chapter 14

Lymphatic System and Immunity

THE IMMUNE SYSTEM ACCEPTS A TRANSPLANT. Organ transplants succeed only when the recipient's immune system accepts the healing foreign tissue. Sometimes people in dire need of organ transplants get them from unexpected sources. Here are two transplant tales.

Bobbie diSabatino, fifty-six years old, had been awaiting a heart transplant at the University of Maryland Medical Center for four months, after suffering a heart attack. She awoke Valentine's Day, 1998, with a new heart—thanks to a friendship her daughter had struck up with another hospital visitor, Bob Bradshaw. Bob's wife, thirty-eight-year-old Cheryl, had a cluster of abnormal blood vessels in her brain that caused her death, following a one-month hospital stay. During that time, Bob and Cheryl made the difficult decision to bequeath Cheryl's heart to Bobbie. The organ was a perfect match, and the transplant saved the older woman's life.

Peter F. was sixteen years old in 1996 when an automobile accident left him paralyzed from the waist down. Much of his small intestine had to be removed. As a result, Peter had to be fed intravenously, but developed liver failure and recurrent infections at the site where the catheter was inserted. A vicious cycle set in. He lost so much weight because of his deficient small intestine that doctors could no longer find veins to deliver nutrients. The next step was to transplant a small intestine from a cadaver, but no match was found. His doctors at the University of Minnesota then looked for a living donor—Peter's father, who was a close enough match immunologically. The father donated 200 centimeters of his small intestine to his son, and both are now healthy. Peter eats normally again.

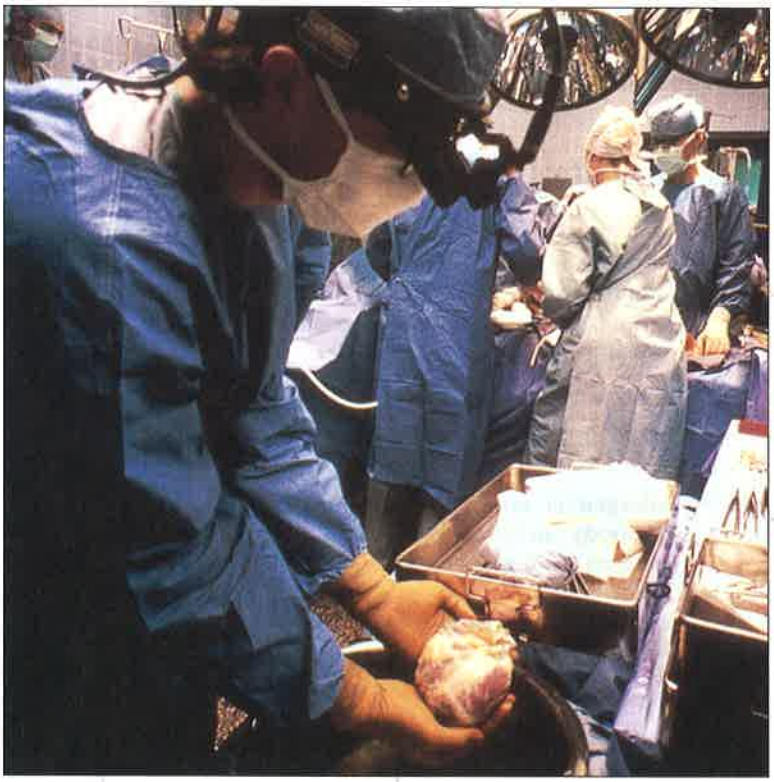


Photo:
Through heart transplantation, a heart that might have died with its donor years ago can provide life for a recipient, thanks to our understanding of the immune system—and a well-trained medical team!

Chapter Objectives

After studying this chapter, you should be able to do the following:

14.1 Introduction

1. Describe the general functions of the lymphatic system. (p. 367)

14.2 Lymphatic Pathways

2. Identify the locations of the major lymphatic pathways. (p. 367)

14.3 Tissue Fluid and Lymph

3. Describe how tissue fluid and lymph form, and explain the function of lymph. (p. 369)

14.4 Lymph Movement

4. Explain how lymphatic circulation is maintained. (p. 369)

14.5 Lymph Nodes

5. Describe a lymph node and its major functions. (p. 370)

14.6 Thymus and Spleen

6. Discuss the functions of the thymus and spleen. (p. 371)

14.7 Body Defenses Against Infection

7. Distinguish between specific and nonspecific defenses, and provide examples of each. (p. 373)

14.8 Nonspecific Defenses

8. List six nonspecific body defense mechanisms, and describe the action of each mechanism. (p. 373)

14.9 Specific Defenses (Immunity)

9. Explain how two major types of lymphocytes are formed and activated, and how they function in immune mechanisms. (p. 375)
10. Name the major types of immunoglobulins, and discuss their origins and actions. (p. 378)
11. Distinguish between primary and secondary immune responses. (p. 380)
12. Distinguish between active and passive immunity. (p. 381)
13. Explain how allergic reactions, tissue rejection reactions, and autoimmunity arise from immune mechanisms. (p. 381)

Aids to Understanding Words

gen- [be produced] aller*gen:* Substance that stimulates an allergic response.

humor- [fluid] *humor*al immunity: Immunity resulting from antibodies in body fluids.

immun- [free] *immun*ity: Resistance to (freedom from) a specific disease.

inflamm- [set on fire] *inflamm*ation: Localized redness, heat, swelling, and pain in tissues.

nod- [knot] *nod*ule: Small mass of lymphocytes surrounded by connective tissue.

path- [disease] *path*ogen: Disease-causing agent.

Key Terms

allergen (al´-er-jen)
antibody (an´tĭ-bod´´e)
antigen (an´tĭ-jen)
clone (klōn)
complement (kom´plĕ-ment)
hapten (hap´ten)
immunity (ĭmu´nĭ-te)
immunoglobulin (im´´u-no-glob´-u-lin)
lymph (limf)
lymphatic pathway (lim-fat´ik path´wa)
lymph node (limf nōd)
lymphocyte (lim´fo-sīt)
macrophage (mak´ro-fāj)
pathogen (path´o-jen)
reticuloendothelial tissue (rĕ-tik´´u-lo-en´´do-the´le-al tish´u)
spleen (splēn)
thymus (thī´mus)

14.1 Introduction

Like the cardiovascular system, the lymphatic system includes a network of vessels that transports fluids. The lymphatic system is a vast collection of cells and biochemicals that travel in lymphatic vessels, and the organs and glands that produce them. Lymphatic vessels carry away excess fluid from interstitial spaces in most tissues and return it to the bloodstream (fig. 14.1). Without the lymphatic system, this fluid would accumulate in tissue spaces. Special lymphatic capillaries, called lacteals, are located in the lining of the small intestine, where they absorb digested fats and transport them to the venous circulation.

The lymphatic system has a major second function—it enables us to live in a world filled with different types of organisms, some of which take up residence in the human body and cause infectious diseases. Cells and biochemicals of the lymphatic system launch both generalized and targeted attacks against "foreign" particles, enabling the body to destroy infectious microorganisms and viruses. This immunity function of the lymphatic system also attacks toxins and cancer cells, and when abnormal, can cause cancer, autoimmune disorders in which the body attacks itself, and allergies.

14.2 Lymphatic Pathways

The **lymphatic pathways** (lim-fat´ik path´wāz) begin as lymphatic capillaries. These tiny tubes merge to form larger lymphatic vessels. These, in turn, lead to larger vessels that unite with the veins in the thorax.

Lymphatic Capillaries

Lymphatic capillaries are microscopic, closed-ended tubes (fig. 14.2). They extend into interstitial spaces,

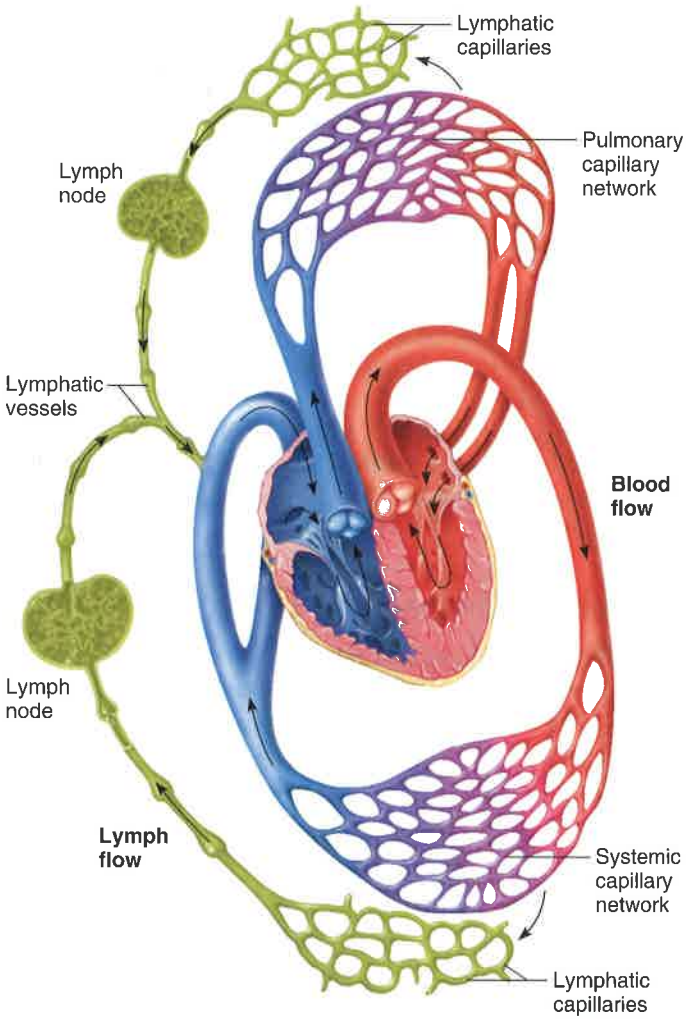


Figure 14.1
Schematic representation of lymphatic vessels transporting fluid from interstitial spaces to the bloodstream.

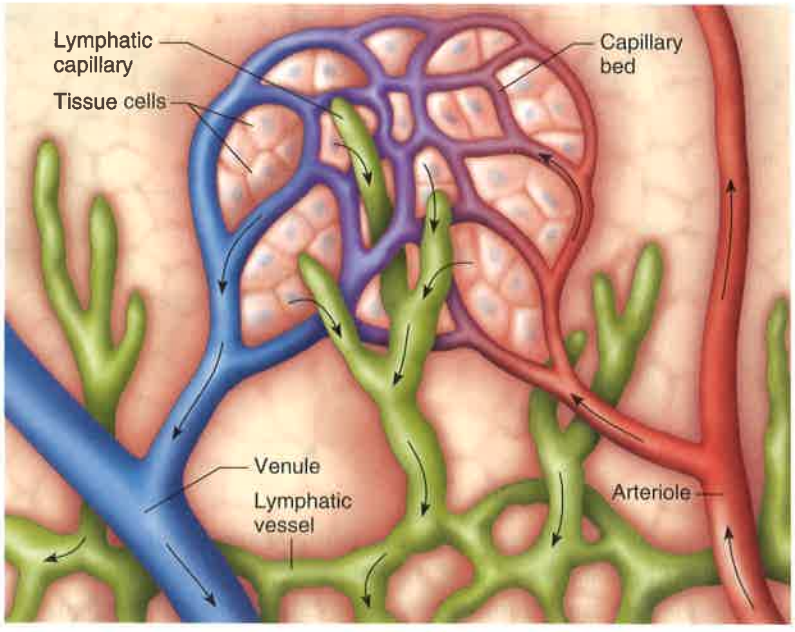


Figure 14.2
Lymphatic capillaries are microscopic, closed-ended tubes that begin in the interstitial spaces of most tissues.

forming complex networks that parallel those of blood capillaries. The walls of lymphatic capillaries, like those of blood capillaries, are formed from a single layer of squamous epithelial cells. These thin walls make it possible for tissue fluid to enter lymphatic capillaries. Fluid inside lymphatic capillaries is called **lymph** (limf).

Lymphatic Vessels

The walls of **lymphatic vessels** are similar to those of veins, but thinner. Also like veins, lymphatic vessels have flaplike valves that help prevent backflow of lymph (fig. 14.3).

The larger lymphatic vessels lead to specialized organs called **lymph nodes** (limf nōdz). After leaving the nodes, the vessels merge to form still larger **lymphatic trunks.**

Lymphatic Trunks and Collecting Ducts

Lymphatic trunks, which drain lymph, are named for the regions they serve. They join one of two **collecting ducts**—the thoracic duct or the right lymphatic duct (fig. 14.4*A*).

The **thoracic duct** is the larger and longer collecting duct. It receives lymph from the lower limbs and abdominal regions, left upper limb, and left side of the thorax, head, and neck, and empties into the left sub-

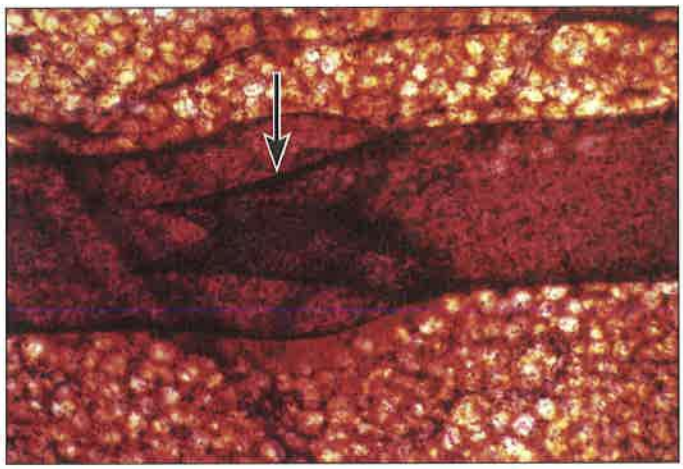


Figure 14.3
Light micrograph of the flaplike valve (arrow) within a lymphatic vessel (25×).

