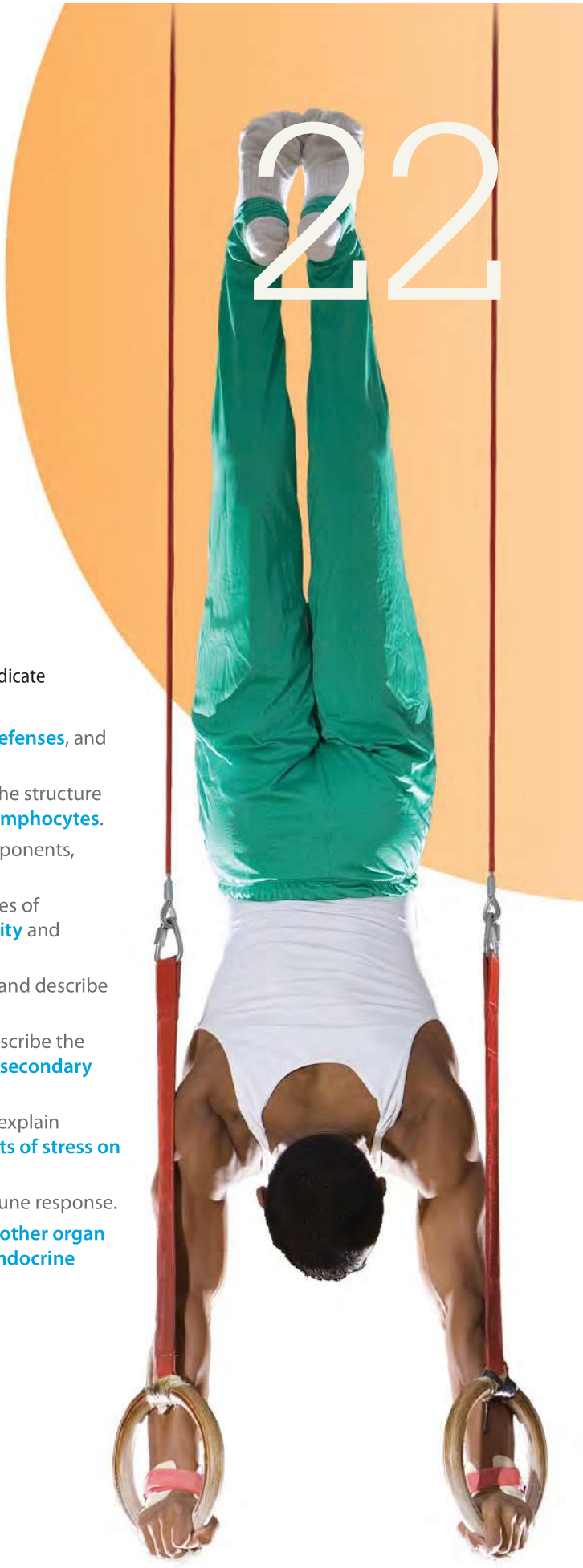
22

The Lymphatic System and Immunity



Learning Outcomes

These Learning Outcomes correspond by number to this chapter's sections and indicate what you should be able to do after completing the chapter.

22-1 Distinguish between **innate (nonspecific) and adaptive (specific) defenses**, and explain the **role of lymphocytes** in the immune response.

22-2 Identify the major **components of the lymphatic system**, describe the structure and functions of each component, and discuss the **importance of lymphocytes**.

22-3 List the body's **innate (nonspecific) defenses**, and describe the components, mechanisms, and functions of each.

22-4 Define **adaptive (specific) defenses**, identify the forms and properties of immunity, and distinguish between **cell-mediated (cellular) immunity** and **antibody-mediated (humoral) immunity**.

22-5 Discuss the **types of T cells** and their roles in the immune response, and describe the **mechanisms of T cell activation and differentiation**.

22-6 Discuss the **mechanisms of B cell activation and differentiation**, describe the **structure and function of antibodies**, and explain the **primary and secondary responses** to antigen exposure.

22-7 Describe the development of **immunological competence**, list and explain **examples of immune disorders and allergies**, and discuss the **effects of stress on immune function**.

22-8 Describe the **effects of aging** on the lymphatic system and the immune response.

22-9 Give **examples of interactions between the lymphatic system and other organ systems** we have studied so far and explain how the **nervous and endocrine systems** influence the **immune response**.

Clinical Notes

Spotlight

An Introduction to the Lymphatic System and Immunity

Many organs and systems work together to keep us alive and healthy. The lymphatic system plays a central role in the ongoing struggle to maintain health. In this chapter we discuss the components of the lymphatic system and the ways those components interact.

The world is not always kind to the human body. Accidental bumps, cuts, and scrapes; chemical and thermal burns; extreme cold; and ultraviolet radiation are just a few of the hazards in our physical environment. Making matters worse, the world around us contains an assortment of viruses, bacteria, fungi, and parasites capable of not only surviving but thriving inside our bodies—and potentially causing us great harm. These disease-causing organisms, called **pathogens,** are responsible for many diseases in humans. Each pathogen has a different lifestyle and attacks the body in a specific way. For example, viruses spend most of their time hidden within cells, which they often eventually destroy. Some of the largest parasites actually burrow through internal organs. Many bacteria multiply in interstitial fluids, where they release foreign proteins—enzymes or toxins—that can damage cells, tissues, even entire organ systems. And as if that were not enough, we are constantly at risk from renegade body cells that have the potential to produce lethal cancers. p. 101

22-1 Surface barriers and internal defenses constitute innate defenses, and lymphocytes provide adaptive defenses

The **lymphatic system** includes the cells, tissues, and organs responsible for defending the body. This system acts both against environmental hazards, such as various pathogens, and against internal threats, such as cancer cells. We introduced *lymphocytes*, the primary cells of the lymphatic system, in Chapters 4 and 19. pp. 127, 657 These cells are vital to the body's ability to resist or overcome infection and disease. Lymphocytes respond to invading pathogens (such as bacteria or viruses), abnormal body cells (such as virus-infected cells or cancer cells), and foreign proteins (such as the toxins released by some bacteria). They act to eliminate these threats or render them harmless through a combination of physical and chemical attacks.

