapy?

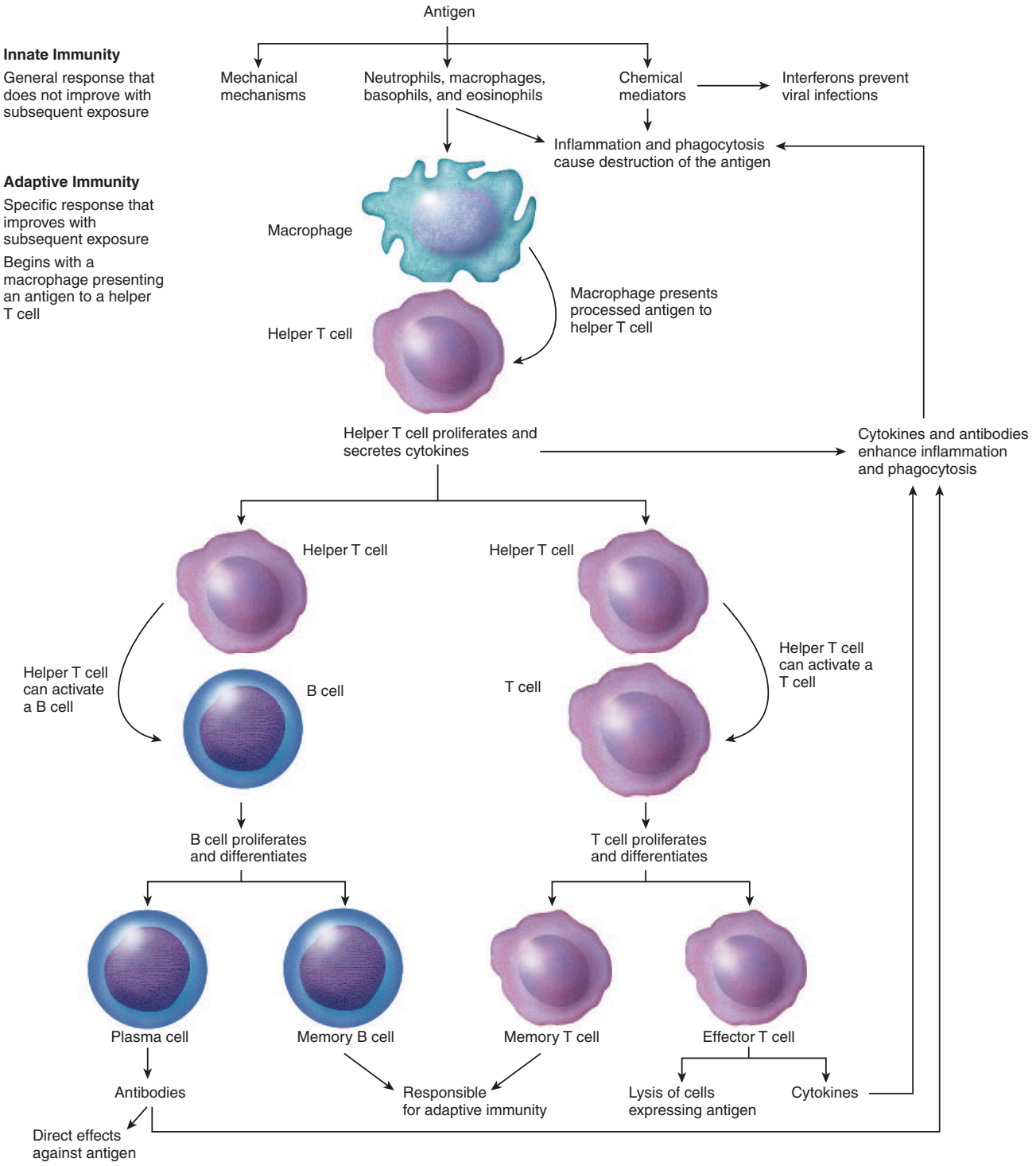


Figure 22.22 The Major Interactions and Responses of Innate and Adaptive Immunity to an Antigen

Clinical Focus Acquired Immunodeficiency Syndrome

Acquired immunodeficiency syndrome (AIDS) is a life-threatening disease caused by the **human immunodeficiency virus (HIV).** Two strains of HIV are recognized: HIV-1 is responsible for most cases of AIDS, whereas HIV-2 is increasingly being found in West Africa. AIDS was first reported in 1981 in the United States. Since then, over 800,000 cases have been reported in the United States to the Centers for Disease Control and Prevention (CDC). The United Nations Program on AIDS (UNAIDS) estimates that 60 million people have been infected by HIV worldwide, and 18 million have died. The course of HIV infection varies. After contracting HIV, some people die within a year; most, however, survive for 10 or 11 years, and some have survived beyond 20 years.

HIV is transmitted from an infected to a noninfected person in body fluids, such as blood, semen, or vaginal secretions. The major methods of transmission are unprotected intimate sexual contact, contaminated needles used by intravenous drug users, tainted blood products, and from a pregnant woman to her fetus. Present evidence indicates that household, school, or work contacts do not result in transmission.

In the United States, most cases of AIDS during the 1980s occurred in homosexual or bisexual men and in intravenous drug users. A small percentage of cases have resulted from transfusions or contaminated clotting factors used by hemophiliacs. Children can be infected before birth, during delivery, or after birth from breast- feeding. A few cases of AIDS have occurred in health-care workers accidentally exposed to HIV-infected blood or body fluids, and even fewer cases of health-care workers infecting patients have been documented. The most rapidly increasing group of AIDS patients in the United States is heterosexual women or men who have had sexual contact with an infected person. In other countries the pattern of AIDS cases is different from that in the United States. UNAIDS estimates that over 90% of all HIV infections globally are transmitted heterosexually.

Preventing transmission of HIV is presently the only way to prevent AIDS. The risk of transmission can be reduced by educating the public about relatively safe sexual practices, such as reducing the number of one's sexual partners, avoiding anal intercourse, and using condoms. Public education also includes warnings to intravenous drug users of the dangers of using contaminated needles. Ensuring the safety of the blood supply is another important preventive measure. In 1985, a test for HIV antibodies in blood became available. Heat treatment of clotting factors taken from blood has also been effective in preventing transmission of HIV to hemophiliacs.