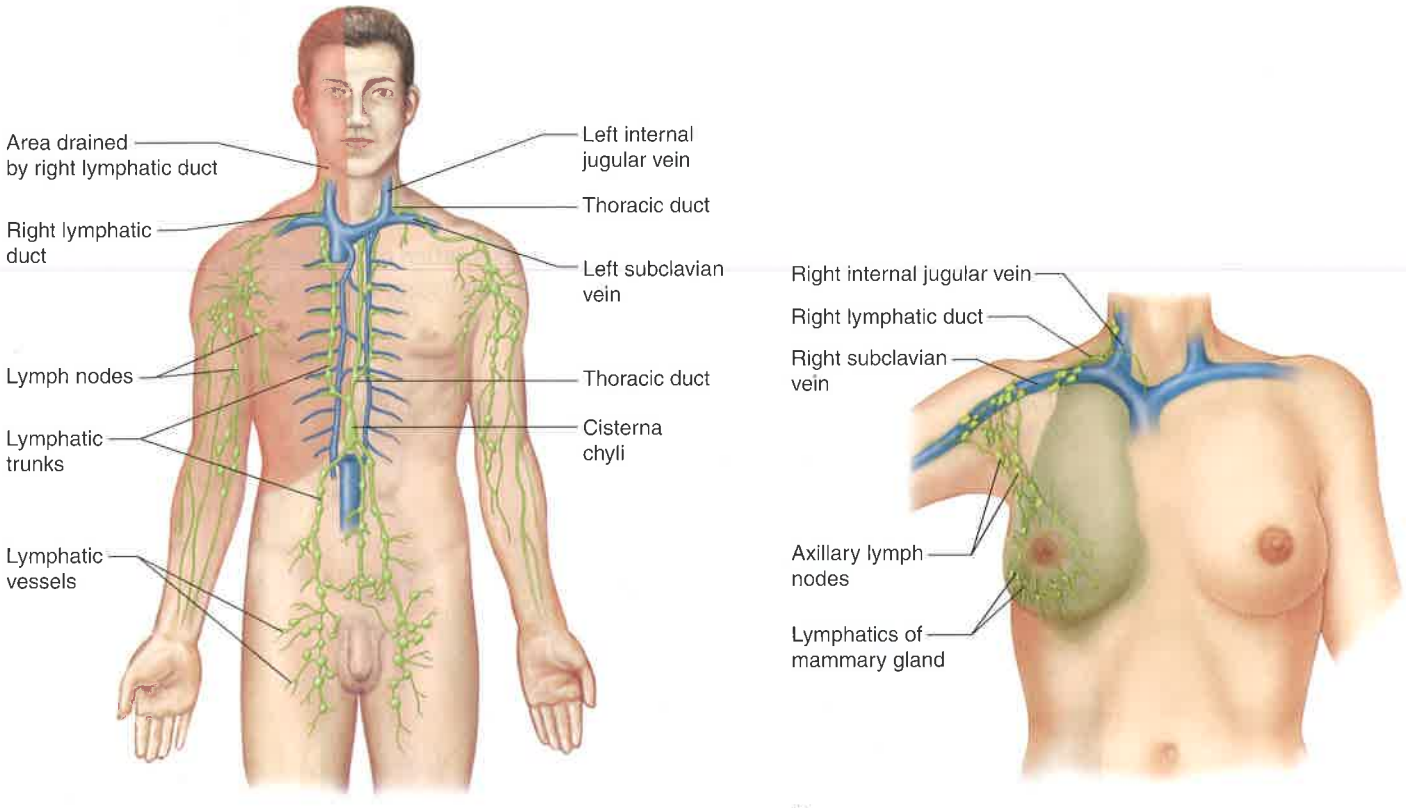


Figure 14.4
Lymphatic pathways. (*A*) The right lymphatic duct drains lymph from the upper right side of the body, whereas the thoracic duct drains lymph from the rest of the body. (*B*) Lymph drainage of the right breast illustrates a localized function of the lymphatic system. Surgery to remove a cancerous breast can disrupt this drainage, causing painful swelling.

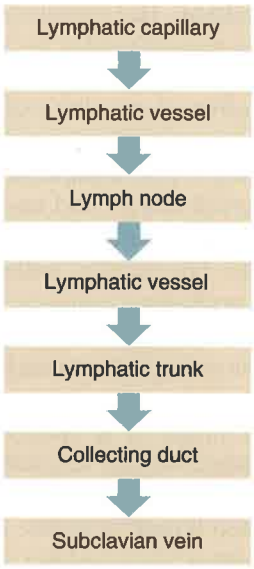


Figure 14.5
The lymphatic pathway.

clavian vein near the junction of the left jugular vein. The **right lymphatic duct** receives lymph from the right side of the head and neck, right upper limb, and right thorax, and empties into the right subclavian vein near the junction of the right jugular vein.

After leaving the collecting ducts, lymph enters the venous system and becomes part of the plasma just before blood returns to the right atrium. Figure 14.5 summarizes the typical lymphatic pathway.

The skin has many lymphatic capillaries. Consequently, if the skin is broken or if something is injected into it (such as venom from a stinging insect), foreign substances rapidly enter the lymphatic system.

CHECK YOUR RECALL

1. What are the general functions of the lymphatic system?
2. Distinguish between the thoracic duct and the right lymphatic duct.

14.3 Tissue Fluid and Lymph

Lymph is essentially tissue fluid that has entered a lymphatic capillary. Thus, lymph formation depends upon tissue fluid formation.

Tissue Fluid Formation

Recall from chapter 13 (p. 345) that tissue fluid originates from blood plasma and is composed of water and dissolved substances that leave blood capillaries. Capillary blood pressure causes filtration of water and small molecules from the plasma. The resulting fluid has much the same composition as the blood plasma (including nutrients, gases, and hormones), with the important exception of the plasma proteins, which are generally too large to pass through the capillary walls. The osmotic effect of these (called the *plasma colloid osmotic pressure*) helps draw fluid back into the capillaries by osmosis.

Lymph Formation and Function

Filtration from the plasma normally exceeds reabsorption, leading to the net formation of tissue fluid (interstitial fluid). This increases the interstitial fluid hydrostatic pressure somewhat, favoring movement of tissue fluid into lymphatic capillaries, forming lymph (see fig. 14.2). Lymph returns to the bloodstream most of the small proteins that leak out of blood capillaries. At the same time, lymph transports foreign particles, such as bacteria or viruses, to lymph nodes.

CHECK YOUR RECALL

1. What is the relationship between tissue fluid and lymph?
2. How do plasma proteins in tissue fluid affect lymph formation?
3. What are the major functions of lymph?

14.4 Lymph Movement

The hydrostatic pressure of tissue fluid drives the entry of lymph into lymphatic capillaries. However, muscular activity largely influences the movement of lymph through the lymphatic vessels.

Lymph, like venous blood, is under low hydrostatic pressure and may not flow readily through lymphatic vessels without outside help. These forces include contraction of skeletal muscles, contraction of the smooth muscle in the walls of the larger lymphatic trunks, and pressure changes associated with breathing.

Contracting skeletal muscles compress lymphatic vessels and move the lymph inside lymphatic vessels. These vessels contain valves that prevent backflow, so lymph can only move toward a collecting duct. Additionally, the smooth muscle in the walls of larger lymphatic trunks can contract and compress the lymph inside, forcing the fluid onward.

Breathing aids lymph circulation by creating a relatively low pressure in the thoracic cavity during inhalation. At the same time, the contracting diaphragm increases the pressure in the abdominal cavity. Together, these actions squeeze lymph out of the abdominal vessels and force it into the thoracic vessels. Once again, valves within lymphatic vessels prevent lymph backflow.

The continuous movement of fluid from interstitial spaces into blood and lymphatic capillaries stabilizes the volume of fluid in these spaces. Conditions that interfere with lymph movement cause tissue fluids to accumulate within the interstitial spaces, producing *edema,* or swelling. This may happen when surgery removes lymphatic tissue, obstructing certain lymphatic vessels. For example, a surgeon removing a cancerous breast tumor also usually removes nearby axillary lymph nodes to prevent associated lymphatic vessels from transporting cancer cells to other sites. Removing the lymphatic tissue can obstruct drainage from the upper limb, causing edema (fig. 14.4*B*).

CHECK YOUR RECALL

1. What factors promote lymph flow?
2. What is the consequence of lymphatic obstruction?

14.5 Lymph Nodes

Lymph nodes (lymph glands) are located along the lymphatic pathways. They contain large numbers of **lymphocytes** (lim´fo-sīts) and **macrophages** (mak´ro-fājez) that fight invading microorganisms.

Structure of a Lymph Node

Lymph nodes vary in size and shape, but are usually less than 2.5 centimeters long and somewhat bean-shaped (figs. 14.6 and 14.7). Blood vessels and nerves join a lymph node through the indented region of the node, called the **hilum.** The lymphatic vessels leading to a node (afferent vessels) enter separately at various points on its convex surface, but the lymphatic vessels leaving the node (efferent vessels) exit from the hilum.

A *capsule* of connective tissue encloses each lymph node and subdivides it into compartments that contain dense masses of lymphocytes and macrophages. These masses, called **lymph nodules,** are the structural units of the lymph node. The spaces within a node, called **lymph sinuses,** provide a complex network of chambers and channels through which lymph circulates. Macrophages are most highly concentrated in the lymph sinuses.

Nodules occur singly or in groups associated with the mucous membranes of the respiratory and digestive tracts. The *tonsils,* described in chapter 15 (p. 396), are partially encapsulated lymph nodules. Also, aggregations of nodules called *Peyer's patches* are scattered throughout the mucosal lining of the ileum of the small intestine.

Locations of Lymph Nodes

Lymph nodes generally occur in groups or chains along the paths of the larger lymphatic vessels throughout the body, but are absent in the central nervous system. Figure 14.8 shows the locations of the major lymph nodes.

Functions of Lymph Nodes

Lymph nodes have two primary functions: (1) filtering potentially harmful particles from lymph before returning it to the bloodstream, and (2) immune surveillance, provided by lymphocytes and macrophages. Along with

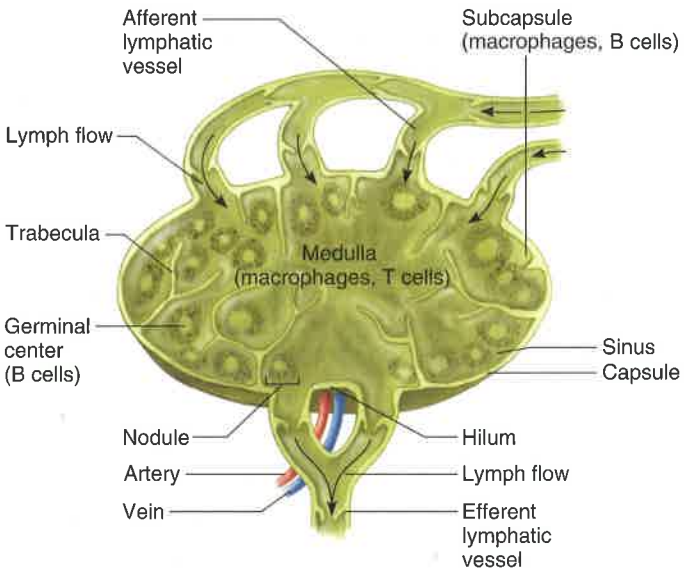


Figure 14.6
A section of a lymph node.

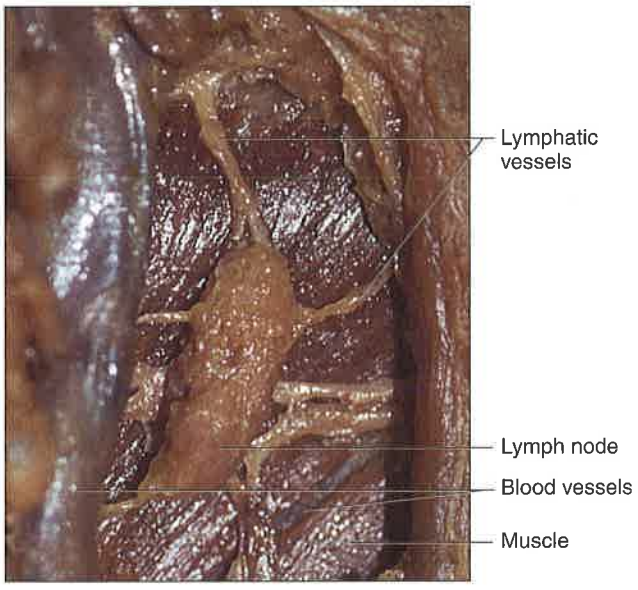


Figure 14.7
Lymph enters and leaves a lymph node through lymphatic vessels.

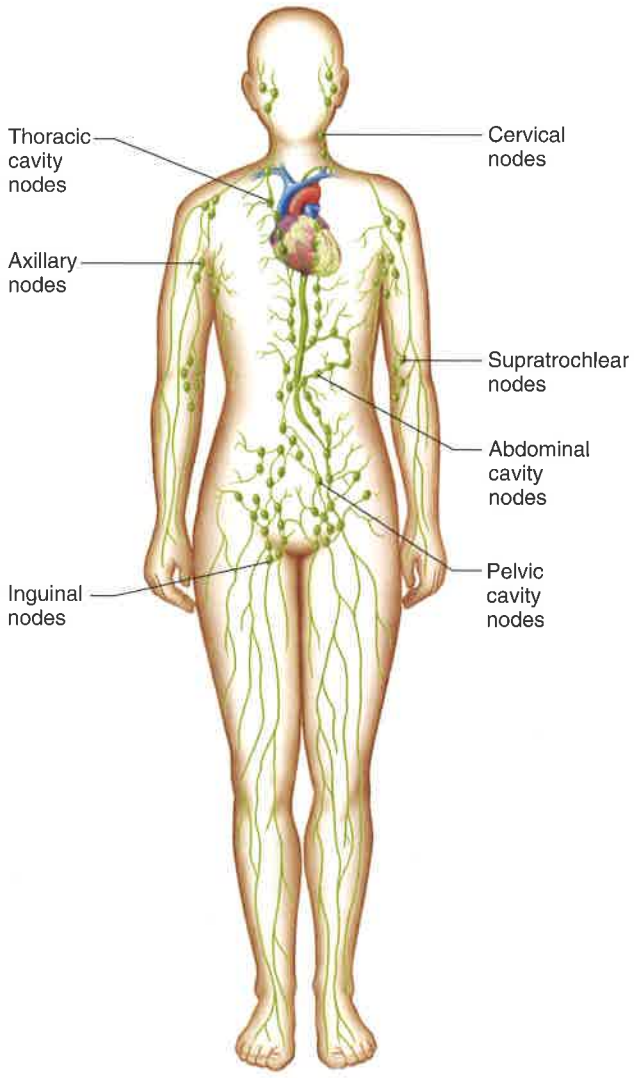


Figure 14.8
Major locations of lymph nodes.

red bone marrow, the lymph nodes are centers for lymphocyte production. Lymphocytes attack invading viruses, bacteria, and other parasitic cells that lymphatic vessels bring to the nodes. Macrophages in the nodes engulf and destroy foreign substances, damaged cells, and cellular debris.