The ability to resist infection and disease is **immunity.** We have two forms of immunity that work independently or together. These forms are *innate (nonspecific) immunity* and *adaptive (specific) immunity*. The body has several anatomical barriers and defense mechanisms. They either prevent or slow the entry of infectious organisms, or attack them if they do enter. These mechanisms are called innate (nonspecific) defenses because they do not distinguish one potential threat from another. In contrast, lymphocytes respond specifically. If a bacterial pathogen invades peripheral tissues, lymphocytes organize a defense against that particular type of bacterium. For this reason, we say that lymphocytes provide an adaptive (specific) defense, known as the **immune response.** All the cells and tissues involved in producing immunity are sometimes considered part of an *immune system*. This physiological system includes not only the lymphatic system, but also parts of the integumentary, cardiovascular, respiratory, digestive, and other systems. For example, lymphocytes interact with dendritic (Langerhans) cells of the skin to mobilize specific defenses against skin infections.

We begin this chapter by examining the organization of the lymphatic system. We then consider the body's other defenses. Finally, we will see how the lymphatic system interacts with cells and tissues of other systems to defend the body against infection and disease.

Checkpoint

1. **Define pathogen.**
2. **Explain the difference between nonspecific defense and specific defense.**

See the blue Answers tab at the back of the book.

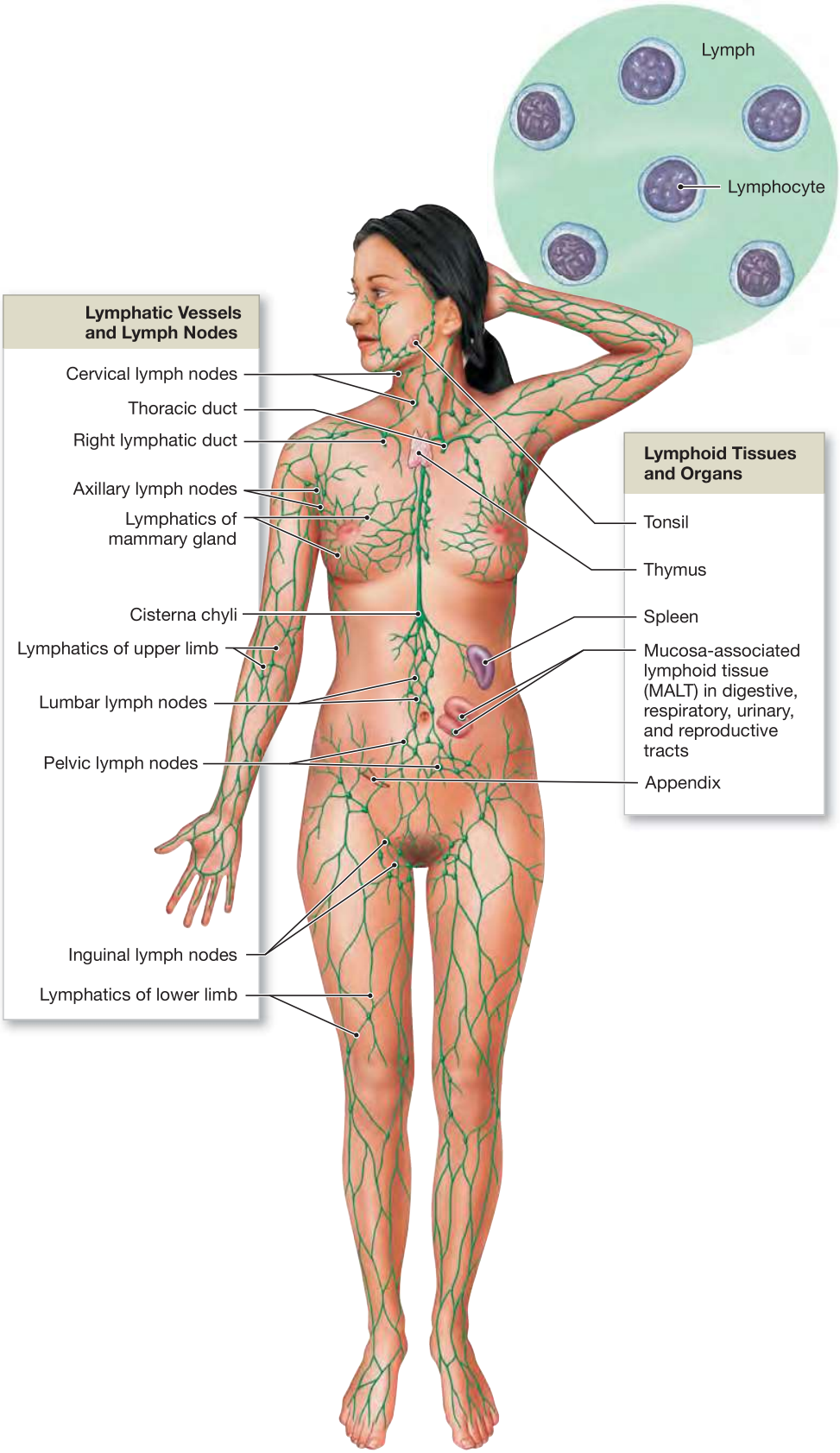
22-2 Lymphatic vessels, lymphocytes, lymphoid tissues, and lymphoid organs function in body defenses

The lymphatic system consists of (1) **lymph,** a fluid that resembles plasma but contains a much lower concentration of suspended proteins; (2) a network of **lymphatic vessels,** often called **lymphatics,** which begin in peripheral tissues and connect to veins; (3) an array of **lymphoid tissues** and **lymphoid organs** scattered throughout the body; and (4) lymphocytes and smaller numbers of phagocytes and other cells. **Figure 22–1** provides a general overview of the primary vessels, tissues, and organs of this system.