HIV infection begins when a protein on the surface of the virus, called gp120, binds to a CD4 molecule on the surface of a cell. The CD4 molecule is found primarily on helper T cells, and it normally enables helper T cells to adhere to other lymphocytes, for example, during the process of antigen presentation. Certain monocytes, macrophages, neurons, and neuroglial cells also have CD4 molecules. Once attached to the CD4 molecules, the virus injects its genetic material (RNA) and enzymes into the cell and begins to replicate. Copies of the virus are manufactured using the organelles and materials within the cell. Replicated viruses escape from the cell and infect other cells.

Following infection by HIV, within 3 weeks to 3 months, many patients develop mononuculeosis-like symptoms, such as fever, sweats, fatigue, muscle and joint aches, headache, sore throat, diarrhea, rash, and swollen lymph nodes. Within 1–3 weeks, these symptoms disappear as the immune system responds to the virus by producing antibodies and activating cytotoxic T cells that kill HIV-infected cells. The immune system is not able to completely eliminate HIV, however, and by about 6 months a kind of "set point" is achieved in which the virus continues to replicate at a low, but steady, rate. This chronic stage of infection lasts, on the average, for 8–10 years, and the infected person feels good and exhibits few, if any, symptoms.

Although helper T cells are infected and destroyed during the chronic stage of HIV infection, the body responds by producing large numbers of helper T cells. Nonetheless, over a period of years the HIV numbers gradually increase and helper T cell numbers decrease. Normally approximately 1200 helper T cells are present per cubic millimeter of blood. An HIV-infected person is considered to have AIDS when one or more of the following conditions appear: the helper T cell count falls below 200 cells/mm^3, an opportunistic infection occurs, or Kaposi's sarcoma develops.

Opportunistic infections involve organisms that normally don't cause disease but can do so when the immune system is depressed. Without helper T cells, cytotoxic T- and B-cell activation is impaired, and

adaptive resistance is suppressed. Examples of opportunistic infections include pneumocystis (noo-mō-sis′tis) pneumonia (caused by an intracellular fungus, *Pneumocystis carinii*), tuberculosis (caused by an intracellular bacterium, *Myocobacterium tuberculosis*), syphilis (caused by a sexually transmitted bacterium, *Treponema pallidum*), candidiasis (kan-di-dī′ă-sis; a yeast infection of the mouth or vagina caused by *Candida albicans*), and protozoans that cause severe, persistent diarrhea. Kaposi's sarcoma is a type of cancer that produces lesions in the skin, lymph nodes, and visceral organs. Also associated with AIDS are symptoms resulting from the effects of HIV on the nervous system, including motor retardation, behavioral changes, progressive dementia, and possibly psychosis.

No cure for AIDS has yet been discovered. Management of AIDS can be divided into two categories: (1) management of secondary infections or malignancies associated with AIDS and (2) treatment of HIV. In order for HIV to replicate, the viral RNA is used to make viral DNA, which is inserted into the host cell's DNA. The inserted viral DNA directs the production of new viral RNA and proteins, which are assembled to form new HIV. Key steps in the replication of HIV require viral enzymes. **Reverse transcriptase** promotes the formation of viral DNA from viral RNA, and **integrase** (in′te-grās) inserts the viral DNA into the host cell's DNA. A viral **protease** (prō′tē-ās) breaks large viral proteins into smaller proteins, which are incorporated into the new HIV.

Blocking the activity of HIV enzymes can inhibit replication of HIV. The first effective treatment of AIDS was the drug azidothymidine (AZT) (az′i-dō-thī′mi-dēn), also called zidovudine (zī-dō′voo-dēn). AZT is a **reverse transcriptase inhibitor,** which prevents HIV RNA from producing viral DNA. AZT can delay the onset of AIDS but doesn't appear to increase the survival time of AIDS patients. However, the number of babies who contract AIDS from their HIV-infected mothers can be dramatically reduced by giving AZT to the mothers during pregnancy and to the babies following birth. AZT can produce serious side effects such as anemia or even total bone marrow failure.

Often after 6–18 months of treatment with AZT, viral mutations result in HIV that are resistant to AZT. Other drugs that inhibit viral nucleic acid replication, such as dideoxyinosine (DDI) (dī′dē-oks-ē-ī′nō-sēn), have been developed. These drugs have been used for patients who are resistant to, or do not respond to, AZT.

Protease inhibitors are drugs that interfere with viral proteases. Examples of protease inhibitors are ritonavir and indinavir. The current treatment for suppressing HIV replication is a combination of three drugs, such as two reverse transcriptase inhibitors and one protease inhibitor. It's less likely that HIV will develop resistance to all three drugs. This strategy has proven very effective in reducing the death rate from AIDS and partially restoring health in some individuals.

Still in the research stage are **integrase inhibitors,** which prevent the insertion of viral DNA into the host cell's DNA. Perhaps someday integrase inhibitors will be part of a combination drug therapy for AIDS.

Another advance in AIDS treatment is a test for measuring **viral load,** which measures the number of viral RNA molecules in a milliliter of blood. The actual level of HIV is one-half the RNA count because each HIV has two RNA strands. Viral load is a good predictor of how soon a person will develop AIDS. If viral load is high, the onset of AIDS is much sooner than if it is low. It's also possible to detect developing viral resistance by an increase in viral load. In response, a change in drug dose or type may slow viral replication. Current treatment guidelines are to keep viral load below 500 RNA molecules per milliliter of blood.

An effective treatment for AIDS is not a cure. Even if viral load decreases to the point that the virus is undetected in the blood, the virus still remains in cells throughout the body. It's possible that the virus will eventually mutate and escape drug suppression. In addition, the long-term effects of these drug therapies are unknown.

The long-term goal for dealing with AIDS is to develop a vaccine that prevents HIV infection. Vaccines under development stimulate the production of antibodies against HIV, stimulate a cell-mediated response against HIV-infected cells, or both. In June 1998, the first large-scale testing of a vaccine that stimulates antibody production against HIV gp120 protein began in the United States, Canada, and Thailand.