Superficial lymphatic vessels inflamed by bacterial infection appear as red streaks beneath the skin, a condition called *lymphangitis.* Inflammation of the lymph nodes, called *lymphadenitis,* often follows. Affected nodes enlarge and may be quite painful.

CHECK YOUR RECALL

1. Distinguish between a lymph node and a lymph nodule.
2. What are the major functions of the lymph nodes?

14.6 Thymus and Spleen

Two other lymphatic organs whose functions are similar to those of the lymph nodes are the thymus and the spleen.

Thymus

The **thymus** (thī´mus) gland is a soft, bilobed structure enclosed in a connective tissue capsule and located anterior to the aorta and posterior to the upper part of the sternum (fig. 14.9*A*). The thymus is relatively large during infancy and early childhood, but shrinks after puberty and may be quite small in an adult. In elderly persons, adipose and connective tissues replace lymphatic tissue in the thymus.

Connective tissues extend inward from the thymus surface, subdividing the thymus into *lobules* (fig. 14.9*B*). The lobules contain abundant lymphocytes. Most of these cells (thymocytes) are inactive; however, some mature into **T cells** (T lymphocytes), which leave the thymus and provide immunity. Epithelial cells in the thymus secrete hormones called *thymosins,* which stimulate maturation of T cells after they leave the thymus and migrate to other lymphatic tissues.

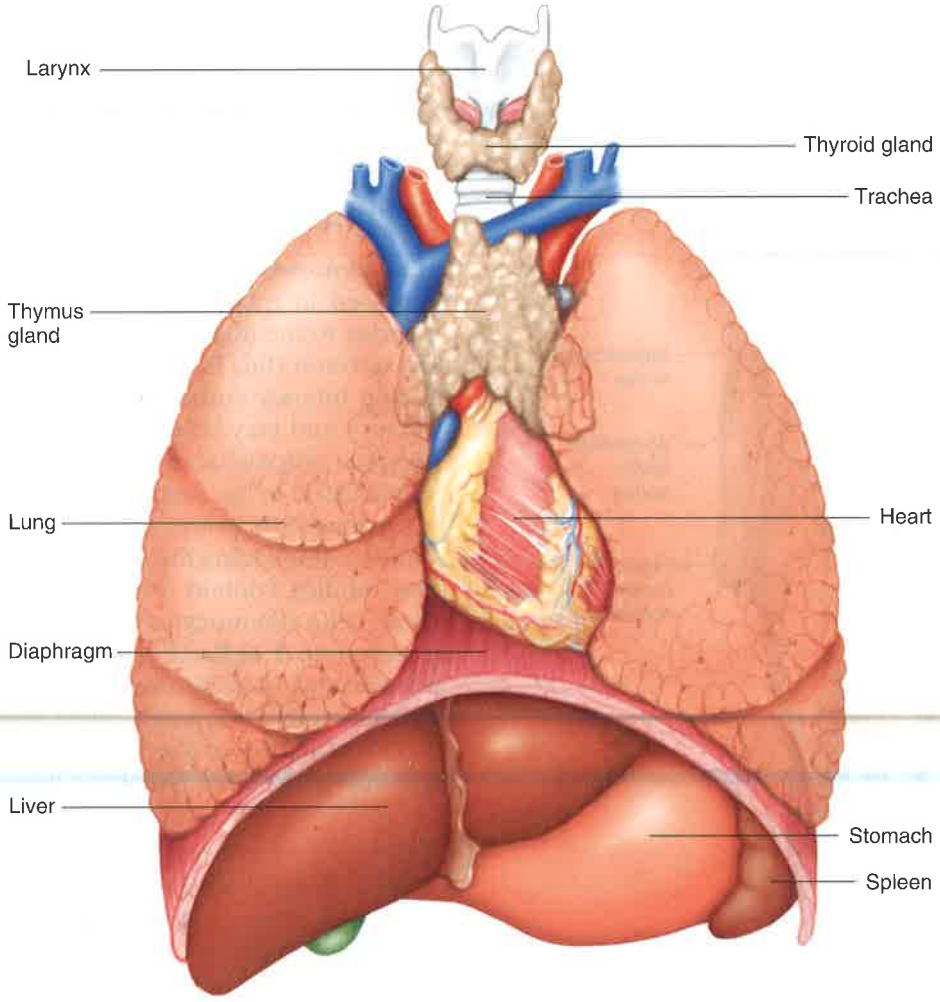
By age 70 years, the thymus is one-tenth the size it was at the age of 10, and the immune system is only 25% as powerful.

Spleen

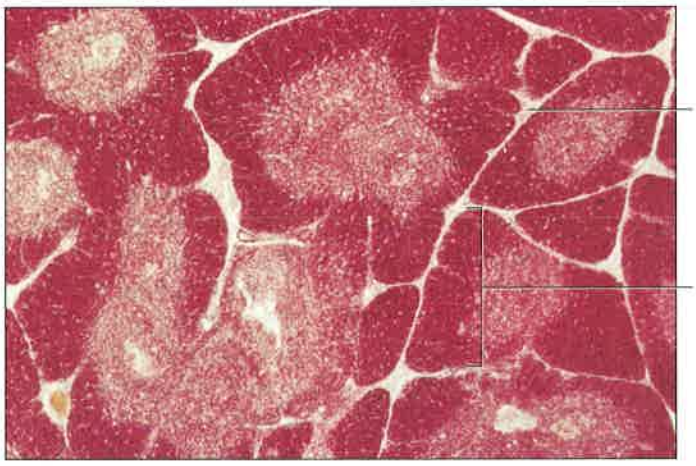
The **spleen** (splēn), the largest lymphatic organ, is in the upper left portion of the abdominal cavity, just inferior to the diaphragm and posterior and lateral to the stomach (fig. 14.9*A*). The spleen resembles a large lymph node and is subdivided into lobules. However, unlike the sinuses of a lymph node, the spaces (venous sinuses) of the spleen contain blood instead of lymph (fig. 14.10).

The tissues within splenic lobules are of two types. The *white pulp* is distributed throughout the spleen in tiny islands. This tissue is composed of splenic nodules, which are similar to those in lymph nodes and contain many lymphocytes. The *red pulp,* which fills the remaining spaces of the lobules, surrounds the venous sinuses. This pulp contains numerous red blood cells, which impart its color, plus many lymphocytes and macrophages.

Blood capillaries within the red pulp are quite permeable. Red blood cells can squeeze through the pores in these capillary walls and enter the venous sinuses. The older, more fragile red blood cells may rupture as they make this passage, and the resulting cellular debris

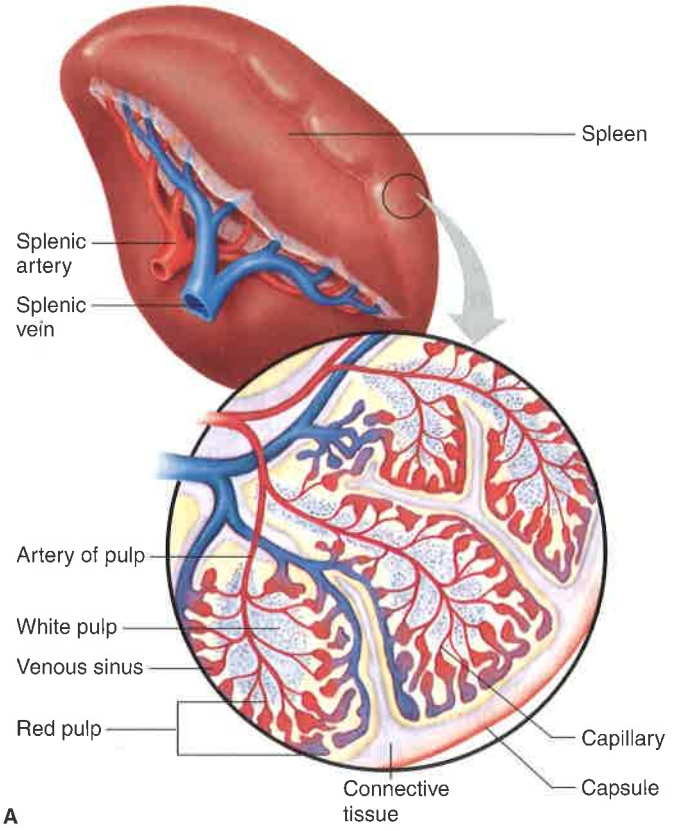


A



B

Figure 14.9
Thymus and spleen. (*A*) The thymus gland is bilobed and located between the lungs and superior to the heart. The spleen is located inferior to the diaphragm and posterior and lateral to the stomach. (*B*) A cross section of the thymus (20×). Note how the gland is subdivided into lobules.



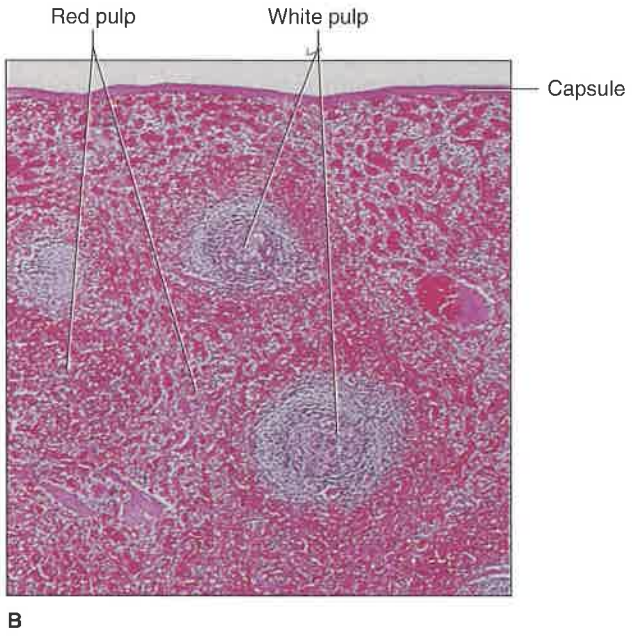


Figure 14.10
Spleen. (*A*) The spleen resembles a large lymph node. (*B*) Light micrograph of the spleen (15×).

is removed by phagocytic macrophages within the splenic sinuses. These macrophages also engulf and destroy foreign particles, such as bacteria, that may be carried in the blood as it flows through the sinuses. Thus, the spleen filters blood much as the lymph nodes filter lymph.

CHECK YOUR RECALL

1. Why are the thymus and spleen considered organs of the lymphatic system?
2. What are the major functions of the thymus and the spleen?

14.7 Body Defenses Against Infection

The presence and multiplication of a disease-causing agent, or **pathogen** (path´o-jen), causes an **infection.** Pathogens include viruses, bacteria, fungi, and protozoans.

The human body can prevent entry of pathogens or destroy them if they enter. Some mechanisms are quite general and protect against many types of pathogens, providing **nonspecific defense.** These mechanisms include species resistance, mechanical barriers, chemical barriers (enzyme action and interferon), fever, inflammation, and phagocytosis. Other defense mechanisms are very precise, targeting certain pathogens and providing **specific defense,** or **immunity** (ĭmu´nĭ-te). Specialized lymphocytes that recognize foreign molecules (nonself antigens) in the body and respond to them execute specific defense mechanisms. Nonspecific and specific defense mechanisms work together to protect the body against infection. While the nonspecific defenses, which respond quite rapidly, are being activated, the slower-to-respond specific defenses are being activated as well.

A word on terminology: nonspecific and specific immunity are also termed innate and acquired immunity. "Innate" refers to inborn protection mechanisms, whereas "acquired" aspects of immunity are stimulated by environmental factors. Acquired immunity is increasingly called "adaptive immunity."

14.8 Nonspecific Defenses

Species Resistance

Species resistance refers to the fact that a given kind of organism, or *species* (such as the human species, *Homo sapiens*), develops a set of diseases that is unique to it. At the same time, a species may be resistant to diseases

that affect other species because its tissues somehow fail to provide the temperature or chemical environment that a particular pathogen requires. For example, the infectious agents that cause measles, mumps, gonorrhea, and syphilis infect humans, but not other animal species.

Mechanical Barriers

The skin and mucous membranes lining the passageways of the respiratory, digestive, urinary, and reproductive systems create **mechanical barriers** that prevent entry of some infectious agents. Along with the hair that traps infectious agents associated with the skin and mucous membranes is the fluid (sweat and mucus) that rinses away microorganisms. These barriers provide a *first line of defense.* As long as the skin and mucous membranes remain intact, they can keep out many pathogens. The rest of the nonspecific defenses discussed in this section are part of the *second line of defense.*

Chemical Barriers

Enzymes in body fluids provide a **chemical barrier** to pathogens. Gastric juice, for example, contains the protein-splitting enzyme pepsin and has a low pH due to the presence of hydrochloric acid (HCl) (see chapter 15, p. 403). The combined effect of pepsin and HCl is lethal to many pathogens that enter the stomach. Similarly, tears contain the enzyme lysozyme, which has an antibacterial action against certain pathogens that may get onto eye surfaces. Finally, the accumulation of salt from perspiration kills certain bacteria on the skin.