Functions of the Lymphatic System

The primary function of the lymphatic system is to produce, maintain, and distribute lymphocytes that provide defense against infections and other environmental hazards. Lymphoid tissues (such as the tonsils) and lymphoid organs (such as the spleen and thymus) produce and store most of the

Figure 22–1 An Overview of the Lymphatic System.



body's lymphocytes. However, areas of red bone marrow also produce lymphocytes, along with other defense cells, such as monocytes and macrophages.

To provide an effective defense, lymphocytes must detect problems, and they must be able to reach the site of injury or infection. Lymphocytes, macrophages, and microphages circulate within the blood. They are able to enter or leave the capillaries that supply most of the tissues of the body. As noted in Chapter 21, capillaries normally deliver more fluid to peripheral tissues than they carry away. ↩ p. 724 The excess fluid returns to the bloodstream through lymphatic vessels. This continuous circulation of extracellular fluid helps transport lymphocytes and other defense cells from one organ to another. In the process, it maintains normal blood volume. It also eliminates local variations in the composition of the interstitial fluid by distributing hormones, nutrients, and wastes from their tissues of origin to the general circulation.

Lymphatic Vessels

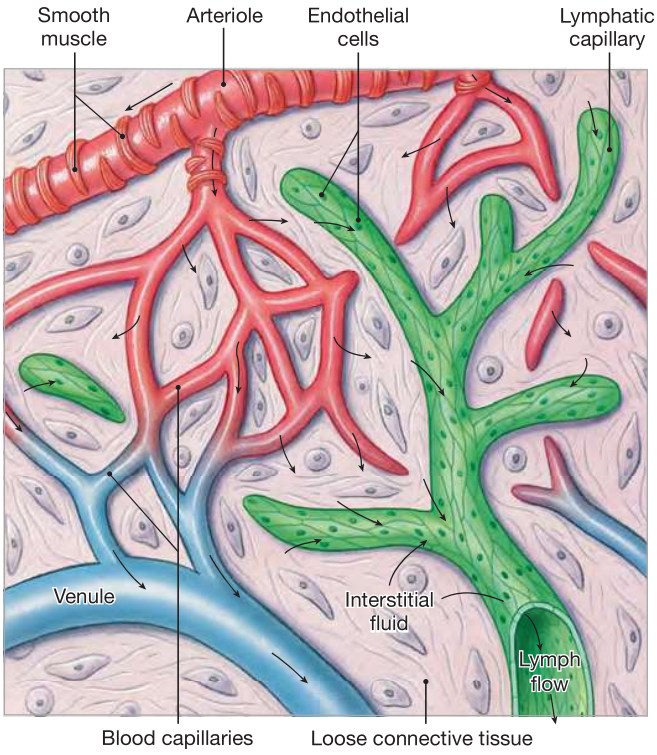
Lymphatic vessels carry lymph from peripheral tissues to the venous system. The smallest lymphatic vessels are called *lymphatic capillaries*.

Lymphatic Capillaries

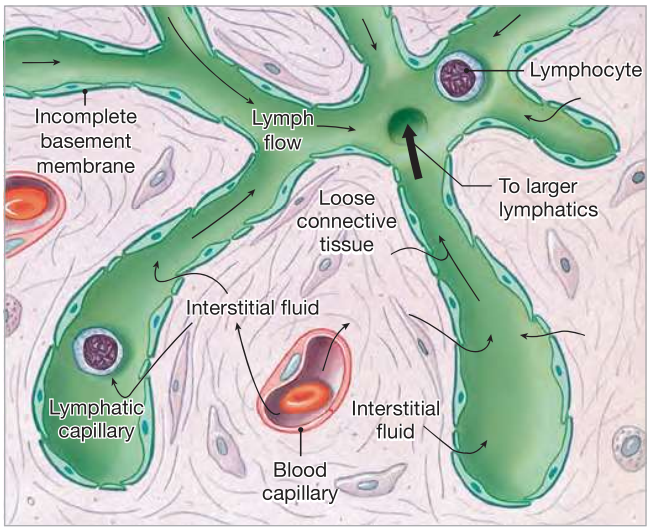
The lymphatic network begins with **lymphatic capillaries,** or *terminal lymphatics*, which branch through peripheral tissues. Lymphatic capillaries differ from blood capillaries in several ways. They (1) originate as pockets rather than forming continuous tubes, (2) have larger diameters, (3) have thinner walls, and (4) typically have a flattened or irregular outline in sectional view (**Figure 22–2**).

Lymphatic capillaries are lined by endothelial cells, but the basement membrane is incomplete or

Figure 22–2 Lymphatic Capillaries.



a The interwoven network formed by blood capillaries and lymphatic capillaries. Arrows indicate the movement of fluid out of blood vessels and the net flow of interstitial fluid and lymph.



b A sectional view indicating the movement of fluid from the plasma, through the tissues as interstitial fluid, and into the lymphatic system as lymph.

absent. The endothelial cells of a lymphatic capillary are not bound tightly together, but they do overlap. The region of overlap acts as a one-way valve. It permits fluids and solutes (including those as large as proteins) to enter, along with viruses, bacteria, and cell debris, but it prevents them from returning to the intercellular spaces.

Lymphatic capillaries are present in almost every tissue and organ in the body. Prominent lymphatic capillaries in the small intestine called *lacteals* are important in the transport of lipids absorbed by the digestive tract. Lymphatic capillaries are absent in areas that lack a blood supply, such as the cornea of the eye. The bone marrow and the central nervous system also lack lymphatic vessels.