Because of improved treatment, people with HIV/AIDS can now live for many years. HIV/AIDS is, therefore, being viewed increasingly as a chronic disease, not as a death sentence. A multidisciplinary team that includes occupational therapists, physical therapists, nutritionists/dieticians, psychologists, infectious disease physicians, and others can work together to manage patients with HIV/AIDS to help them have a better quality of life.

Acquired Immunity

Objective

- *Describe the ways in which adaptive immunity can be acquired.*

It's possible to acquire adaptive immunity in four ways: active natural, active artificial, passive natural, and passive artificial immunity (figure 22.23). The terms *natural* and *artificial* refer to the method of exposure. Natural exposure implies that contact with an antigen or antibody occurs as part of everyday living and is not deliberate. Artificial exposure, also called **immunization,** is a deliberate introduction of an antigen or antibody into the body.

The terms *active* and *passive* indicate whether or not an individual's immune system is directly responding to the antigen. When an individual is naturally or artificially exposed to an antigen, an adaptive immune system response can occur that produces antibodies. This is called **active immunity** because the individual's own immune system is the cause of the immunity. **Passive immunity** occurs when another person or animal develops antibodies and the antibodies are transferred to a nonimmune individual. This is called passive immunity because the nonimmune individual didn't produce the antibodies.

How long the immunity lasts differs for active and passive immunity. Active immunity can persist for a few weeks (common cold) to a lifetime (whooping cough and chickenpox). Immunity can be long lasting if enough B or T memory cells are produced and persist to respond to later antigen exposure. Passive immunity is not long lasting because the individual doesn't produce his or her own memory cells. Because active immunity can last longer than passive immunity, it's the preferred method. Passive immunity is preferred, however, in some situations when immediate protection is needed.

Active Natural Immunity

Natural exposure to an antigen, such as a disease-causing microorganism, can cause an individual's immune system to mount an adaptive immune system response against the antigen and achieve **active natural immunity.** Because the individual is not immune during the first exposure, he or she usually develops the symptoms of the disease. Interestingly, exposure to an antigen doesn't always produce symptoms. Many people, if exposed to the poliomyelitis virus at an early age, have an immune system response and produce poliomyelitis antibodies, yet they don't exhibit any disease symptoms.

Active Artificial Immunity

In **active artificial immunity,** an antigen is deliberately introduced into an individual to stimulate the immune system. This process is **vaccination,** and the introduced antigen is a **vaccine.** Injection of the vaccine is the usual mode of administration. Examples of injected vaccinations are the DTP injection against diphtheria, tetanus, and pertussis (whooping cough); and the MMR injection against mumps, measles, and rubella (German measles). Sometimes the vaccine is ingested, as in the oral poliomyelitis vaccine (OPV).

The vaccine usually consists of some part of a microorganism, a dead microorganism, or a live, altered microorganism. The antigen has been changed so that it will stimulate an immune response but will not cause the symptoms of disease. Because active artificial immunity produces long-lasting immunity without disease symptoms, it's the preferred method of acquiring adaptive immunity.

P R E D I C T 6

In some cases, a booster shot is used as part of a vaccination procedure. A booster shot is another dose of the original vaccine given some time after the original dose was administered. Why are booster shots given?

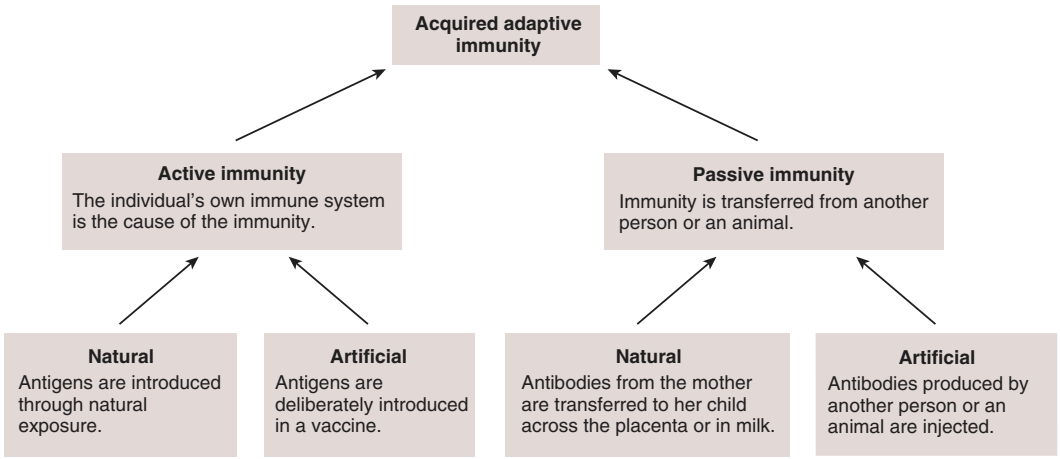


Figure 22.23 Ways to Acquire Adaptive Immunity

Passive Natural Immunity

Passive natural immunity results from the transfer of antibodies from a mother to her child across the placenta before birth. During her life, the mother has been exposed to many antigens, either naturally or artificially, and she has antibodies against many of these antigens. These antibodies protect the mother and the developing fetus against disease. Some of the antibodies (IgG) can cross the placenta and enter the fetal blood. Following birth, the antibodies provide protection for the first few months of the baby's life. Eventually the antibodies are broken down, and the baby must rely on his or her own immune system. If the mother nurses her baby, antibodies (IgA) in the mother's milk may also provide some protection for the baby.

Passive Artificial Immunity

Achieving **passive artificial immunity** usually begins with vaccinating an animal, such as a horse. After the animal's immune system responds to the antigen, antibodies (sometimes T cells) are removed from the animal and injected into the individual requiring immunity. In some cases, a human who has developed immunity through natural exposure or vaccination is used as a source of antibodies. Passive artificial immunity provides immediate protection for the individual receiving the antibodies and is therefore preferred when time might not be available for the individual to develop his or her own immunity. This technique provides only temporary immunity, however, because the antibodies are used or eliminated by the recipient.