Certain cells, including lymphocytes and fibroblasts, produce hormonelike peptides called **interferons** in response to viruses or tumor cells. Once released from the virus-infected cell, interferon binds to receptors on uninfected cells, stimulating them to synthesize proteins that block replication of a variety of viruses. Thus, the effect of interferon is nonspecific. Interferons also stimulate phagocytosis and enhance the activity of other cells that help the body resist infections and the growth of tumors.

Fever

Elevated body temperature due to **fever** offers powerful protection. Higher body temperature causes the liver and spleen to sequester iron, which reduces the level of iron in the blood. Since bacteria and fungi require more iron as temperature rises, their growth and reproduction in a fever-ridden body slow and may cease. Also, phagocytic cells attack more vigorously when the temperature rises. For these reasons, low-grade fever of short duration may be a desired response, not something to be treated aggressively with medications.

Inflammation

Inflammation is a tissue response to injury or infection, producing localized redness, swelling, heat, and pain. The redness is a result of blood vessel dilation and the consequent increase in blood volume within the affected tissues. This effect, coupled with an increase in the permeability of nearby capillaries, swells tissues (edema). The heat comes from blood from deeper body parts, which is generally warmer than that near the surface. Pain results from stimulation of nearby pain receptors.

Inflammation reactions result in walling off the site so infection cannot spread and bringing more blood with circulating phagocytes to remove the microorganisms from the site. Local heat speeds up phagocytic activity.

Infected cells release chemicals that attract white blood cells to inflammation sites, where they phagocytize pathogens. In bacterial infections, the resulting mass of white blood cells, bacterial cells, and damaged tissue may form a thick fluid called **pus.**

Body fluids also collect in inflamed tissues. These fluids contain fibrinogen and other blood-clotting factors. Clotting forms a network of fibrin threads within the affected region. Later, fibroblasts may arrive and secrete fibers until the area is enclosed in a sac of connective tissue containing many fibers. This action inhibits the spread of pathogens and toxic substances to adjacent tissues.

Phagocytosis

Recall from chapter 12 (p. 313) that blood's most active phagocytic cells are *neutrophils* and *monocytes*. These cells can leave the bloodstream by squeezing between the cells of blood vessel walls (diapedesis). Chemicals released from injured tissues attract these cells (chemotaxis). Neutrophils engulf and digest smaller particles; monocytes phagocytize larger ones.

Monocytes give rise to *macrophages* (histiocytes), which become fixed in various tissues and attach to the inner walls of blood and lymphatic vessels. These relatively nonmotile phagocytic cells, which can divide and produce new macrophages, are found in the lymph nodes, spleen, liver, and lungs. This diffuse group of phagocytic cells constitutes the **mononuclear phagocytic system** (reticuloendothelial system).

Phagocytosis removes foreign particles from the lymph as it moves from the interstitial spaces to the bloodstream. Phagocytes in the blood vessels and in the tissues of the spleen, liver, or bone marrow remove particles that reach the blood.

CHECK YOUR RECALL

1. What is an infection?
2. Explain six nonspecific defense mechanisms.

14.9 Specific Defenses (Immunity)

The *third line of defense,* immunity, is resistance to particular pathogens or to their toxins or metabolic byproducts. Lymphocytes and macrophages that recognize and remember specific foreign molecules carry out immune responses.

Antigens

Antigens (an´tĭ-jenz) may be proteins, polysaccharides, glycoproteins, or glycolipids, usually located on a cell's surface. Before birth, body cells inventory the proteins and other large molecules in the body, learning to recognize them as "self." The lymphatic system responds to nonself, or foreign antigens, but not normally to self antigens. Receptors on lymphocyte surfaces enable these cells to recognize foreign antigens.

The antigens that are most effective in eliciting an immune response are large and complex, with few repeating parts. Sometimes, a smaller molecule that cannot by itself stimulate an immune response combines with a larger one, which makes it able to do so. Such a small molecule is called a **hapten** (hap´ten). Stimulated lymphocytes react either to the hapten or to the larger molecule of the combination. Haptens are found in certain drugs such as penicillin, in household and industrial chemicals, in dust particles, and in products of animal skins (dander).

Lymphocyte Origins

During fetal development (before birth), red bone marrow releases undifferentiated lymphocytes into the circulation. About half of these cells reach the thymus, where they specialize into T cells. Later, some of these T cells comprise 70–80% of the circulating lymphocytes in blood. Other T cells reside in lymphatic organs and are particularly abundant in the lymph nodes, thoracic duct, and spleen.

Other lymphocytes are thought to remain in the red bone marrow until they differentiate into **B cells** (B lymphocytes). The blood distributes B cells, which constitute 20–30% of circulating lymphocytes. B cells settle in lymphatic organs along with T cells and are abundant in the lymph nodes, spleen, bone marrow, and intestinal lining (figs. 14.11 and 14.12).

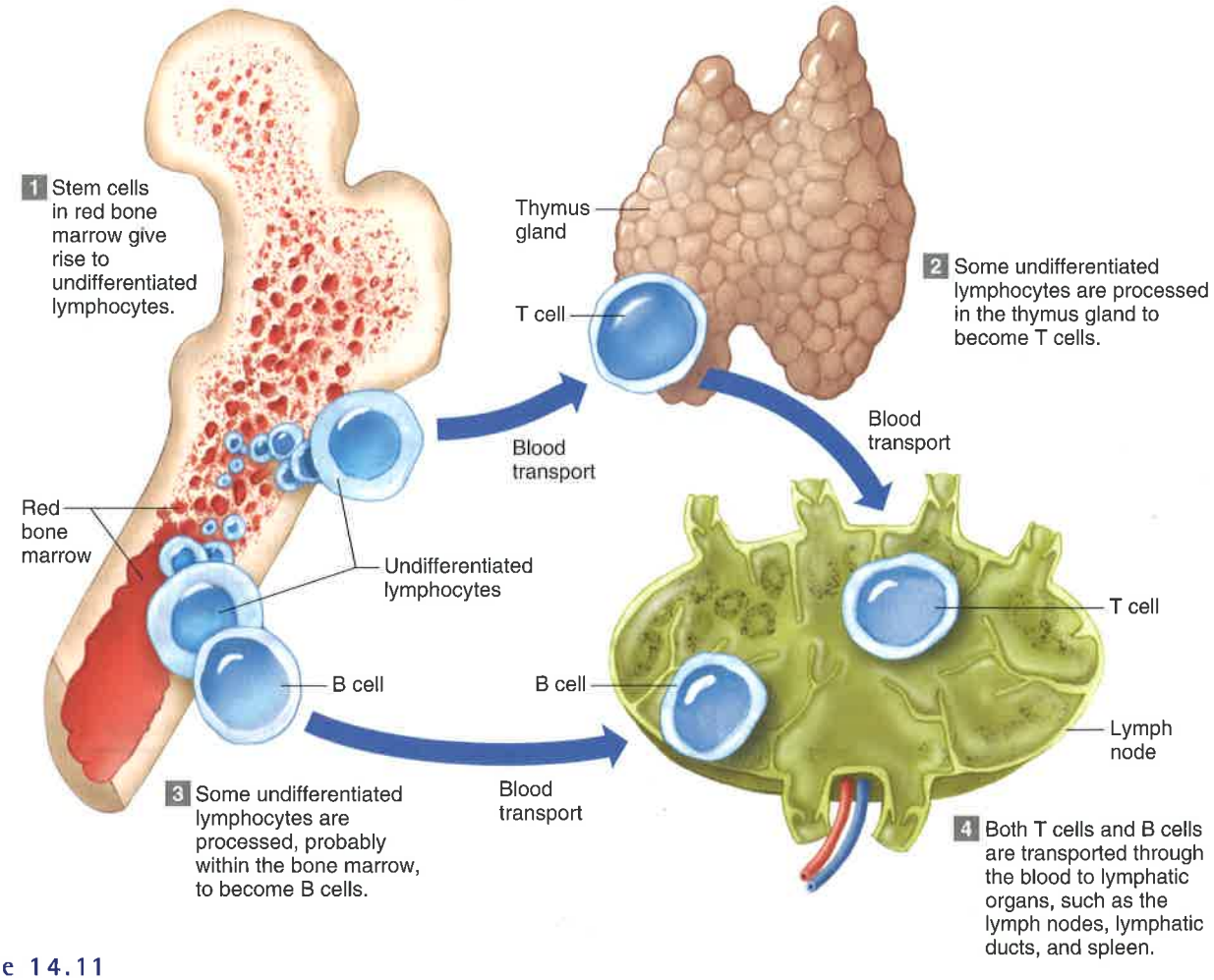


Figure 14.11
Bone marrow releases undifferentiated lymphocytes, which after processing become T cells (T lymphocytes) or B cells (B lymphocytes). Note that in the fetus the medullary cavity contains red marrow.

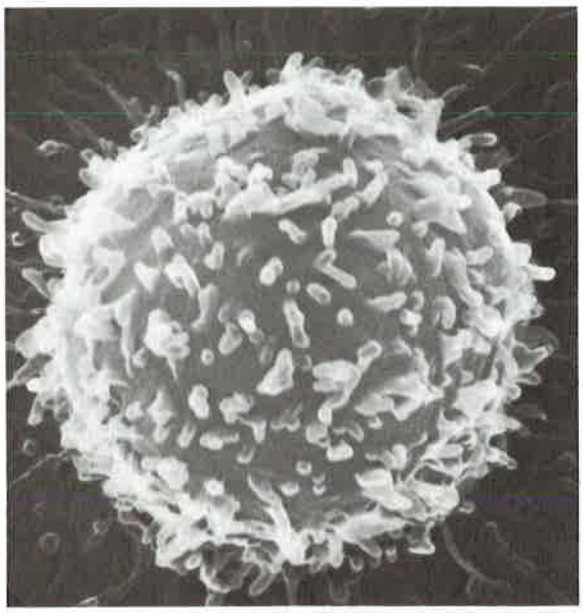


Figure 14.12
Scanning electron micrograph of a human circulating lymphocyte (7,000×).

CHECK YOUR RECALL

1. What is immunity?
2. What is the difference between an antigen and a hapten?
3. How do T cells and B cells originate?

Lymphocyte Functions

T cells and B cells respond to antigens they recognize in different ways. T cells attach to foreign, antigen-bearing cells, such as bacterial cells, and interact directly—that is, by cell-to-cell contact. This is called the **cellular immune response** or cell-mediated immunity.

T cells (and some macrophages) also synthesize and secrete polypeptides called *cytokines* (or, more specifically, lymphokines) that enhance certain cellular responses to antigens. For example, *interleukin-1* and *interleukin-2* stimulate synthesis of several cytokines from other T cells. In addition, interleukin-1 helps activate T cells, whereas interleukin-2 causes T cells to proliferate and activates another type of T cell (cytotoxic T cells). Other cytokines called *colony stimulating factors (CSFs)* stimulate leukocyte production in red bone marrow, cause B cells to grow and mature, and activate macrophages. T cells may also secrete toxins that kill their antigen-bearing target cells: growth-inhibiting factors that prevent target-cell growth or interferon that inhibits the proliferation of viruses and tumor cells.

B cells attack foreign antigens in a different way. They differentiate into **plasma cells,** which produce and secrete large globular proteins called **antibodies** (an´tĭ-bod´´ēz), or **immunoglobulins** (im´´u-no-glob´u-linz). Body fluids carry antibodies, which then react in various ways to destroy specific antigens or antigen-bearing particles. This antibody-mediated immune response is called the **humoral immune response** ("humoral" refers to fluid).

Each person has millions of varieties of T and B cells. Because the members of each variety originate from a single early cell, they are all alike, forming a **clone** (klōn) of cells (identical cells originating from division of a single cell). The members of each variety have a particular type of antigen receptor on their cell membranes that can respond only to a specific antigen. Table 14.1 compares the characteristics of T cells and B cells.

T Cells and the Cellular Immune Response

A lymphocyte must be activated before it can respond to an antigen. T cell activation requires the presence of processed fragments of antigen attached to the surface of another kind of cell, called an **antigen-presenting cell** (accessory cell). Macrophages, B cells, and several other cell types can be antigen-presenting cells.

T cell activation begins when a macrophage phagocytizes a bacterium, digesting it in its lysosomes. Some bacterial antigens exit the lysosomes and move to the macrophage's surface. Here, they are displayed on the cell membrane near certain protein molecules that are part of a group of proteins called the *major histocompatibility complex (MHC)*. A specialized type of T cell,

TABLE 14.1 A COMPARISON OF T CELLS AND B CELLS

CHARACTERISTIC	T CELLS	B CELLS
Origin of undifferentiated cell	Red bone marrow	Red bone marrow
Site of differentiation	Thymus	Probably the red bone marrow
Primary locations	Lymphatic tissues, 70–80% of the circulating lymphocytes	Lymphatic tissues, 20–30% of the circulating lymphocytes
Primary functions	Provides cellular immune response in which T cells interact directly with the antigens or antigen-bearing agents to destroy them	Provides humoral immune response in which B cells interact indirectly, producing antibodies that destroy the antigens or antigen-bearing agents

called a *helper T cell,* contacts a displayed foreign antigen. If the displayed antigen fits and combines with the helper T cell's antigen receptors, the helper cell becomes activated. Once activated, the helper T cell stimulates the B cell to produce antibodies that are specific for the displayed antigen.

A second type of T cell is a *cytotoxic T cell,* which recognizes nonself antigens that cancerous cells or virally infected cells display on their surfaces near certain MHC proteins. A cytotoxic T cell becomes activated when it combines with an antigen that fits its receptors. Next, the T cell proliferates, enlarging its clone of cells. Cytotoxic T cells then bind to the surfaces of antigen-bearing cells, where they release a protein that cuts porelike openings, destroying these cells. In this way, cytotoxic T cells continually monitor body cells, recognizing and eliminating tumor cells and cells infected with viruses.