Small Lymphatic Vessels

From the lymphatic capillaries, lymph flows into larger lymphatic vessels that lead toward the body's trunk. The walls of these vessels contain layers comparable to those of veins. Like veins, the larger lymphatic vessels also contain valves (**Figure 22–3**). The valves are quite close together, and produce noticeable bulges. As a result, large lymphatic vessels have a beaded appearance (**Figure 22–3a**). The valves prevent the backflow of lymph within lymph vessels, especially in the limbs. Pressures within the lymphatic system are minimal, and the valves are essential to maintaining normal lymph flow toward the thoracic cavity.

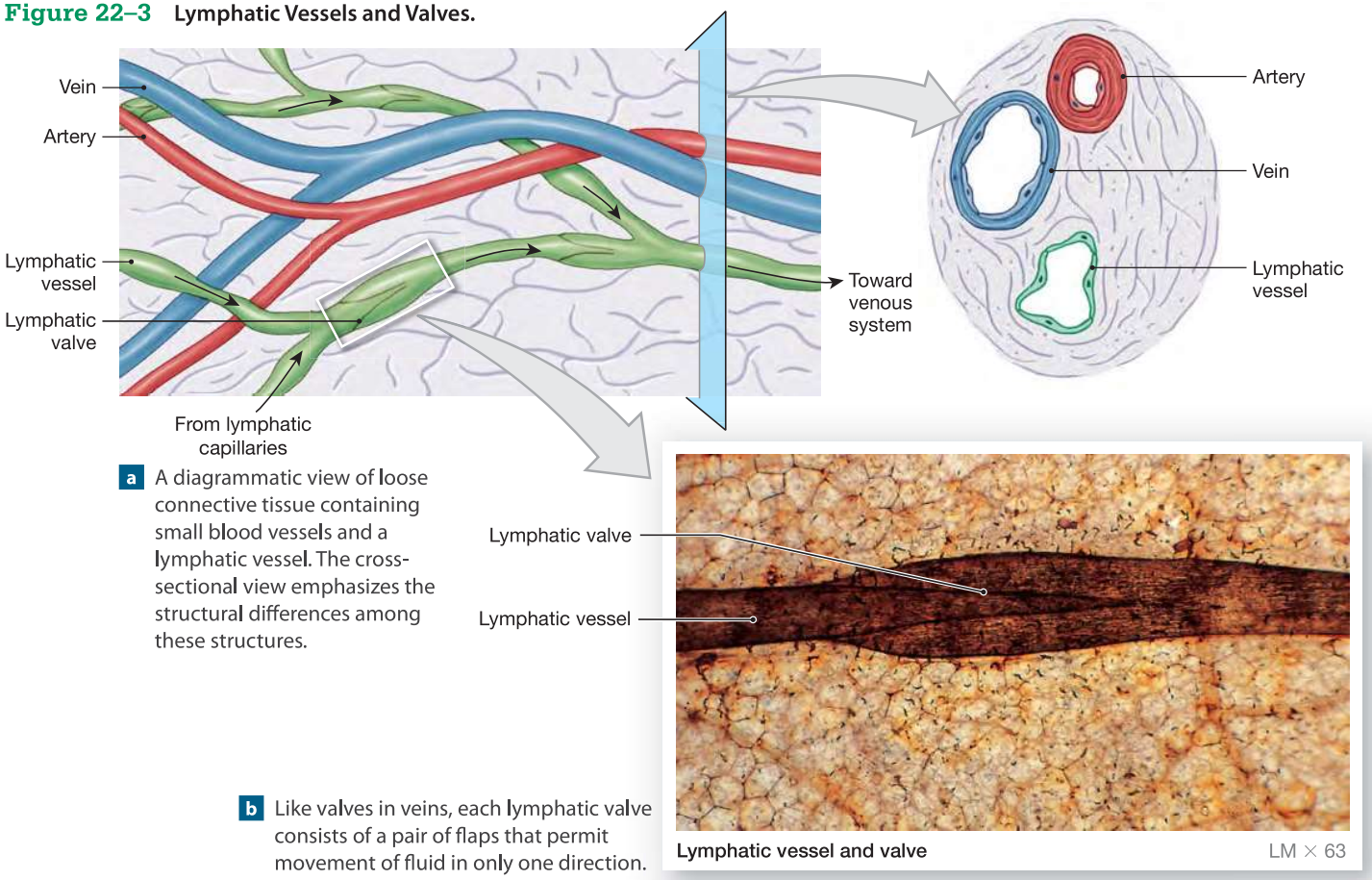
Lymphatic vessels are often associated with blood vessels (**Figure 22–3a**). Differences in size, general appearance, and branching pattern distinguish lymphatic vessels from arteries and veins. We can see characteristic color differences in living tissues. Most arteries are bright red, veins are dark red (although usually illustrated as blue to distinguish them from arteries), and lymphatic vessels are a pale golden color. In general, a tissue contains many more lymphatic vessels than veins, but the lymphatic vessels are much smaller.

Major Lymph-Collecting Vessels

Two sets of lymphatic vessels collect lymph from the lymphatic capillaries: superficial lymphatics and deep lymphatics. **Superficial lymphatics** are located in the subcutaneous layer deep to the skin; in the areolar tissues of the mucous membranes lining the digestive, respiratory, urinary, and reproductive tracts; and in the areolar tissues of the serous membranes lining the pleural, pericardial, and peritoneal cavities. **Deep lymphatics** are larger lymphatic vessels that accompany deep arteries and veins supplying skeletal muscles and other organs of the neck, limbs, and trunk, and the walls of visceral organs.