Antiserum is the general term used for serum, which is plasma minus the clotting factors, that contains antibodies responsible for passive artificial immunity. Antisera are available against microorganisms that cause diseases such as rabies, hepatitis, and measles; bacterial toxins such as tetanus, diphtheria, and botulism; and venoms from poisonous snakes and black widow spiders.

- *50. Distinguish between active and passive immunity.*
- *51. State four general ways of acquiring adaptive immunity. Which two provide the longest lasting immunity?*

Effects of Aging on the Lymphatic System and Immunity

Objective

- ■ *Describe the effects of aging on the lymphatic system and the immune response.*

Aging appears to have little effect on the ability of the lymphatic system to remove fluid from tissues, absorb fats from the digestive tract, or remove defective red blood cells from the blood.

Aging also seems to have little direct effect on the ability of B cells to respond to antigens, and the number of circulating B cells remains stable in most individuals. With age, thymic tissue is replaced with adipose tissue, and the ability to produce new, mature T cells in the thymus is eventually lost. Nonetheless, the number of T cells remains stable in most individuals due to the replication (not maturation) of T cells in secondary lymphatic tissues. In many individuals, however, there is a decreased ability of helper T cells to proliferate in response to antigens. Thus, antigen exposure produces fewer helper T cells, which results in less stimulation of B cells and effector T cells. Consequently, both antibody-mediated immunity and cell-mediated immunity responses to antigens decrease.

Primary and secondary antibody responses decrease with age. More antigen is required to produce a response, the response is slower, less antibody is produced, and fewer memory cells result. Thus, the ability to resist infections and develop immunity decreases. It's recommended that vaccinations should be given well before age 60 because these declines are most evident after age 60. Vaccinations, however, can be beneficial at any age, especially if the individual has reduced resistance to infection.

The ability of cell-mediated immunity to resist intracellular pathogens decreases with age. For example, the elderly are more susceptible to influenza (flu) and should be vaccinated every year. Some pathogens cause disease but are not eliminated from the body. With age, a decrease in immunity can result in reactivation of the pathogen. For example, the virus that causes chickenpox in children can remain latent within nerve cells even though the disease seems to have disappeared. Later in life, the virus can leave the nerve cells and infect skin cells, causing painful lesions known as herpes zoster or shingles.

Autoimmune disease occurs when immune responses destroy otherwise healthy tissue (see "Autoimmune Diseases" on p. 795). There is very little increase in the number of new-onset autoimmune diseases in the elderly. However, the chronic inflammation and immune responses that began earlier in life have a cumulative, damaging effect. The increased incidence of cancer in the elderly is assumed to be related to a decrease in the immune response.

- *52. What effect does aging have on the major functions of the lymphatic system?*
- *53. Describe the effects of aging on B cells and T cells. Give examples of how this affects antibody-mediated immunity and cell-mediated immunity responses.*

Systems Pathology

Systemic Lupus Erythematosus

Mrs. L is a 30-year-old divorced woman with two children. Despite the fact that she has to work to support herself and the children, she entered college, determined to become a nurse and provide a better life for her family. Mrs. L was an excellent student, but her class attendance and her performance on tests were somewhat erratic. Sometimes she seemed very energetic and earned high grades, but other times she seemed depressed and didn't do as well. Toward the end of the course, she developed a rash on her face (figure A), a large red lesion on her arm, and was obviously not feeling well. Mrs. L went to the instructor to ask if she could take an incomplete grade and take the last exam at a later time. She explained that she has had lupus since she was 25 years old. Normally, medication helps to control her symptoms, but the stress of being a single parent combined with the challenges of school seemed to be making her condition worse. She further explained that the symptoms of lupus come and go, and bed rest was often helpful. Mrs. L finished the course requirements later that summer. She went on to complete her education and now has a full-time job as a nurse at a local hospital.

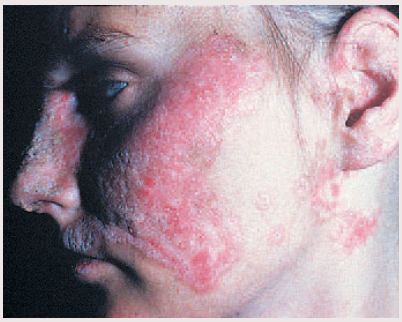


Figure A Systemic Lupus Erythematosus

The butterfly rash resulting from inflammation in the skin caused by systemic lupus erythematosus.

Background Information

Systemic lupus erythematosus (SLE) is a disease of unknown cause in which tissues and cells are damaged by the immune system. The name describes some of the characteristics of the disease. The term *lupus* literally means wolf and was originally used to refer to eroded (as if gnawed by a wolf) lesions of the skin. Erythematosus refers to a redness of the skin resulting from inflammation. Unfortunately, as the term *systemic* implies, the disorder is not confined to the skin but can affect tissues and cells throughout the body. Another systemic effect is the presence of low-grade fever in most cases of active SLE.

SLE is an autoimmune disorder in which a large variety of antibodies are produced that recognize self-antigens, such as nucleic acids, phospholipids, coagulation factors, red blood cells, and platelets. The combination of the antibodies with self-antigens forms immune complexes that circulate throughout the body to be deposited in various tissues, in which they stimulate inflammation and tissue destruction. Thus, SLE is a disease that can affect many different systems of the body. For example, the most common antibodies act against DNA that is released from damaged cells. Normally the liver removes the DNA, but when DNA and antibodies form immune complexes, they tend to be deposited in the kidneys and other tissues. Approximately 40%–50% of individuals with SLE develop renal disease. In some cases, the antibodies can bind to antigens on cells, resulting in lysis of the cells. For example, the binding of antibodies to red blood cells results in hemolysis and the development of anemia.

The cause of SLE is unknown. The most popular hypothesis is that a viral infection disrupts the function of suppressor T cells, resulting in loss of tolerance to self-antigens. The picture is probably more complicated, however, because not all SLE patients have reduced numbers of suppressor T cells. In addition, some patients have decreased numbers of the helper T cells that normally stimulate suppressor T-cell activity.