Some of the T cells do not respond to the antigen on first exposure. Rather, they remain as *memory cells* that immediately differentiate into cytotoxic T cells upon subsequent exposure to the same antigen.

CHECK YOUR RECALL

1. What are the functions of T cells and B cells?
2. How do T cells become activated?
3. What is the function of cytokines?
4. How do cytotoxic T cells destroy antigen-bearing cells?

B Cells and the Humoral Immune Response

A B cell may become activated when it encounters an antigen whose molecular shape fits the shape of the B cell's antigen receptors. In response to the receptor-antigen combination, the B cell divides repeatedly, expanding its clone. However, most antigens require T cell "help" to activate B cells.

When an activated helper T cell encounters a B cell that has already combined with an identical foreign antigen, the helper cell releases certain cytokines. These cytokines stimulate the B cell to proliferate, thus enlarging its clone of antibody-producing cells (figs. 14.13 and 14.14). The cytokines also attract macrophages and leukocytes into inflamed tissues and help keep them there.

Some members of the activated B cell's clone differentiate further into *memory cells.* Like memory T cells, these memory B cells respond rapidly to subsequent exposure to a specific antigen.

Other members of the activated B cell's clone differentiate further into *plasma cells,* which secrete antibodies. These antibodies are similar in structure to the antigen receptor molecules on the original B cell's surface. Thus, antibodies can combine with the antigen-bearing agent that has invaded the body, and react against it. Table 14.2 summarizes the steps leading to antibody production as a result of B cell and T cell actions.

A plasma cell, during its brief lifespan, secretes up to 2,000 identical antibodies per second.

An individual's B cells can produce an estimated 10 million to 1 billion different varieties of antibodies, each reacting against a specific antigen. The enormity and diversity of the antibody response defends against many pathogens.

TABLE 14.2 STEPS IN ANTIBODY PRODUCTION

B CELL ACTIVITIES
1. Antigen-bearing agents enter tissues.
2. B cell becomes activated when it encounters an antigen that fits its antigen receptors, either alone or more often in conjunction with helper T cells.
3. Activated B cell proliferates, enlarging its clone.
4. Some of the newly formed B cells differentiate further to become plasma cells.
5. Plasma cells synthesize and secrete antibodies whose molecular structure is similar to the activated B cell's antigen receptors.
6. Antibodies combine with antigen-bearing agents, helping to destroy them.

T CELL ACTIVITIES
1. Antigen-bearing agents enter tissues.
2. Accessory cell, such as a macrophage, phagocytizes antigen-bearing agent, and the macrophage's lysosomes digest the agent.
3. Antigens from the digested antigen-bearing agents are displayed on the surface membrane of the accessory cell.
4. Helper T cell becomes activated when it encounters a displayed antigen that fits its antigen receptors.
5. Activated helper T cell releases cytokines when it encounters a B cell that has previously combined with an identical antigen-bearing agent.
6. Cytokines stimulate the B cell to proliferate.
7. Some of the newly formed B cells differentiate into antibody-secreting plasma cells.
8. Antibodies combine with antigen-bearing agents, helping to destroy them.

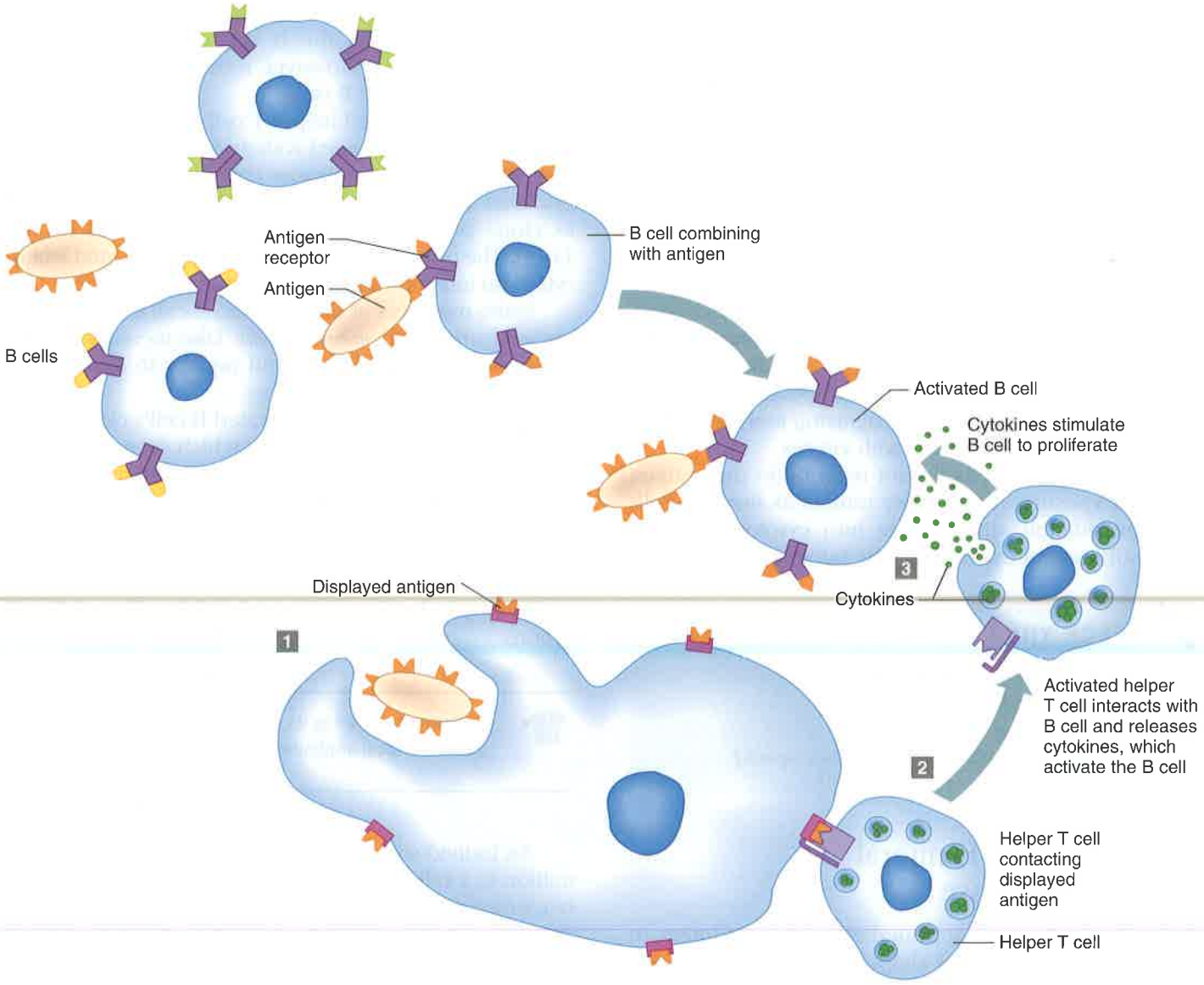


Figure 14.13
T cell and B cell activation. (*1*) After digesting antigen-bearing agents, a macrophage displays antigens on its surface. (*2*) Helper T cells become activated when they contact displayed antigens that fit their antigen receptors. (*3*) An activated helper T cell interacts with a B cell that has combined with an identical antigen and causes the B cell to proliferate.

Types of Antibodies

Antibodies (immunoglobulins) are soluble, globular proteins that constitute the *gamma globulin* fraction of plasma proteins (see chapter 12, p. 316). Of the five major types of immunoglobulins, the most abundant are immunoglobulin G, immunoglobulin A, and immunoglobulin M.

Immunoglobulin G (IgG) is in plasma and tissue fluids and is particularly effective against bacteria, viruses, and toxins. It also activates a group of immune system enzymes called complement, which is described later in this section.

Immunoglobulin A (IgA) is commonly found in exocrine gland secretions. It is in breast milk, tears, nasal fluid, gastric juice, intestinal juice, and bile. It is also in urine.

Immunoglobulin M (IgM) is a type of antibody that develops in the blood plasma in response to contact with certain antigens in foods or bacteria. The antibodies anti-A and anti-B, described in chapter 12 (p. 320), are examples of IgM. IgM also activates complement.

Immunoglobulin D (IgD) is found on the surfaces of most B cells, especially those of infants. IgD is important in activating B cells.

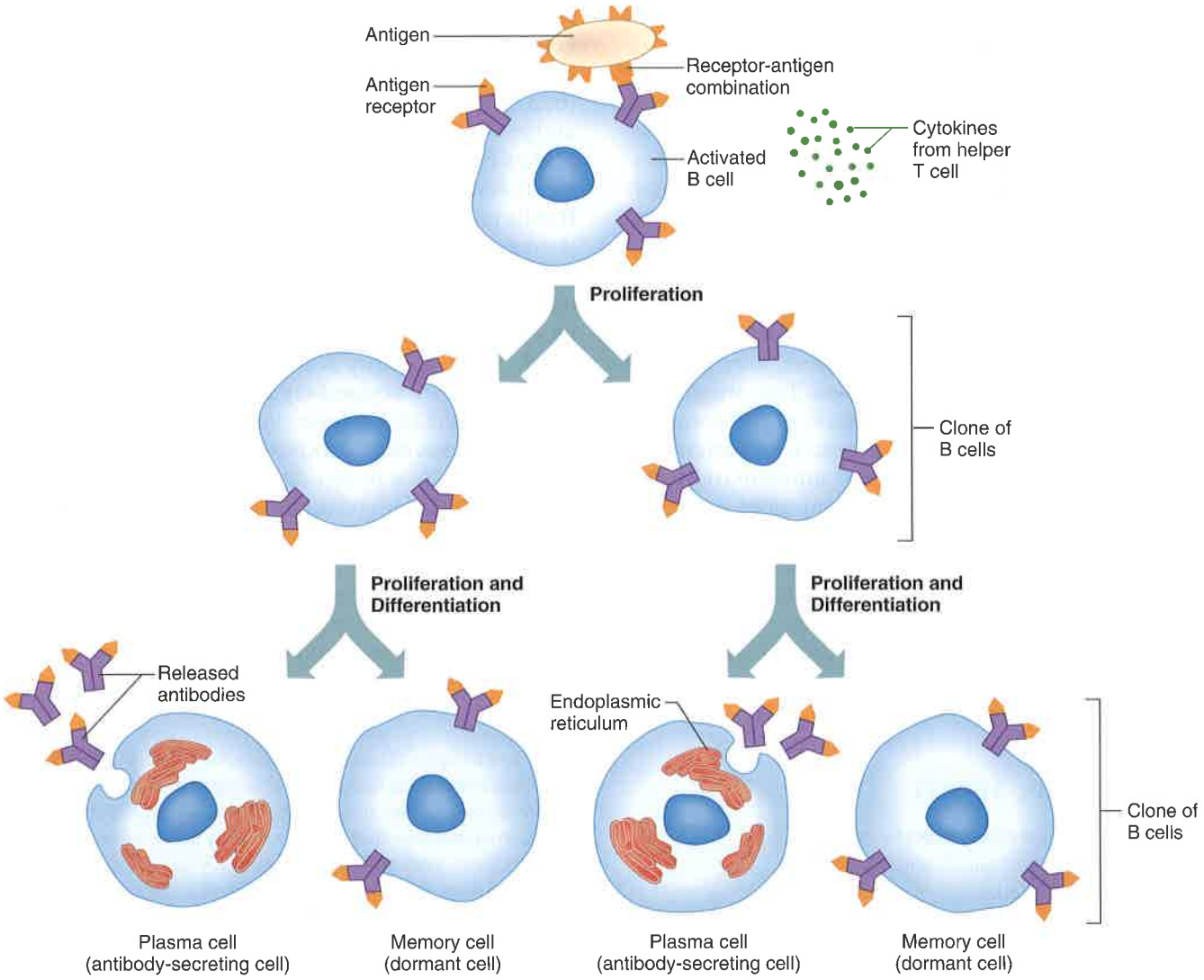


Figure 14.14
An activated B cell proliferates after stimulation by cytokines released by helper T cells. The B cell's clone enlarges. Some cells of the clone give rise to antibody-secreting plasma cells and others to dormant memory cells.

Immunoglobulin E (IgE) appears in exocrine secretions along with IgA. It is associated with allergic reactions, which are described later in this chapter.

A newborn does not yet have its own antibodies, but does retain IgG that passed through the placenta from the mother. These maternal antibodies protect the infant against some illnesses to which the mother is immune. Just as the maternal antibody supply falls, the infant begins to manufacture its own. The newborn receives IgA from colostrum, a substance secreted from the mother's breasts for the first few days after birth. Antibodies in colostrum protect against certain digestive and respiratory infections.

CHECK YOUR RECALL

1. How are B cells activated?
2. How does the antibody response protect against diverse infections?
3. Which immunoglobulins are most abundant, and how do they differ from each other?

Antibody Actions

In general, antibodies directly attack antigens, activate complement to attack the antigens, or stimulate changes in local areas that help prevent the spread of the antigens.

In a direct attack, antibodies combine with antigens and cause them to clump together (agglutinate) or to form insoluble substances (precipitate). Such actions make it easier for phagocytic cells to engulf the antigen-bearing agents and eliminate them. In other instances, antibodies cover the toxic portions of antigen molecules and neutralize their effects. However, under normal conditions, complement activation is more important in protecting against infection than is direct antibody attack.

Complement (kom´plĕ-ment) is a group of proteins in plasma and other body fluids. When certain IgG or IgM antibodies combine with antigens, they expose reactive sites on antibody molecules. This triggers a series of reactions, leading to activation of the complement proteins, which in turn produce a variety of effects. These include: coating the antigen-antibody complexes (opsonization), making them more susceptible to phagocytosis; attracting macrophages and neutrophils into the region (chemotaxis); clumping antigen-bearing agents; rupturing membranes of foreign cells (lysis); and altering the molecular structure of viruses, rendering them harmless. Other proteins promote inflammation, which helps prevent the spread of infectious agents (fig. 14.15).