Superficial and deep lymphatics converge to form even larger vessels called **lymphatic trunks.** The trunks in turn empty into two large collecting vessels: the thoracic duct and the right lymphatic duct. The **thoracic duct** collects lymph from the body inferior to the diaphragm and from the left side of the body superior to the diaphragm. The smaller **right lymphatic duct** collects lymph from the right side of the body superior to the diaphragm (**Figure 22–4a**).

Figure 22–3 Lymphatic Vessels and Valves.



a A diagrammatic view of loose connective tissue containing small blood vessels and a lymphatic vessel. The cross-sectional view emphasizes the structural differences among these structures.

b Like valves in veins, each lymphatic valve consists of a pair of flaps that permit movement of fluid in only one direction.

Lymphatic vessel and valve LM × 63

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The thoracic duct begins inferior to the diaphragm at the level of vertebra L_2 (**Figure 22–4b**). The base of the thoracic duct is an expanded, saclike chamber called the **cisterna chyli** (KĪ-1ī; *chylos*, juice). The cisterna chyli receives lymph from the inferior part of the abdomen, the pelvis, and the lower limbs by way of the *right* and *left lumbar trunks* and the *intestinal trunk*.

The inferior segment of the thoracic duct lies anterior to the vertebral column. From the second lumbar vertebra, it passes posterior to the diaphragm alongside the aorta. It then ascends along the left side of the vertebral column to the level of the left clavicle. It collects lymph from the *left bronchomediastinal trunk*, the *left subclavian trunk*, and the *left jugular trunk*, and then empties into the left subclavian vein near the left internal jugular vein (**Figure 22–4b**). In this way, lymph reenters the venous circulation from the left side of the head, neck, and thorax, as well as from the entire body inferior to the diaphragm.

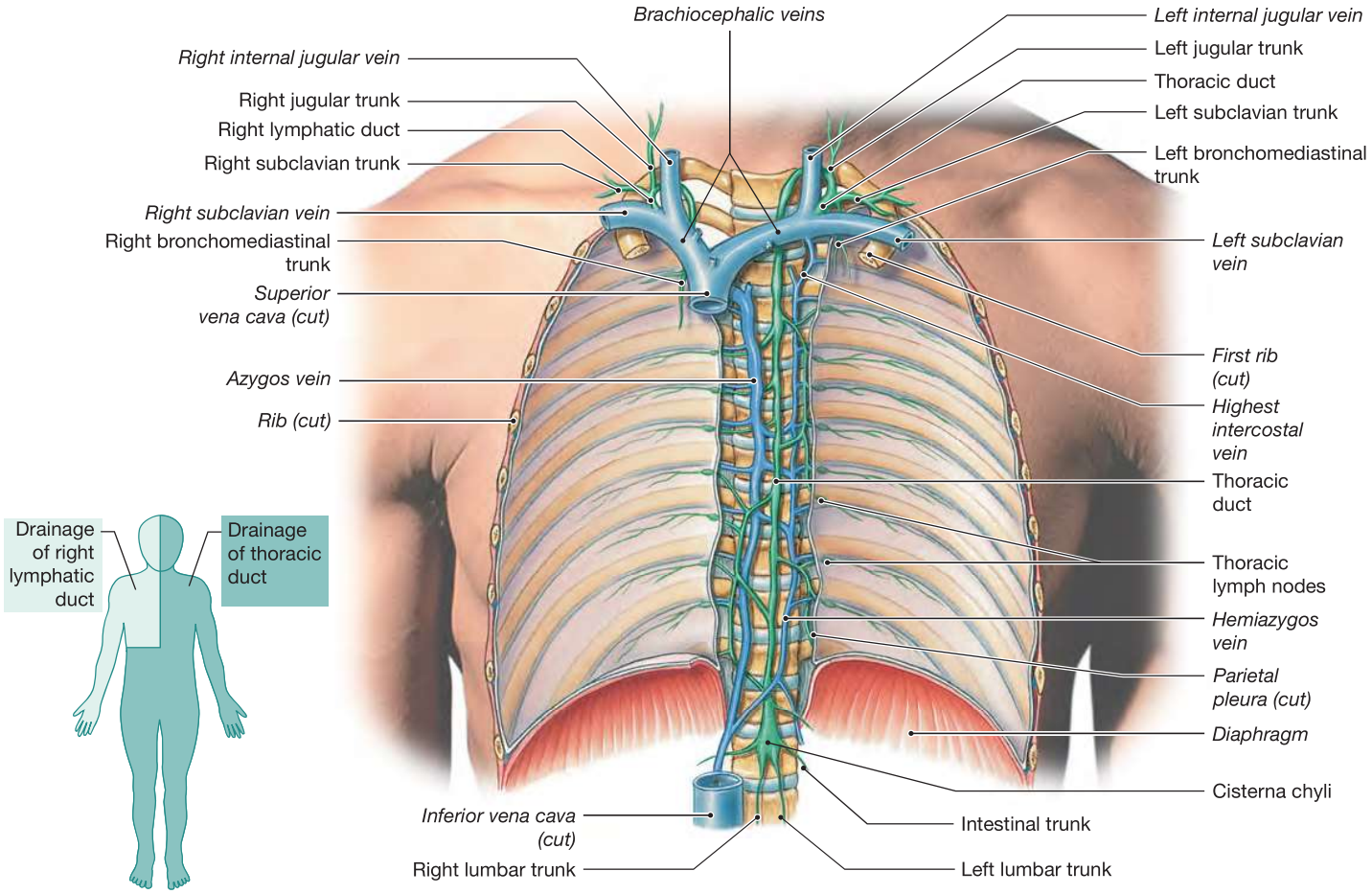
The *right lymphatic duct* is formed by the merging of the *right jugular*, *right subclavian*, and *right bronchomediastinal trunks* in the area near the right clavicle. This duct empties into the right subclavian vein, delivering lymph from the right side of the body superior to the diaphragm.