Genetic factors probably contribute to the development of the disease. The likelihood of developing SLE is much higher if a family member also has it. In addition, family members of SLE patients who

System Interactions

System	The Effect of Systemic Lupus Erythematosus on Other Systems
Integumentary	Skin lesions frequently occur and are made worse by exposure to the sun. There are three forms: (1) an inflammatory redness that can take the form of the butterfly rash, which extends from the bridge of the nose to the cheeks; (2) small, localized pimplelike eruptions accompanied by scaling of the skin; (3) areas of atrophied, depigmented skin with borders of increased pigmentation. Diffuse thinning of the hair results from hair loss.
Skeletal	Arthritis, tendonitis, and death of bone tissue can occur.
Muscular	Destruction of muscle tissue and muscular weakness can occur.
Nervous	Memory loss, intellectual deterioration, disorientation, psychosis, reactive depression, headache, seizures, nausea, and loss of appetite can occur. Stroke is a major cause of dysfunction and death. Cranial nerve involvement results in facial muscle weakness, drooping of the eyelid, and double vision. Central nervous system lesion can cause paralysis.
Endocrine	Sex hormones may play a role in SLE because 90% of the cases occur in females and females with SLE have reduced levels of androgens.
Cardiovascular	Inflammation of the pericardium (pericarditis) with chest pain can develop. Damage to heart valves, inflammation of cardiac tissue, tachycardia, arrhythmias, angina, and myocardial infarction can also occur. Hemolytic anemia, and leukopenia can be present (see chapter 19). Antiphospholipid antibody syndrome, through an unknown mechanism, increases coagulation and thrombus formation, which increases the risk of stroke and heart attack.
Respiratory	Chest pain caused by inflammation of the pleural membranes; fever, shortness of breath, and hypoxemia caused by inflammation of the lungs; and alveolar hemorrhage can develop.
Digestive	Ulcers develop in the oral cavity and pharynx. Abdominal pain and vomiting are common, but no cause can be found. Inflammation of the pancreas and occasionally enlargement of the liver and minor abnormalities in liver function tests occur.
Urinary	Renal lesions and glomerulonephritis can result in progressive failure of kidney function. Excess proteins are lost in the urine, resulting in lower-than-normal blood proteins, which can produce edema.

don't have SLE are much more likely to have DNA antibodies than does the general population.

Approximately 1 out of 2000 individuals in the United States has SLE. The first symptoms usually appear between 15 and 25 years of age and affect women approximately nine times as often as men. The progress of the disease is unpredictable, with flare-ups of symptoms followed by periods of remission. The survival after diagnosis is greater than 90% after 10 years. The most frequent causes of death involve kidney failure, central nervous system dysfunction, infections, and cardiovascular disease.

No cure for SLE exists, nor does one standard of treatment, because the course of the disease is highly variable and many differences can be found among patients. Treatment usually begins with mild medications and proceeds to more and more potent therapies as conditions warrant. Aspirin and nonsteroidal anti-inflammatory drugs are used to suppress inflammation. Antimalarial drugs are used to treat skin rash and arthritis in SLE, but the mechanism of action is unknown. Patients who don't respond to these drugs or those with severe SLE are helped by steroids. Although steroids effectively suppress inflammation, they can produce undesirable side effects, including suppression of normal adrenal gland functions. In patients with life-threatening SLE, very high doses of steroids are used.

P R E D I C T 7

The red lesion Mrs. L developed on her arm is called purpura (pŭr′poo-ră), which is caused by bleeding into the skin. The lesions gradually change color and disappear in 2–3 weeks. Explain how SLE produces purpura.

S U M M A R Y

Lymphatic System (p. 772)

The lymphatic system consists of lymph, lymphatic vessels, lymphatic tissue, lymphatic nodules, lymph nodes, tonsils, the spleen, and the thymus.

Functions of the Lymphatic System

The lymphatic system maintains fluid balance in tissues, absorbs fats from the small intestine, and defends against microorganisms and foreign substances.

Lymphatic Vessels

1. Lymphatic vessels carry lymph away from tissues.
2. Lymphatic capillaries lack a basement membrane and have loosely overlapping epithelial cells. Fluids and other substances easily enter the lymphatic capillary.
3. Lymphatic capillaries join to form lymphatic vessels.
   - Lymphatic vessels have valves that ensure one-way flow of lymph.
   - Skeletal muscle action, contraction of lymphatic vessel smooth muscle, and thoracic pressure changes move the lymph.
4. Lymph nodes are along the lymphatic vessels. After passing through lymph nodes, lymphatic vessels form lymphatic trunks and lymphatic ducts.
5. Lymphatic trunks and ducts empty into the blood at thoracic veins (junctions of the internal jugular and subclavian veins).
   - Lymph from the right thorax, the upper-right limb, and the right side of the head and the neck enters right thoracic veins.
   - Lymph from the lower limbs, pelvis, and abdomen; the left thorax; the upper-left limb; and the left side of the head and the neck enters left thoracic veins.
6. The jugular, subclavian, and brochomediastinal trunks may unite to form the right lymphatic duct.
7. The thoracic duct is the largest lymphatic vessel.
8. The intestinal and lumbar trunks may converge on the cisterna chyli, a sac that joins the inferior end of the thoracic duct.

Lymphatic Tissue and Organs

1. Lymphatic tissue is reticular connective tissue that contains lymphocytes and other cells.
2. Lymphatic tissue can be surrounded by a capsule (lymph nodes, spleen, thymus).
3. Lymphatic tissue can be nonencapsulated (diffuse lymphatic tissue, lymphatic nodules, tonsils). Mucosa-associated lymphoid tissue is nonencapsulated lymphatic tissue located in and below the mucous membranes of the digestive, respiratory, urinary, and reproductive tracts.
4. Diffuse lymphatic tissue consists of dispersed lymphocytes and has no clear boundaries.
5. Lymphatic nodules are small aggregates of lymphatic tissue (e.g., Peyer's patches in the small intestines).
6. The tonsils
   - The tonsils are large groups of lymphatic nodules in the oral cavity and nasopharynx.
   - The three groups of tonsils are the palatine, pharyngeal, and lingual tonsils.
7. Lymph nodes
   - Lymphatic tissue in the node is organized into the cortex and the medulla. Lymphatic sinuses extend through the lymphatic tissue.
   - Substances in lymph are removed by phagocytosis, or they stimulate lymphocytes (or both).
   - Lymphocytes leave the lymph node and circulate to other tissues.
8. The spleen
   - The spleen is in the left superior side of the abdomen.
   - Foreign substances stimulate lymphocytes in the white pulp (periarterial lymphatic sheath and lymphatic nodules).
   - Foreign substances and defective red blood cells are removed from the blood by phagocytes in the red pulp (splenic cords and venous sinuses).
   - The spleen is a limited reservoir for blood.
   - Most blood flows through the spleen in a few seconds. About 20% of the blood takes a few minutes to flow through the spleen, and about 2% takes an hour or more.
9. The thymus
   - The thymus is a gland in the superior mediastinum and is divided into a cortex and a medulla.
   - Lymphocytes in the cortex are separated from the blood by reticular cells.
   - Lymphocytes produced in the cortex migrate through the medulla, enter the blood, and travel to other lymphatic tissues, where they can proliferate.