CHECK YOUR RECALL

1. In what general ways do antibodies function?
2. What is the function of complement?
3. How is complement activated?

Immune Responses

When B cells or T cells become activated after first encountering the antigens for which they are specialized to react, their actions constitute a **primary immune response.** During such a response, plasma cells release antibodies (IgM, followed by IgG) into lymph. The antibodies are transported to the blood and then throughout the body, where they help destroy antigen-bearing agents. Production and release of antibodies continues for several weeks.

Following a primary immune response, some of the B cells produced during proliferation of the clone remain dormant as memory cells (fig. 14.14). If the identical antigen is encountered in the future, the clones of these memory cells enlarge, and they can respond rapidly with IgG to the antigen to which they were previously sensitized. These memory B cells, along with the memory T cells, produce a **secondary immune response.**

As a result of a primary immune response, detectable concentrations of antibodies usually appear in the body fluids within five to ten days following an exposure to antigens. If the identical antigen is encountered some time later, a secondary immune response may produce additional antibodies within a day or two (fig. 14.16). Although newly formed antibodies may persist in the body for only a few months or years, memory cells live much longer. Consequently, the ability to produce a secondary immune response may be long-lasting.

Superantigens are foreign antigens that elicit unusually vigorous lymphocyte responses. The bacterium *Staphylococcus aureus* produces two such superantigens. One type causes food poisoning until digestive enzymes destroy it. The second type causes toxic shock syndrome, a potentially fatal condition producing high fever, diarrhea, vomiting, confusion, and plummeting blood pressure.

CHECK YOUR RECALL

1. How do primary and secondary immune responses differ?

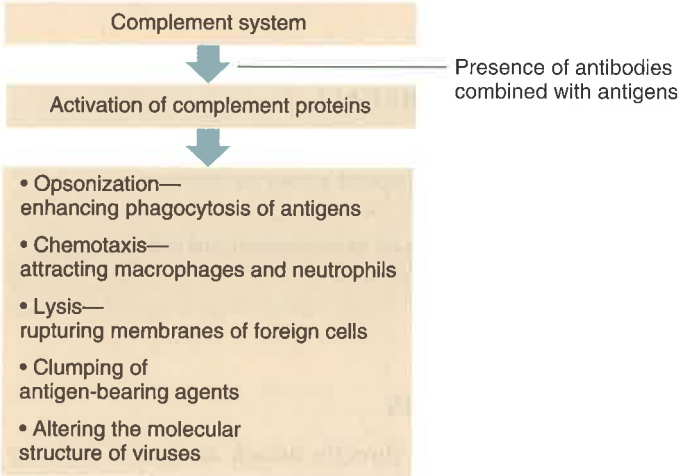


Figure 14.15
Actions of the complement system.

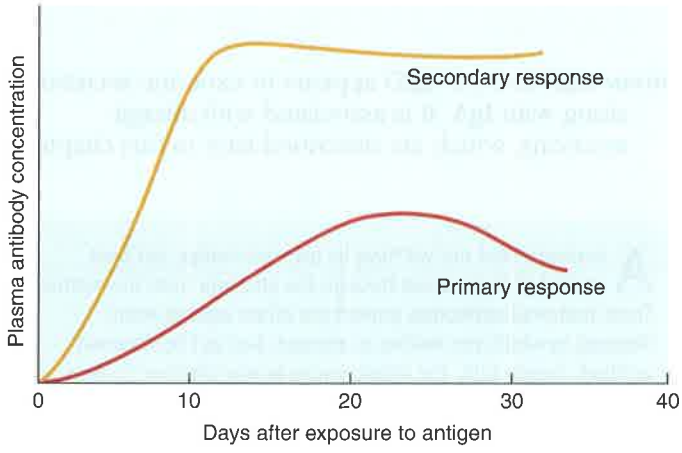


Figure 14.16
A primary immune response produces a lesser concentration of antibodies than does a secondary immune response.

Practical Classification of Immunity

Acquired immunity can arise in response to natural events or be induced artificially by injecting or orally administering a suspension of killed or weakened pathogens. Both naturally and artificially acquired immunities can be either active or passive. Active immunity results when the person produces an immune response (including memory cells) to the antigen; it is long-lasting. Passive immunity occurs when a person receives antibodies produced by another individual. Since the person does not produce an immune response, passive immunity is short-term, and the individual will be susceptible upon exposure to the antigen at some later date.

Naturally acquired active immunity occurs when a person exposed to a pathogen develops a disease. Resistance to that pathogen is the result of a primary immune response.

A **vaccine** produces another type of active immunity. A vaccine might consist of bacteria or viruses that have been killed or weakened so that they cannot cause a serious infection, or a toxoid, which is a toxin from an infectious organism that has been chemically altered to destroy its toxic effects. Whatever its composition, a vaccine includes the antigens that stimulate a primary immune response but does not produce the severe symptoms of disease. A vaccine causes a person to develop *artificially acquired active immunity.*

Vaccines stimulate active immunity against a variety of diseases, including typhoid fever, cholera, whooping cough, diphtheria, tetanus, polio, chicken pox, measles (rubeola), German measles (rubella), mumps, influenza, hepatitis B, and bacterial pneumonia. Vaccines have virtually eliminated natural smallpox from the world, but vaccination may resume in light of the possibility of smallpox being used as a bioweapon. Unfortunately, vaccine distribution is not equitable worldwide. Many thousands of people in underdeveloped countries die of infectious diseases for which vaccines are available in other nations.

Some people were afraid of the first vaccinations, which were derived from cows. They were afraid that their vaccinated children might behave like cows.

Sometimes a person who has been exposed to infection needs protection against a disease-causing microorganism but lacks the time to develop active immunity. An injection of antiserum (ready-made antibodies) may help. These antibodies may be obtained from gamma globulin (see chapter 12, p. 316) separated from the plasma of persons who have already developed immunity against the particular disease. A gamma globulin injection provides *artificially acquired passive immunity.*

During pregnancy, certain antibodies (IgG) pass from the maternal blood into the fetal bloodstream. As a result, the fetus acquires limited immunity against pathogens that the pregnant woman has developed active immunities against. The fetus thus has *naturally acquired passive immunity,* which may last for six months to a year after birth. Table 14.3 summarizes the types of acquired immunity.

CHECK YOUR RECALL

1. Distinguish between active and passive immunity.

Allergic Reactions

An allergic response is an immune attack against a nonharmful substance, such as chocolate. Allergic reactions are similar to immune responses because they sensitize lymphocytes, and antibodies may bind antigens. However, unlike normal immune responses, allergic reactions can damage tissues. Antigens that trigger allergic responses are called **allergens** (al´er-jenz).

A *delayed-reaction allergy* may affect anyone. It results from repeated exposure of the skin to certain chemicals—commonly, household or industrial chemicals

TABLE 14.3 PRACTICAL CLASSIFICATION OF IMMUNITY

TYPE	MECHANISM	RESULT
Naturally acquired active immunity	Exposure to live pathogens	Symptoms of a disease and stimulation of an immune response
Artificially acquired active immunity	Exposure to a vaccine containing weakened or dead pathogens or their components	Stimulation of an immune response without the severe symptoms of a disease
Artificially acquired passive immunity	Injection of gamma globulin containing antibodies	Short-term immunity without stimulating an immune response
Naturally acquired passive immunity	Antibodies passed to fetus from pregnant woman with active immunity	Short-term immunity for infant without stimulating an immune response

Topic of Interest IMMUNITY BREAKDOWN: AIDS

Infection by the *human immunodeficiency virus (HIV)* causes *acquired immune deficiency syndrome (AIDS),* a progressive breakdown of the immune system. The virus attacks lymphocytes by attaching to receptors on helper T cells and sending in its RNA. Within the cell's nucleus, a viral enzyme, *reverse transcriptase,* catalyzes construction of a DNA strand complementary to the viral RNA. The initial viral DNA strand replicates to form a DNA double helix.

Using the invaded cell's protein-synthesizing machinery, HIV replicates, filling the cell with its RNA and proteins. Not only can the dying T cell no longer release cytokines or stimulate B cells to manufacture antibodies, but it bursts, unleashing new HIV particles. HIV replicates rapidly and soon overwhelms the immune system. Specific symptoms in different individuals reflect the infectious agents to which they are exposed. Common AIDS-related conditions include:

Persistent lymphadenopathy (swollen lymph glands)
Constant low-grade fever
Nausea and vomiting
Fatigue
Night sweats
Headaches
Wasting syndrome (persistent diarrhea, severe weight loss, weakness, fever)
Dementia (confusion, apathy, inability to concentrate, memory loss, insomnia, disorientation, sudden strong emotions)
Cancers (Kaposi sarcoma, cervical cancer, lymphoma, others)
Opportunistic infections (pneumonia, brain infection, diarrhea, spinal meningitis, tuberculosis, fungal infections, many others)

HIV infection has three stages: initial symptoms, a latency period, and AIDS. The initial, acute stage may include weakness, recurrent fever, night sweats, swollen neck glands, and weight loss. This stage varies in duration and severity. Often it lasts only a few days, and the person may think it is the flu. Then comes a latency period, typically lasting five to ten years, during which the person feels well. This well-being is deceptive because the immune system is struggling to contain the growing HIV population, first in the lymph nodes and then in the bloodstream. The third stage, AIDS, brings opportunistic infections, so called because they appear when the immune system is compromised.

Modes of Transmission

AIDS transmission requires contact with a body fluid containing abundant HIV, such as blood or semen. Although the virus has been detected in sweat, tears, and saliva, levels are so low that transmission is highly unlikely. Whether or not a person becomes infected appears to depend on the amount of infected fluid contacted, the site of exposure in the body, and the individual's health. Table 14A lists some of the ways that HIV infection can and cannot spread.

or some cosmetics. After repeated contacts, the presence of the foreign substance activates T cells, many of which collect in the skin. The T cells and the macrophages they attract release chemical factors, which in turn cause eruptions and inflammation of the skin (dermatitis). This reaction is called *delayed* because it usually takes about 48 hours to occur.

An *immediate-reaction allergy* occurs within minutes after contact with an allergen. Persons with this type of allergy have an inherited tendency to overproduce IgE antibodies in response to certain antigens. IgE normally comprises a minute fraction of plasma proteins.

An immediate-reaction allergy activates B cells, which become sensitized when the allergen is first encountered. Subsequent exposures to the allergen trigger allergic reactions. In the initial exposure, IgE attaches to the membranes of widely distributed mast cells and basophils. When a subsequent allergen-antibody reaction occurs, these cells release allergy mediators such as *histamine, prostaglandin* D_2, and *leukotrienes*. These substances cause a variety of physiological effects, including dilation of blood vessels, increased vascular permeability that swells tissues, contraction of bronchial and intestinal smooth muscles, and increased mucus production. The result is a severe inflammation reaction that is responsible for the symptoms of the allergy, such as hives, hay fever, asthma, eczema, or gastric disturbances.

Anaphylactic shock is a severe form of immediate-reaction allergy in which mast cells release allergy mediators throughout the body. The person may at first feel an inexplicable apprehension, and then suddenly the entire body itches and breaks out in red hives. Vomiting and diarrhea may follow. The face, tongue, and larynx begin to swell, and breathing becomes difficult. Unless the person receives an injection of epinephrine (adrenalin) and sometimes a tracheotomy (an incision into the windpipe to restore breathing), he or she will lose consciousness and may die within 5 minutes. Anaphylactic shock most often results from an allergy to penicillin or insect stings. Fortunately, thanks to prompt medical attention and avoidance of allergens by people who know they have allergies, fewer than 100 people a year actually die from anaphylactic shock.

Progress

Three groups of people are providing the clues that may lead to conquering HIV infection:

1. Infected individuals who never develop symptoms ("long-term nonprogressors"). These people have a weakened strain of HIV that lacks part of a gene HIV normally uses to replicate. Enough of the virus remains to alert the immune system to protect against other strains. A vaccine might be based on this weakened strain.
2. People exposed repeatedly who never become infected. About 1% of the population has a gene variant that protects them from becoming infected with HIV. The cells of these individuals lack either of two receptor molecules that HIV requires to enter cells.
3. Infected individuals who apparently become uninfected. Several infants infected at birth have apparently lost the virus as their immune systems matured.

Researchers are identifying how these people survive, evade, or vanquish HIV infection, and will use this knowledge to develop prevention and treatment strategies.

Several classes of drugs target HIV infection at various stages. The first drugs, such as AZT, ddI, ddC, and 3TC, block viral replication. Drugs called protease inhibitors prevent HIV from processing its proteins to a functional size, crippling the virus. A third class of drugs, called fusion inhibitors, block the binding of HIV to T cell surfaces. Combining drugs can keep viral load low and delay symptom onset and progression, although viral variants emerge that resist the drugs. The goal is to enable infected people to live normal life spans in relatively good health. More than 200 drugs are also available to treat AIDS-associated opportunistic infections and cancers.

Better understanding of the biology of HIV infection, plus new drug weapons and clues from survivors, are providing what has long been lacking in the global fight against AIDS—hope. Slowly, HIV infection is becoming a chronic illness, rather than a death sentence.

TABLE 14A HIV TRANSMISSION

HOW HIV IS TRANSMITTED
Sexual contact, particularly anal intercourse, but including vaginal intercourse and oral sex
Contaminated needles (intravenous drug use, injection of anabolic steroids, accidental needle stick in medical setting)
During birth from infected mother
Receiving infected blood or other tissue (precautions usually prevent this)
HOW HIV IS NOT TRANSMITTED
Casual contact (social kissing, hugging, handshakes)
Objects (toilet seats, deodorant sticks, doorknobs)
Mosquitoes
Sneezing and coughing
Sharing food
Swimming in the same water
Donating blood

Transplantation and Tissue Rejection

Transplantation of tissues or an organ, such as the skin, kidney, heart, or liver, from one person to another can replace a nonfunctional, damaged, or lost body part. The danger the immune system poses to transplanted tissue is that the recipient's cells may recognize the donor's tissues as foreign and attempt to destroy the transplanted tissue. Such a response is called a **tissue rejection reaction.**

Tissue rejection resembles the cellular immune response against a nonself antigen. The greater the antigenic difference between the cell surface molecules of the recipient's tissues and the donor's tissues, the more rapid and severe the rejection reaction. Matching donor and recipient tissues can minimize the rejection reaction. This means locating a donor whose tissues are antigenically similar to those of the person needing a transplant—a procedure much like matching the blood of a donor with that of a recipient before giving a blood transfusion.