Blockage of the lymphatic drainage from a limb produces **lymphedema** (limf-e-DĒ-muh). In this condition, interstitial fluids accumulate and the limb gradually becomes swollen and grossly distended. If the condition persists, the connective tissues lose their elasticity and the swelling becomes permanent. Lymphedema by itself does not pose a major threat to life. The danger comes from the constant risk that an uncontrolled infection will develop in the affected area. Because the interstitial fluids are essentially stagnant, toxins and pathogens can accumulate and overwhelm local defenses without fully activating the immune system.

Lymphocytes

Lymphocytes account for 20–30 percent of circulating leukocytes. However, circulating lymphocytes are only a small fraction of the total lymphocyte population. The body contains some 10^{12} lymphocytes, with a combined weight of more than a kilogram (2.2 lb).

Figure 22–4 The Relationship between the Lymphatic Ducts and the Venous System. ATLAS: Plate 48a,b



a The thoracic duct carries lymph originating in tissues inferior to the diaphragm and from the left side of the upper body. The smaller right lymphatic duct delivers lymph from the rest of the body.

b The thoracic duct empties into the left subclavian vein. The right lymphatic duct drains into the right subclavian vein.

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Types of Lymphocytes

Three classes of lymphocytes circulate in blood: (1) **T** (**t**hymus-dependent) **cells**, (2) **B** (**b**one marrow–derived) **cells**, and (3) **NK** (**n**atural **k**iller) **cells**. Each type has distinctive biochemical and functional characteristics (**Figure 22–5**).

Most lymphocytes are T cells, and the primary types of T cells include cytotoxic T (T_c) cells, memory T cells, helper T (T_H) cells, and suppressor T (T_S) cells. Cytotoxic T cells are involved in direct cellular attack. These lymphocytes are the primary cells involved in the production of *cell-mediated immunity*, or *cellular immunity*. The interplay between suppressor and helper T cells helps establish and control the sensitivity of the immune response. For this reason, these cells are also known as *regulatory T cells*.

We will examine these T cells throughout this chapter. Other types of T cells also participate in the immune response. For example, *inflammatory T cells* stimulate regional inflammation and local defenses in an injured tissue. *Suppressor/inducer T cells* suppress B cell activity but stimulate other T cells.

Under proper stimulation, B cells differentiate into **plasma cells** that secrete antibodies. These antibodies are soluble proteins, also known as *immunoglobulins*. ↩ p. 641 B cells are responsible for *antibody-mediated immunity*, which is also known as *humoral* ("liquid") *immunity* because antibodies occur in body fluids.

Antibodies bind to specific chemical targets called **antigens.** Most antigens are pathogens, parts or products of pathogens, or other foreign compounds. Antigens are usually proteins, but some lipids, polysaccharides, and nucleic acids are also antigens. The binding of an antibody to its target antigen starts a chain reaction leading to the destruction of the target compound or organism.

NK cells are also known as **large granular lymphocytes.** NK cells attack foreign cells, normal cells infected with viruses, and cancer cells that appear in normal tissues. Their continuous "policing" of peripheral tissues has been called *immunological surveillance* (**Figure 22–5**).

Life Span and Circulation of Lymphocytes

The various types of lymphocytes are not evenly distributed in the blood, bone marrow, spleen, thymus, and peripheral lymphoid tissues. The ratio of B cells to T cells varies among tissues and organs. For example, B cells are seldom found in the thymus, but T cells outnumber B cells in blood by a ratio of 8:1.

The lymphocytes in these organs are visitors, not residents. All types of lymphocytes move throughout the body. They wander through tissues and then enter blood vessels or lymphatic vessels for transport.

T cells move quickly. For example, a wandering T cell may spend about 30 minutes in the blood, 5–6 hours in the spleen, and 15–20 hours in a lymph node. B cells, which are responsible for antibody production, move more slowly. A typical B cell spends about 30 hours in a lymph node before moving on.