Immunity (p. 779)

Immunity is the ability to resist the harmful effects of microorganisms and other foreign substances.

Innate Immunity (p. 780)

Mechanical Mechanisms

Mechanical mechanisms prevent the entry of microbes (skin and mucous membranes) or remove them (tears, saliva, and mucus).

Chemical Mediators

1. Chemical mediators promote phagocytosis and inflammation.
2. Complement can be activated by either the alternative or the classical pathway. Complement lyses cells, increases phagocytosis, attracts immune system cells, and promotes inflammation.
3. Interferons prevent viral replication. Interferons are produced by virally infected cells and move to other cells, which are then protected.

Cells

1. Chemotactic factors are parts of microorganisms or chemicals that are released by damaged tissues. Chemotaxis is the ability of white blood cells to move to tissues that release chemotactic factors.
2. Phagocytosis is the ingestion and destruction of materials.
3. Neutrophils are small phagocytic cells.
4. Macrophages are large phagocytic cells.
   - Macrophages can engulf more than neutrophils can.
   - Macrophages in connective tissue protect the body at locations where microbes are likely to enter, and macrophages clean blood and lymph.
5. Basophils and mast cells release chemicals that promote inflammation.
6. Eosinophils release enzymes that reduce inflammation.
7. Natural killer cells lyse tumor cells and virus-infected cells.

Inflammatory Response

1. The inflammatory response can be initiated in many ways.
   - Chemical mediators cause vasodilation and increase vascular permeability, which allows the entry of other chemical mediators.
   - Chemical mediators attract phagocytes.
   - The amount of chemical mediators and phagocytes increases until the cause of the inflammation is destroyed. Then the tissue undergoes repair.

2. Local inflammation produces the symptoms of redness, heat, swelling, pain, and loss of function. Symptoms of systemic inflammation include an increase in neutrophil numbers, fever, and shock.

Adaptive Immunity (p. 785)

1. Antigens are large molecules that stimulate an adaptive immune system response. Haptens are small molecules that combine with large molecules to stimulate an adaptive immune system response.
2. B cells are responsible for humoral, or antibody-mediated, immunity. T cells are involved with cell-mediated immunity.

Origin and Development of Lymphocytes

1. B cells and T cells originate in red bone marrow. T cells are processed in the thymus, and B cells are processed in bone marrow.
2. Positive selection ensures the survival of lymphocytes that can react against antigens, and negative selection eliminates lymphocytes that react against self-antigens.
3. A clone is a group of identical lymphocytes that can respond to a specific antigen.
4. B cells and T cells move to lymphatic tissue from their processing sites. They continually circulate from one lymphatic tissue to another.
5. Primary lymphatic organs (red bone marrow and thymus) are where lymphocytes mature into functional cells. Secondary lymphatic organs and tissues are where lymphocytes produce an immune response.

Activation of Lymphocytes

1. The antigenic determinant is the specific part of the antigen to which the lymphocyte responds. The antigen receptor (T-cell receptor or B-cell receptor) on the surface of lymphocytes combines with the antigenic determinant.
2. MHC class I molecules display antigens on the surface of nucleated cells, resulting in the destruction of the cells.
3. MHC class II molecules display antigens on the surface of antigen-presenting cells, resulting in the activation of immune cells.
4. MHC/antigen complex and costimulation are usually necessary to activate lymphocytes. Costimulation involves cytokines and certain surface molecules.
5. Antigen-presenting cells stimulate the proliferation of helper T cells, which stimulate the proliferation of B or T effector cells.

Inhibition of Lymphocytes

1. Tolerance is suppression of the immune system's response to an antigen.
2. Tolerance is produced by deletion of self-reactive cells, by preventing lymphocyte activation, and by suppressor T cells.

Antibody-Mediated Immunity

1. Antibodies are proteins.
   - The variable region of an antibody combines with the antigen. The constant region activates complement or binds to cells.
   - Five classes of antibodies exist: IgG, IgM, IgA, IgE, and IgD.
2. Antibodies affect the antigen in many ways.
   - Antibodies bind to the antigen and interfere with antigen activity or bind the antigens together.
   - Antibodies act as opsonins (a substance that increases phagocytosis) by binding to the antigen and to macrophages.
   - Antibodies can activate complement through the classical pathway.
   - Antibodies attach to mast cells or basophils and cause the release of inflammatory chemicals when the antibody combines with the antigen.
3. The primary response results from the first exposure to an antigen. B cells form plasma cells, which produce antibodies and memory cells.
4. The secondary response results from exposure to an antigen after a primary response, and memory B cells quickly form plasma cells and additional memory cells.

Cell-Mediated Immunity

1. Antigen activates effector T cells and produces memory T cells.
2. Cytotoxic T cells lyse virus-infected cells, tumor cells, and tissue transplants.
3. Cytotoxic T cells produce cytokines, which promote phagocytosis and inflammation.

Immune Interactions (p. 800)

Innate immunity, antibody-mediated immunity, and cell-mediated immunity can function together to eliminate an antigen.

Immunotherapy (p. 800)

Immunotherapy stimulates or inhibits the immune system to treat diseases.

Acquired Immunity (p. 804)

Active Natural Immunity

Active natural immunity results from natural exposure to an antigen.