Immunosuppressive drugs are used to reduce rejection of transplanted tissues. These drugs interfere with the recipient's immune response by suppressing formation of antibodies or production of T cells, thereby dampening the humoral and cellular immune responses. Unfortunately, the use of immunosuppressive drugs can leave a recipient unprotected against infections. It is not uncommon for a patient to survive a transplant, but die of infection because of a weakened immune system.

Donated organs need to be transplanted quickly. How long can donated organs last outside the body?

- A heart lasts 3 to 5 hours.
- A liver lasts 10 hours.
- A kidney lasts 24 to 48 hours.

Autoimmunity

Sometimes the immune system fails to distinguish self from nonself, producing **autoantibodies** and cytotoxic T cells that attack and damage tissues and organs. This attack against self is called **autoimmunity.** The specific

Genetics Connection

CONQUERING INHERITED IMMUNE DEFICIENCY—CHILDREN WHO MADE MEDICAL HISTORY

T cells are the linchpins of the immune system. If they cannot function, they cannot activate B cells, and both the cellular and humoral immune responses shut down. We know well the importance of T cells in establishing and maintaining immunity from AIDS, which is acquired. Immune deficiency can also be inherited, resulting from mutations (changes in genes) that adversely affect receptors on T cells or cytokine production. We know of more than twenty forms of this severe combined immune deficiency, or SCID. A look at five children born with SCID also provides a compelling view of how quickly technology is making their lives easier, although it came too late for one young man, David Vetter.

David's Story

David Vetter was born in Texas in 1971 without a thymus gland. He therefore could not make mature T cells or activate his B cells. He spent his short life in a vinyl bubble, awaiting a treatment that never came (fig. 14A). David appeared on news programs, and a TV movie starring John Travolta depicted his life. In the era before AIDS, living without immunity was very unusual.

As David reached adolescence, he desperately wanted to leave the bubble. After receiving a bone marrow transplant, he did so. But the transplant hadn't worked, and within days, David began vomiting and developed diarrhea, both signs of infection. He soon died.

Laura's Story

For the first few years of her life, Laura Cay Boren didn't know what it felt like to be well (fig. 14B). From her birth in July 1982, she fought infection after infection. Colds would land her in the hospital with pneumonia, and routine vaccines caused severe skin abscesses. Laura had inherited a form of SCID in which the body lacks an enzyme, adenosine deaminase (ADA). Lack of ADA blocks a biochemical pathway that breaks down a metabolic toxin, which instead builds up and destroys T cells. The T cells in turn can no longer activate B cells. Immunity fails.

Laura spent her first and second birthdays at the Duke University Medical Center and then underwent two bone marrow transplants, which temporarily restored her immune defenses. Transfusions also helped. But by the end of 1985, Laura was near death. Then she was chosen to receive an experimental treatment, injections of ADA altered in a way that causes it to remain in the bloodstream long enough to help T cells survive. It worked! Within hours of the first treatment, Laura's ADA level increased twenty-fold. After three months, her blood was free of toxins, although her immunity was still suppressed. After six months, though, her immune function neared normal for the first time ever—and stayed that way, with weekly ADA shots. By the summer of 1988, she could play with other children, and by the following year, began school. She is healthy today.

Figure 14A

David Vetter was born without a thymus gland. Because his T cells could not mature, he was virtually defenseless against infection.

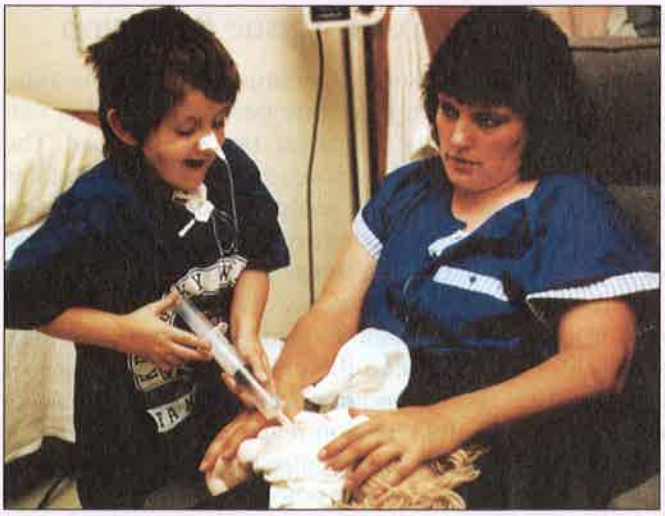


Figure 14B

Laura Cay Boren spent much of her life in hospitals until she received the enzyme her body lacks, adenosine deaminase (ADA). Here, she pretends to inject her doll as her mother looks on.

Ashanti's and Cynthia's Stories

On September 14, 1990, at 12:52 P.M., four-year-old Ashanti DaSilva sat up in bed at the National Institutes of Health in Bethesda, Maryland, and began receiving her own white blood cells intravenously. Earlier, doctors had removed the cells and patched them with normal ADA genes, which she lacked. Soon after that, an eight-year-old, Cynthia Cutshall, received the same treatment. Both girls also received ADA injections to keep them healthy, and doctors monitored their immune responses frequently. Because the gene therapy replaced mature T cells, the procedure had to be repeated as these cells lived out their natural life spans. This gene therapy, although successful (fig. 14C), was still not a permanent cure.

Andrew's Story

Crystal and Leonard Gobea had already lost a five-month-old baby to ADA deficiency when they learned that the fetus Crystal was carrying had also inherited the condition. They and two other couples were asked to allow their newborns to participate in a new type of gene therapy that would replace defective T cells with T cells taken from their umbilical cord blood and bolstered with the missing ADA gene (fig. 14D). The Gobea's baby, Andrew, was featured on the May 31, 1993, cover of *Time* magazine, where his parents told their story.

The three children were also given ADA injections to maintain health, as doctors monitored their immune functions. Since the defective cells were replaced early, the hope was that they would take over the immune system. They did, but slowly. After a few months, each child had about 1 in 10,000 T cells of the healthy type. After a year, that number rose to 1 in 100. Doctors lowered the ADA doses, and the children remained well. By the summer of 1995, the three toddlers had 3 in 100 T cells carrying the ADA gene, and at four years of age, 1–10% of the T cells were the repaired type. However, when the researchers discontinued giving ADA to one child, immune function declined. So although the gene therapy is working on the cellular level, on the organ system level it is not yet a complete cure. Researchers now need to determine what percentage of the T cell population must be "fixed" to completely restore and maintain immunity.

Figure 14C

Three years after receiving her own white blood cells, genetically altered to contain the ADA gene they lack, Ashanti DaSilva rides her bike—something she thought would never be possible.

Figure 14D

Newborn Andrew Gobea received the ADA gene in stem cells taken from his umbilical cord. The percentage of T cells in his blood that carry the needed gene is steadily increasing. He is now healthy.

nature of an autoimmune disorder depends on the cell types that are the target of the immune attack. Juvenile diabetes, rheumatoid arthritis, and systemic lupus erythematosus are some autoimmune disorders.

Why might the immune system attack body tissues? Perhaps a virus, while replicating within a human cell, "borrows" proteins from the host cell's surface and incorporates them onto its own surface. When the immune system "learns" the surface of the virus in order to destroy it, it also learns to attack the human cells that normally bear the particular protein. Another explanation of autoimmunity is that somehow T cells never learn to distinguish self from nonself. A third possible route of autoimmunity is when a nonself antigen coincidentally resembles a self antigen. This is what happens when an infection by *Streptococcus* bacteria triggers inflammation of heart valves, as mentioned in chapter 13 (p. 332).

CHECK YOUR RECALL

1. How are allergic reactions and immune reactions similar yet different?
2. How does a tissue rejection reaction involve an immune response?
3. How is autoimmunity an abnormal functioning of the immune response?

Clinical Terms Related to the Lymphatic System and Immunity

allograft (al´o-graft) Transplantation of tissue from an individual of one species to another individual of that species.
asplenia (ah-sple´ne-ah) Absence of a spleen.
autograft (aw´to-graft) Transplantation of tissue from one part of the body to another part of the same body.
immunocompetence (im´´u-no-kom´pe-tens) Ability to produce an immune response to the presence of antigens.
immunodeficiency (im´´u-no-de-fish´en-se) Inability to produce an immune response.
lymphadenectomy (lim-fad´´ĕ-nek´to-me) Surgical removal of lymph nodes.
lymphadenopathy (lim-fad´´ĕ-nop´ah-the) Enlargement of lymph nodes.
lymphadenotomy (lim-fad´´ĕ-not´o-me) Incision of a lymph node.
lymphocytopenia (lim´´fo-si´´to-pe´ne-ah) Too few lymphocytes in blood.
lymphocytosis (lim´´fo-si´´to´sis) Too many lymphocytes in blood.
lymphoma (lim-fo´mah) Tumor composed of lymphatic tissue.
lymphosarcoma (lim´´fo-sar-ko´mah) Cancer within the lymphatic tissue.
splenectomy (sple-nek´to-me) Surgical removal of the spleen.
splenitis (sple-ni´tis) Inflammation of the spleen.
splenomegaly (sple´´no-meg´ah-le) Abnormal enlargement of the spleen.
splenotomy (sple-not´o-me) Incision of the spleen.
thymectomy (thi-mek´to-me) Surgical removal of the thymus.
thymitis (thi-mi´tis) Inflammation of the thymus.

Clinical Connection

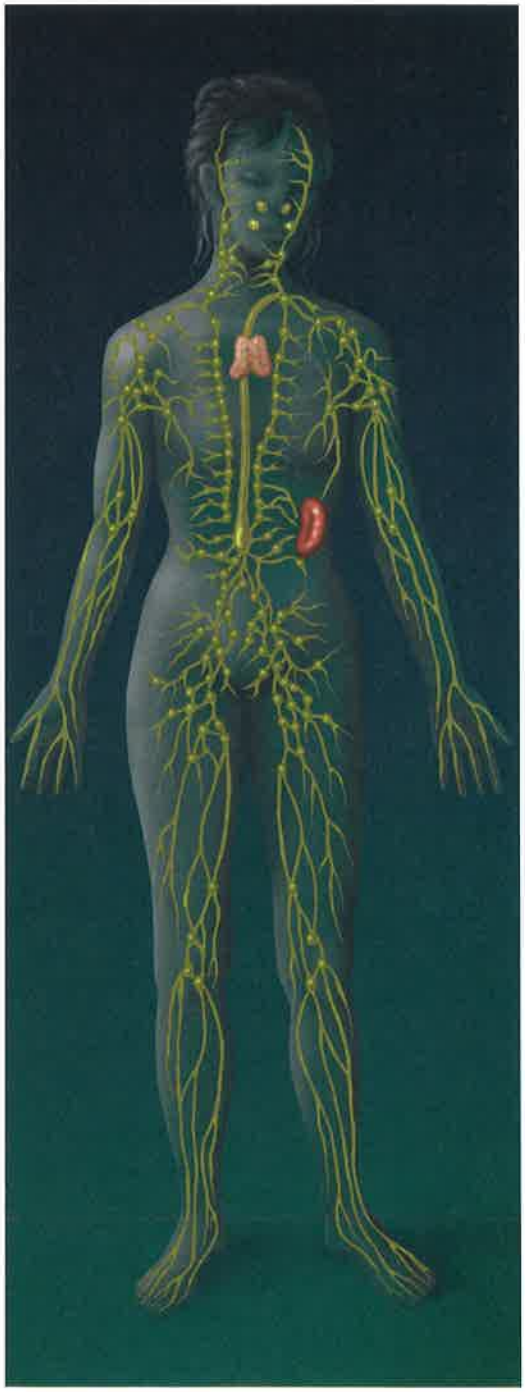
Some disorders thought to be autoimmune may have a more bizarre cause—fetal cells persisting in a woman's circulation, for decades. In response to an as yet unknown trigger, the fetal cells, perhaps "hiding" in a tissue such as skin, emerge, and stimulate antibody production. If we didn't know the fetal cells were there, the resulting antibodies and symptoms would appear to be an autoimmune disorder. This mechanism, called microchimerism ("small mosaic"), may explain the higher prevalence of autoimmune disorders among women. It was discovered in a disorder called scleroderma, which means "hard skin".

Patients describe scleroderma, which typically begins between ages 45 and 55, as "the body turning to stone." Symptoms include fatigue, swollen joints, stiff fingers, and a masklike face. The hardening may affect blood vessels, the lungs, and the esophagus, too. Clues that scleroderma is a delayed response to persisting fetal cells include the following observations:

- It is much more common among women.
- Symptoms resemble those of graft-versus-host disease (GVHD), in which transplanted tissue produces chemicals that destroy the body. Antigens on cells in scleroderma lesions match those involved in GVHD.
- Mothers who have scleroderma and their sons have cell surfaces that are more similar than those of unaffected mothers and their sons. Perhaps the similarity of cell surfaces enabled the fetal cells to escape destruction by the woman's immune system. (Female fetal cells can theoretically cause scleroderma too, but they are harder to detect because male cells can be distinguished by the Y chromosome.)

Perhaps other disorders considered to be autoimmune may actually reflect an immune system response to lingering fetal cells.

Organization



Lymphatic System

The lymphatic system is an important link between the interstitial fluid and the plasma; it also plays a major role in the response to infection.