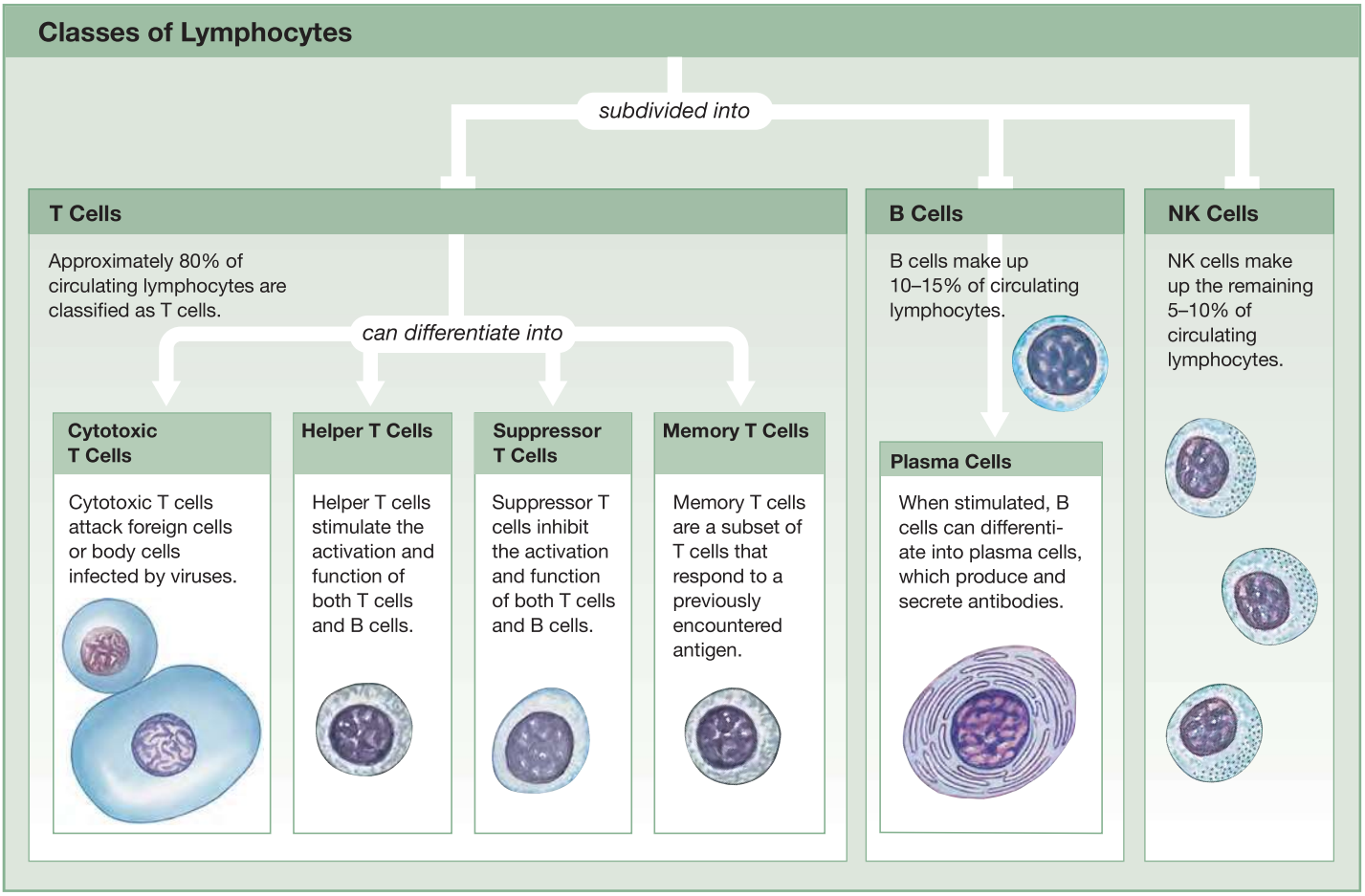
Lymphocytes have relatively long life spans. About 80 percent survive 4 years, and some last 20 years or more. Throughout your life, you maintain normal lymphocyte populations by producing new lymphocytes in your red bone marrow and lymphoid tissues.

Lymphocyte Production

In Chapter 19, we discussed *hemopoiesis*—the formation of the cellular elements of blood. pp. 648, 657 In adults, red blood cell formation, or *erythropoiesis,* is normally confined to red bone marrow. In contrast, lymphocyte production, or **lymphopoiesis** (lim-fō-poy-Ē-sis), involves the red bone marrow, thymus, and peripheral lymphoid tissues (**Figure 22–6**).

Red bone marrow plays the primary role in maintaining normal lymphocyte populations. Hemocytoblasts divide in the bone marrow of adults to generate the lymphoid stem cells that produce all types of lymphocytes. The red bone marrow produces two distinct populations of lymphoid stem cells.

Figure 22–5 Classes of Lymphocytes.



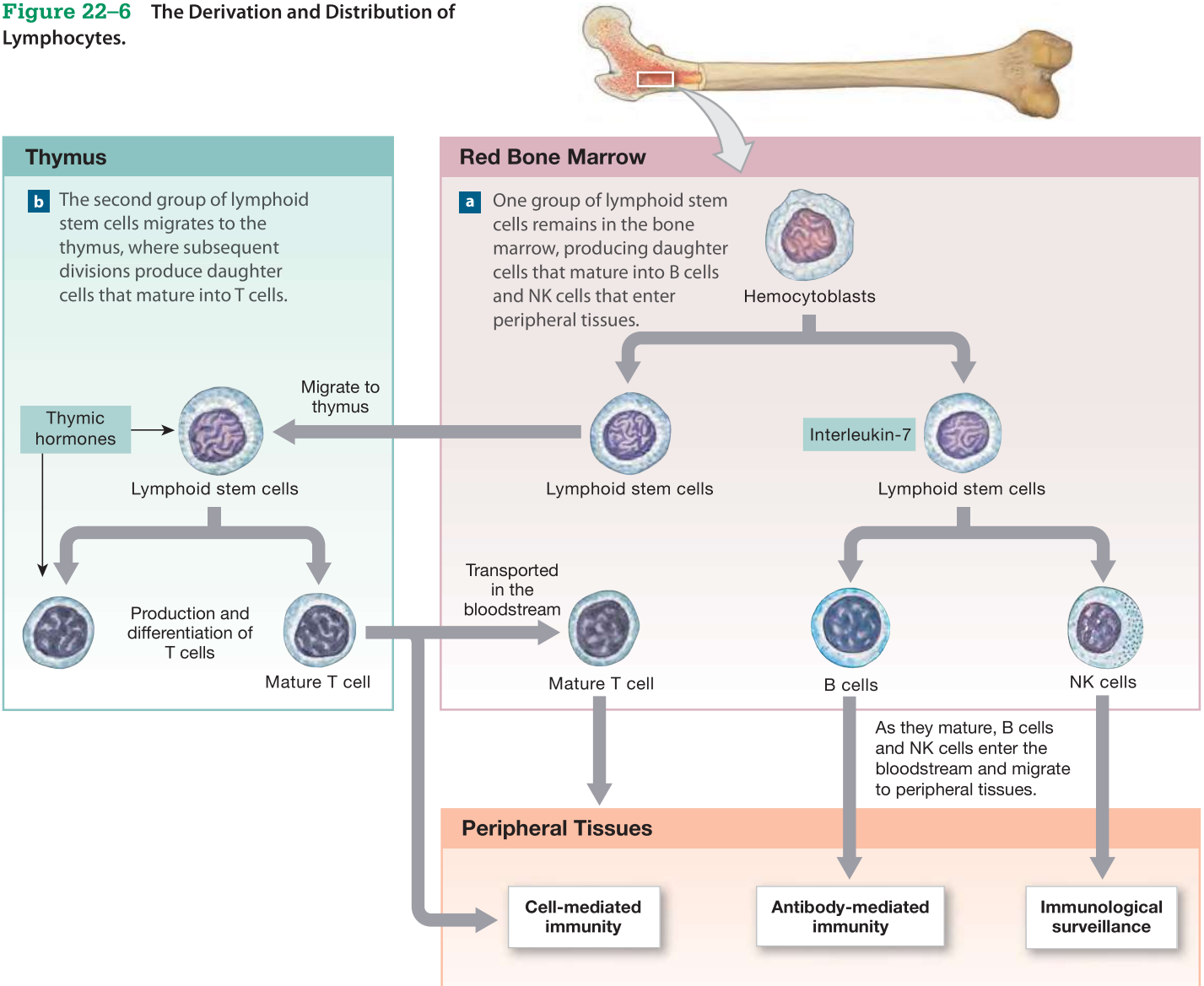
One group of lymphoid stem cells remains in the red bone marrow (Figure 22–6a) and the other group migrates to the thymus. Lymphoid stem cells in the red bone marrow divide to produce immature B cells and NK cells. B cell development involves intimate contact with large **stromal** (*stroma*, a bed) **cells** in the bone marrow. The cytoplasmic extensions of stromal cells contact or even wrap around the developing B cells. Stromal cells produce an immune system hormone, or *cytokine*, called *interleukin-7*. It promotes the differentiation of B cells. (We consider cytokines and their varied effects in a later section.)