Active Artificial Immunity

Active artificial immunity results from deliberate exposure to an antigen.

Passive Natural Immunity

Passive natural immunity results from the transfer of antibodies from a mother to her fetus or baby.

Passive Artificial Immunity

Passive artificial immunity results from transfer of antibodies (or cells) from an immune animal to a nonimmune animal.

Effects of Aging on the Lymphatic System and Immunity (p. 805)

1. Aging has little effect on the ability of the lymphatic system to remove fluid from tissues, absorb fats from the digestive tract, or remove defective red blood cells from the blood.
2. Decreased helper T cell proliferation results in decreased antibody-mediated immunity and cell-mediated immunity responses to antigens.
3. The primary and secondary antibody responses decrease with age.
4. The ability to resist intracellular pathogens increases with age.

REVIEW AND COMPREHENSION

1. The lymphatic system
   a. removes excess fluid from tissues.
   b. absorbs fats from the digestive tract.
   c. defends the body against microorganisms and other foreign substances.
   d. all of the above.
2. Lymph capillaries
   a. have a basement membrane.
   b. are less permeable than blood capillaries.
   c. prevent backflow of lymph into the tissues.
   d. all of the above.
3. Lymph is moved through lymphatic vessels because of
   a. contraction of surrounding skeletal muscles.
   b. contraction of the heart.
   c. pressure changes in the blood vessels.
   d. flapping of the lymph valves.
   e. pumping by lymph nodes.
4. Which of the following statements is true?
   a. Lymphatic vessels do not have valves.
   b. Lymphatic vessels empty into lymph nodes.
   c. Lymph from the right-lower limb passes into the right lymphovenous portal.
   d. Lymph from the jugular and subclavian trunks empties into the cisterna chyli.
   e. All of the above.
5. The tonsils
   a. consist of three groups of lymphatic nodules.
   b. are located in the nasal cavity.
   c. are located in the oral cavity.
   d. increase in size in adults.
   e. all of the above.
6. Lymph nodes
   a. filter lymph.
   b. are where lymphocytes divide and increase in number.
   c. contain a network of reticular fibers.
   d. contain lymphatic sinuses.
   e. all of the above.
7. Which of these statements about the spleen is *not* correct?
   a. The spleen has white pulp associated with the arteries.
   b. The spleen has red pulp associated with the veins.
   c. The spleen destroys defective red blood cells.
   d. The spleen is surrounded by trabeculae located outside the capsule.
   e. The spleen is a limited reservoir for blood.
8. The thymus
   a. increases in size in adults.
   b. produces macrophages that move to other lymphatic tissue.
   c. responds to foreign substances in the blood.
   d. has a blood–thymic barrier.
   e. all of the above.
9. Which of these is an example of innate immunity?
   a. Tears and saliva wash away microorganisms.
   b. Basophils release histamine and leukotrienes.
   c. Neutrophils phagocytize a microorganism.
   d. The complement cascade is activated.
   e. All of the above.
10. Neutrophils
    a. enlarge to become macrophages.
    b. account for most of the dead cells in pus.
    c. are usually the last cell type to enter infected tissues.
    d. are usually located in lymph and blood sinuses.
11. Macrophages
    a. are large phagocytic cells that outlive neutrophils.
    b. develop from mast cells.
    c. often die after a single phagocytic event.
    d. have the same function as eosinophils.
    e. all of the above.
12. Which of these cells is the most important in the release of histamine, which promotes inflammation?
    a. monocyte
    b. macrophage
    c. eosinophil
    d. mast cell
    e. natural killer cell
13. Which of these conditions does *not* occur during the inflammatory response?
    a. histamine and other chemical mediators are released
    b. chemotaxis of phagocytes
    c. fibrinogen enters tissues from the blood
    d. vasoconstriction of blood vessels
    e. increased permeability of blood vessels
14. Which of these is a symptom of systemic inflammation?
    a. large numbers of neutrophils are produced and released
    b. pyrogens stimulate fever production
    c. greatly increased vascular permeability
    d. shock
    e. all of the above
15. Antigens
    a. are foreign substances introduced into the body.
    b. are molecules produced by the body.
    c. stimulate an adaptive immune system response.
    d. all of the above.
16. B cells
    a. are processed in the thymus.
    b. originate in red bone marrow.
    c. once released into the blood, remain in the blood.
    d. are responsible for cell-mediated immunity.
    e. all of the above.
17. MHC molecules
    a. are glycoproteins.
    b. attach to the plasma membrane.
    c. have a variable region that can bind to foreign and self-antigens.
    d. may form an MHC/antigen complex that activates T cells.
    e. all of the above.
18. Antigen-presenting cells can
    a. take in foreign antigens.
    b. process antigens.
    c. use MHC class II molecules to display the antigens.
    d. stimulate other immune system cells.
    e. all of the above.
19. Which of these participates in costimulation?
    a. cytokines
    b. complement
    c. antibodies
    d. histamine
    e. natural killer cells
20. Helper T cells
    a. respond to antigens from macrophages.
    b. respond to cytokines from macrophages.
    c. stimulate B cells with cytokines.
    d. all of the above.

21. The most important function of tolerance is to
    a. increase lymphocyte activity.
    b. increase complement activation.
    c. prevent the immune system from responding to self-antigens.
    d. prevent excessive immune system response to foreign antigens.
    e. process antigens.
22. Variable amino acid sequences on the arms of the antibody molecule
    a. make the antibody specific for a given antigen.
    b. enable the antibody to activate complement.
    c. enable the antibody to attach to basophils and mast cells.
    d. are part of the constant region.
    e. all of the above.
23. Antibodies
    a. prevent antigens from binding together.
    b. promote phagocytosis.
    c. inhibit inflammation.
    d. block complement activation.
    e. block the function of opsonins.
24. The secondary antibody response
    a. is slower than the primary response.
    b. produces fewer antibodies than the primary response.
    c. prevents disease symptoms from occurring.
    d. occurs because of cytotoxic T cells.
25. The type of lymphocyte that is responsible for the secondary antibody response is the
    a. memory B cell.
    b. B cell.
    c. T cell.
    d. helper T cell.
26. The largest percentage of antibodies in the blood are
    a. IgA.
    b. IgD.
    c. IgE.
    d. IgG.
    e. IgM.
27. Antibody-mediated immunity
    a. works best against intracellular antigens.
    b. is involved in tumor control.
    c. cannot be transferred from one person to another person.
    d. is responsible for immediate hypersensitivity reactions.
28. The activation of cytotoxic T cells can result in the
    a. lysis of virus-infected cells.
    b. production of cytokines.
    c. production of memory T cells.
    d. all of the above.
29. Cytokines
    a. promote inflammation.
    b. activate macrophages.
    c. kill target cells by causing them to lyse.
    d. all of the above.
30. Delayed hypersensitivity is
    a. caused by activation of B cells.
    b. a result of antibodies reacting with an allergen.
    c. mediated by T cells.
    d. caused by natural killer cells.
    e. caused by interferon.