Integumentary System

The skin is a first line of defense against infection.

Cardiovascular System

The lymphatic system returns tissue fluid to the bloodstream. Lymph originates as interstitial fluid, formed by the action of blood pressure.

Skeletal System

Cells of the immune system originate in the bone marrow.

Digestive System

Lymph plays a major role in the absorption of fats.

Muscular System

Muscle action helps pump lymph through the lymphatic vessels.

Respiratory System

Cells of the immune system patrol the respiratory system to defend against infection.

Nervous System

Stress may impair the immune response.

Urinary System

The kidneys control the volume of extracellular fluid, including lymph.

Endocrine System

Hormones stimulate lymphocyte production.

Reproductive System

Special mechanisms inhibit the female immune system in its attack of sperm as foreign invaders.

SUMMARY OUTLINE

14.1 Introduction (p. 367)

The lymphatic system is closely associated with the cardiovascular system. It transports excess fluid to the bloodstream, absorbs fats, and helps defend the body against disease-causing agents.

14.2 Lymphatic Pathways (p. 367)

1. Lymphatic capillaries
   a. Lymphatic capillaries are microscopic, closed-ended tubes that extend into interstitial spaces.
   b. They receive lymph through their thin walls.
2. Lymphatic vessels
   a. Lymphatic vessels have walls similar to those of veins, only thinner, and possess valves that prevent backflow of lymph.
   b. Larger lymphatic vessels lead to lymph nodes and then merge into lymphatic trunks.
3. Lymphatic trunks and collecting ducts
   a. Lymphatic trunks lead to two collecting ducts—the thoracic duct and the right lymphatic duct.
   b. Collecting ducts join the subclavian veins.

14.3 Tissue Fluid and Lymph (p. 369)

1. Tissue fluid formation
   a. Tissue fluid originates from blood plasma.
   b. It generally lacks large proteins, but some smaller proteins leak into interstitial spaces.
   c. As the protein concentration of tissue fluid increases, colloid osmotic pressure increases.
2. Lymph formation and function
   a. Increasing pressure within interstitial spaces forces some tissue fluid into lymphatic capillaries, and this fluid becomes lymph.
   b. Lymph returns protein molecules to the bloodstream and transports foreign particles to lymph nodes.

14.4 Lymph Movement (p. 369)

1. Lymph is under low pressure and may not flow readily without external aid.
2. Lymph is moved by the contraction of skeletal muscles and low pressure in the thorax created by breathing movements.

14.5 Lymph Nodes (p. 370)

1. Structure of a lymph node
   a. Lymph nodes are subdivided into nodules.
   b. Nodules contain masses of lymphocytes and macrophages.
2. Locations of lymph nodes
   Lymph nodes aggregate in groups or chains along the paths of larger lymphatic vessels.
3. Functions of lymph nodes
   a. Lymph nodes filter potentially harmful foreign particles from lymph.
   b. Lymph nodes are centers for the production of lymphocytes, and they also contain phagocytic cells.

14.6 Thymus and Spleen (p. 371)

1. Thymus
   a. The thymus is composed of lymphatic tissue subdivided into lobules.
   b. It slowly shrinks after puberty.
   c. Some lymphocytes leave the thymus and provide immunity.
2. Spleen
   a. The spleen resembles a large lymph node subdivided into lobules.
   b. Spaces within splenic lobules are filled with blood.
   c. The spleen contains many macrophages, which filter foreign particles and damaged red blood cells from blood.

14.7 Body Defenses Against Infection (p. 373)

The body has nonspecific and specific defenses against infection.

14.8 Nonspecific Defenses (p. 373)

1. Species resistance
   Each species is resistant to certain diseases that may affect other species.
2. Mechanical barriers
   Mechanical barriers include the skin and mucous membranes, which block entrance of some pathogens.
3. Chemical barriers
   a. Enzymes in gastric juice and tears kill some pathogens.
   b. Interferons stimulate uninfected cells to synthesize antiviral proteins that stimulate phagocytosis, block proliferation of viruses, and enhance activity of cells that help resist infections and stifle tumor growth.
4. Fever
   Higher body temperature and the resulting decrease in blood iron level and increase in phagocytic activity hamper infection.
5. Inflammation
   a. Inflammation is a tissue response to injury or infection, and includes localized redness, swelling, heat, and pain.
   b. Chemicals released by damaged tissues attract white blood cells to the site.
   c. Connective tissue containing many fibers may form a sac around injured tissue and thus block the spread of pathogens.
6. Phagocytosis
   a. The most active phagocytes in blood are neutrophils and monocytes. Monocytes give rise to macrophages, which remain fixed in tissues.
   b. Phagocytic cells are associated with the linings of blood vessels in the bone marrow, liver, spleen, lungs, and lymph nodes.

14.9 Specific Defenses (Immunity) (p. 375)

1. Antigens
   a. Before birth, body cells inventory "self" proteins and other large molecules.
   b. After inventory, lymphocytes develop receptors that allow them to differentiate between nonself (foreign) and self antigens.
   c. Nonself antigens combine with T cell and B cell surface receptors and stimulate these cells to cause an immune reaction.
   d. Haptens are small molecules that can combine with larger ones, becoming antigenic.
2. Lymphocyte origins
   a. Lymphocytes originate in red bone marrow and are released into the blood before they differentiate.
   b. Some reach the thymus, where they mature into T cells.
   c. Others, the B cells, mature in the red bone marrow.
   d. Both T cells and B cells reside in lymphatic tissues and organs.
3. Lymphocyte functions
   a. Some T cells interact with antigen-bearing agents directly, providing the cellular immune response.
   b. T cells secrete cytokines, such as interleukins, that enhance cellular responses to antigens.
   c. T cells may also secrete substances that are toxic to their target cells.
   d. B cells interact with antigen-bearing agents indirectly, providing the humoral immune response.
   e. Varieties of T cells and B cells number in the millions.

f. The members of each variety respond only to a specific antigen.
g. As a group, the members of each variety form a clone.

4. T cells and the cellular immune response
   a. T cells are activated when an antigen-presenting cell displays a foreign antigen.
   b. When a macrophage acts as an accessory cell, it phagocytizes an antigen-bearing agent, digests the agent, and displays the antigens on its cell membrane in association with certain MHC proteins.
   c. A helper T cell becomes activated when it encounters displayed antigens for which it is specialized to react.
   d. An activated helper T cell contacts a B cell that carries the foreign antigen the T cell previously encountered on an antigen-presenting cell.
   e. In response, the T cell secretes cytokines, stimulates B cell proliferation, and attracts macrophages.
   f. Cytotoxic T cells recognize foreign antigens on tumor cells and cells whose surfaces indicate that they are infected by viruses.
   g. Memory T cells respond quickly to subsequent antigen exposure.
5. B cells and the humoral immune response
   a. A B cell is activated when it encounters an antigen that fits its antigen receptors.
   b. An activated B cell proliferates (especially when stimulated by a T cell), enlarging its clone.
   c. Some activated B cells specialize into antibody-producing plasma cells.
   d. Antibodies react against the antigen-bearing agent that stimulated their production.
   e. An individual's diverse B cells defend against a very large number of pathogens.
6. Types of antibodies
   a. Antibodies are soluble proteins called immunoglobulins.
   b. The five major types of immunoglobulins are IgG, IgA, IgM, IgD, and IgE.
7. Antibody actions
   a. Antibodies directly attach to antigens, activate complement, or stimulate local tissue changes that are unfavorable to antigen-bearing agents.
   b. Direct attachment results in agglutination, precipitation, or neutralization.
   c. Activated proteins of complement attract phagocytes, alter cells so they become more susceptible to phagocytosis, and rupture foreign cell membranes (lysis).
8. Immune responses
   a. The first reaction to an antigen is called a primary immune response.
      (1) During this response, antibodies are produced for several weeks.
      (2) Some B cells remain dormant as memory cells.
   b. A secondary immune response occurs rapidly as a result of memory cell response if the same antigen is encountered later.
9. Practical classification of immunity
   a. Naturally acquired immunity arises in the course of natural events, whereas artificially acquired immunity is the consequence of a medical procedure.
   b. Active immunity lasts much longer than passive immunity.
   c. A person who encounters a pathogen and has a primary immune response develops naturally acquired active immunity.
   d. A person who receives a vaccine containing a dead or weakened pathogen, or part of one, develops artificially acquired active immunity.
   e. A person who receives an injection of antibodies has artificially acquired passive immunity.
   f. When antibodies pass through a placental membrane from a pregnant woman to her fetus, the fetus develops naturally acquired passive immunity.
10. Allergic reactions
    a. Allergic reactions are excessive and misdirected immune responses that may damage tissue.
    b. Delayed-reaction allergy, which can occur in anyone and inflame the skin, results from repeated exposure to antigens.
    c. Immediate-reaction allergy is an inborn ability to overproduce IgE.
       (1) Allergic reactions result from mast cells bursting and releasing allergy mediators such as histamine.
       (2) The released chemicals cause allergy symptoms such as hives, hay fever, asthma, eczema, or gastric disturbances.
11. Transplantation and tissue rejection
    a. A transplant recipient's immune system may react against the donated tissue, an event termed a tissue rejection reaction.
    b. Matching donor and recipient tissues and using immunosuppressive drugs can minimize tissue rejection.
    c. Immunosuppressive drugs may increase susceptibility to infection.
12. Autoimmunity
    a. In autoimmune disorders, the immune system manufactures autoantibodies that attack a person's own body tissues.
    b. Autoimmune disorders may result from a previous viral infection, faulty T cell development, or reaction to a nonself antigen that resembles a self antigen.

REVIEW EXERCISES

1. Explain how the lymphatic system is related to the cardiovascular system. (p. 367)
2. Trace the general pathway of lymph from the interstitial spaces to the bloodstream. (p. 367)
3. Describe the primary functions of lymph. (p. 369)
4. Explain why physical exercise promotes lymphatic circulation. (p. 369)
5. Describe the structure and functions of a lymph node. (p. 370)
6. Describe the structure and functions of the thymus. (p. 371)
7. Describe the structure and functions of the spleen. (p. 371)
8. Distinguish between specific and nonspecific body defenses against infection. (p. 373)
9. Explain *species resistance.* (p. 373)
10. Describe how enzymatic actions function as defense mechanisms. (p. 374)
11. Define *interferon,* and explain its action. (p. 374)
12. List the major effects of inflammation, and explain why each occurs. (p. 374)
13. Identify the major phagocytic cells in blood and other tissues. (p. 374)
14. Distinguish between an antigen and an antibody. (p. 375)
15. Define *hapten.* (p. 375)
16. Review the origin of T cells and B cells. (p. 375)
17. Explain *cellular immunity.* (p. 376)
18. Explain the function of *plasma cells.* (p. 376)
19. Explain *humoral immunity.* (p. 376)

20. Define *clone* of lymphocytes. (p. 376)
21. Describe how T cells become activated. (p. 376)
22. Explain the function of *memory cells.* (p. 377)
23. Explain how a B cell is activated. (p. 377)
24. List the major types of immunoglobulins, and describe where each occurs. (p. 378)
25. Explain two mechanisms by which antibodies directly attach to antigens. (p. 380)
26. Explain the function of complement. (p. 380)
27. Distinguish between a primary and a secondary immune response. (p. 380)
28. Distinguish between active and passive immunity. (p. 381)
29. Define *vaccine.* (p. 381)
30. Explain how a vaccine produces its effect. (p. 381)
31. Explain the relationship between an allergic reaction and an immune response. (p. 381)
32. Distinguish between an antigen and an allergen. (p. 381)
33. List the major events leading to a delayed-reaction allergic response. (p. 381)
34. Describe how an immediate-reaction allergic response may occur. (p. 382)
35. Explain the relationship between tissue rejection and an immune response. (p. 383)
36. Describe a method used to reduce the severity of a tissue rejection reaction. (p. 383)
37. Explain the relationship between autoimmunity and an immune response. (p. 383)

CRITICAL THINKING

1. The immune response is specific, diverse, and equipped with memory. Give examples of each of these characteristics.
2. On whom should experimental AIDS vaccines be evaluated?
3. There are more people needing transplants than there are organs available. Discuss the pros and cons of the following proposed rationing systems for determining who should receive transplants: (a) first come, first served; (b) people with the best tissue and blood type match; (c) patients whose need for an organ is caused by infection or disease, as opposed to those whose need for an organ was preventable, such as a lung destroyed by smoking; (d) the youngest people; (e) the wealthiest people; (f) the most important people.
4. Why is a transplant consisting of fetal tissue less likely to provoke an immune rejection response than tissue from an adult?
5. T cells "learn" to recognize self from nonself during prenatal development. How could this learning process be altered to prevent allergies? To enable a person to accept a transplant?
6. Some parents keep their preschoolers away from other children to prevent them from catching illnesses. How might these well-meaning parents actually be harming their children?
7. One out of every 310,000 children who receives the vaccine for pertussis (whooping cough) develops permanent brain damage. The risk of suffering such damage from pertussis is about 1 in 30,000. Some parents refuse to vaccinate their children because of the few reported cases of adverse reaction to the vaccine. What are the dangers, both to the individual and to the population, when parents refuse to allow their children to be vaccinated against pertussis?
8. A xenograft is tissue from a nonhuman animal used to a replace a body part in a human. For example, pigs are being developed to provide cardiovascular spare parts because their hearts and blood vessels are similar to ours. To increase the likelihood of such a xenotransplant working, researchers genetically engineer pigs to produce human antigens on their cell surfaces. How can this improve the chances of a human body not rejecting such a transplant?
9. How can the removal of enlarged lymph nodes for microscopic examination aid in diagnosing certain diseases?
10. Why is injecting a substance into the skin like injecting it into the lymphatic system?
11. Why does vaccination provide long-lasting protection against a disease, while gamma globulin (IgG) provides only short-term protection?
12. What functions of the lymphatic system would be affected by being born without a thymus?

WEB CONNECTIONS

Visit the website for additional study questions and more information about this chapter at:

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