Answers in Appendix F

CRITICAL THINKING

1. A patient is suffering from edema in the lower-right limb. Explain why elevation of the limb and massage helps to remove the excess fluid.
2. If the thymus of an experimental animal is removed immediately after its birth, the animal exhibits the following characteristics: (a) it is more susceptible to infections, (b) it has decreased numbers of lymphocytes in lymphatic tissue, and (c) its ability to reject grafts is greatly decreased. Explain these observations.
3. If the thymus of an adult experimental animal is removed, the following observations can be made: (a) no immediate effect occurs and (b) after 1 year, the number of lymphocytes in the blood decreases, the ability to reject grafts decreases, and the ability to produce antibodies decreases. Explain these observations.
4. Adjuvants are substances that slow but do not stop the release of an antigen from an injection site into the blood. Suppose injection A of a given amount of antigen is given without an adjuvant and injection B of the same amount of antigen is given with an adjuvant that causes the release of antigen over a period of 2–3 weeks. Does injection A or B result in the greater amount of antibody production? Explain.
5. Tetanus is caused by bacteria that enter the body through wounds in the skin. The bacteria produce a toxin that causes spastic muscle contractions. Death often results from failure of the respiration muscles. A patient comes to the emergency room after stepping on a nail. If the patient has been vaccinated against tetanus, the patient is given a tetanus booster shot, which consists of the toxin altered so that it is harmless. If the patient has never been vaccinated against tetanus, the patient is given an antiserum shot against tetanus. Explain the rationale for this treatment strategy. Sometimes both a booster and an antiserum shot are given, but at different locations of the body. Explain why this is done, and why the shots are given in different locations.
6. An infant appears to be healthy until about 9 months of age. Then he develops severe bacterial infections, one after another. Fortunately, the infections are successfully treated with antibiotics. When infected with the measles and other viral diseases, the infant recovers without unusual difficulty. Explain the different immune responses to these infections. Why did it take so long for this disorder to become apparent? (Hint: IgG.)
7. A baby is born with severe combined immunodeficiency disease (SCID). In an attempt to save her life, a bone marrow transplant is performed. Explain how this procedure might help the baby. Unfortunately, there is a graft rejection, and the baby dies. Explain what happened.
8. A patient has many allergic reactions. As part of the treatment scheme, doctors decide to try to identify the allergen that stimulates the immune system's response. A series of solutions, each containing an allergen that commonly causes a reaction, is composed. Each solution is injected into the skin at different locations on the patient's back. The following results are obtained: (a) at one location, the injection site becomes red and swollen within a few minutes; (b) at another injection site, swelling and redness appear 2 days later; and (c) no redness or swelling develops at the other sites. Explain what happened for each observation by describing what part of the immune system was involved and what caused the redness and swelling.

9. Ivy Hurtt developed a poison ivy rash after a camping trip. Her doctor prescribed a cortisol ointment to relieve the inflammation. A few weeks later Ivy scraped her elbow, which became inflamed. Because she had some of the cortisol ointment left over, she applied it to the scrape. Explain why the ointment was or was not a good idea for the poison ivy and for the scrape.
10. Suzy Withitt has just had her ears pierced. To her dismay, she finds that when she wears inexpensive (but tasteful) jewelry, by the end of the day there is an inflammatory (allergic) reaction to the metal in the jewelry. Is this because of antibodies or cytokines?

Answers in Appendix G

ANSWERS TO PREDICT QUESTIONS

1. Cutting and tying off the lymphatic vessels prevents the movement of interstitial fluid from the interstitial spaces. The small amount of fluid that fails to reenter the venous end of the capillaries after it leaves the arteriolar end of the capillaries is normally carried by the lymphatic vessels away from the tissue spaces and back to the general circulation. If the lymphatic vessels are tied off, the fluid accumulates in the interstitial spaces and results in edema.
2. The T cells transferred to mouse B don't respond to the antigen. The T cells are MHC-restricted and must have the MHC proteins of mouse A as well as antigen X to respond.
3. When the antigen is eliminated, it's no longer available for processing and combining with MHC class II molecules. Consequently, no signal takes place to cause lymphocytes to proliferate and produce antibodies.
4. The first exposure to the disease-causing agent (antigen) evokes a primary response. Gradually, however, antibodies degrade, and memory cells die. If, before all the memory cells are eliminated, a second exposure to the antigen occurs, a secondary response results. The memory cells produced then could provide immunity until the next exposure to the antigen.
5. With depression of helper T-cell activity, the ability of antigens to activate effector T cells is greatly decreased. Depression of cell-mediated immunity results in an inability to resist intracellular microorganisms and cancer.
6. The booster shot stimulates a secondary (memory) response, resulting in the formation of large amounts of antibodies and memory cells. Consequently there is better, longer-lasting immunity.
7. SLE is an autoimmune disorder in which self-antigens activate immune responses. Often, this results in the formation of immune complexes and inflammation. But sometimes antibodies bind to antigens on cells, resulting in the lysis of the cells. Purpura results from bleeding into the skin, which means that platelet plug formation, the normal mechanism for repairing small breaks in blood vessels, is not working. In this case of SLE, antibodies are causing the destruction of platelets, and the decreased number of platelets results in decreased platelet plug formation and coagulation (see chapter 19). The condition is called thrombocytopenia.