As they mature, B cells and NK cells enter the bloodstream and migrate to peripheral tissues (Figure 22–6c). Most of the B cells move into lymph nodes, the spleen, or other lymphoid tissues. The NK cells patrol the body, moving through peripheral tissues in search of abnormal cells.

The second group of lymphoid stem cells migrates to the thymus to mature (Figure 22–6b). These stem cells and their descendants develop in an environment that is isolated from the general circulation by the **blood–thymus barrier.** Under the influence of thymic hormones, the lymphoid stem cells divide repeatedly, producing the various kinds of T cells. At least seven thymic hormones have been identified, but their precise functions and interactions have yet to be determined.

When their development nears completion, T cells reenter the bloodstream and return to the red bone marrow. They also

Figure 22–6 **The Derivation and Distribution of Lymphocytes.**



c Mature T cells leave the circulation to take temporary residence in peripheral tissues. All three types of lymphocytes circulate throughout the body in the bloodstream.

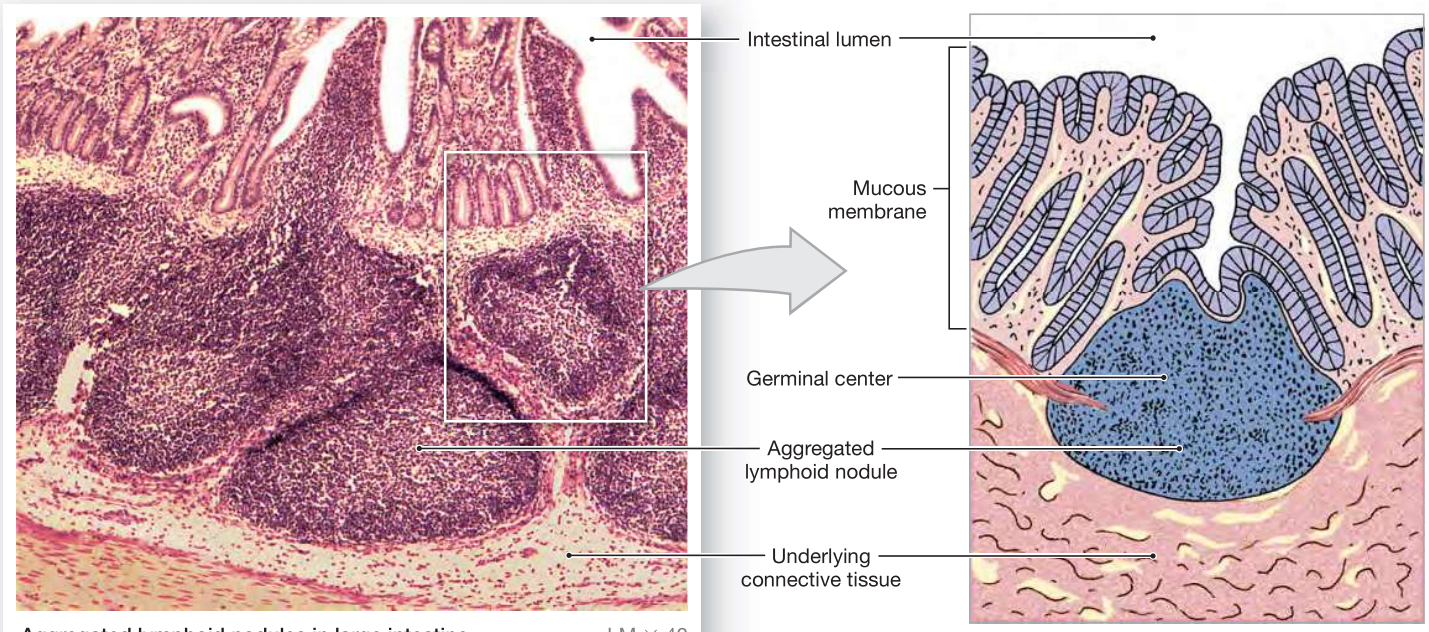
travel to peripheral tissues, including lymphoid tissues and organs, such as the spleen (Figure 22–6c).

The T cells and B cells that migrate from their sites of origin retain the ability to divide, producing daughter cells of the same type. For example, a dividing B cell produces other B cells, not T cells or NK cells. As we will see, the ability of specific types of lymphocytes to increase in number is crucial to the success of the immune response.

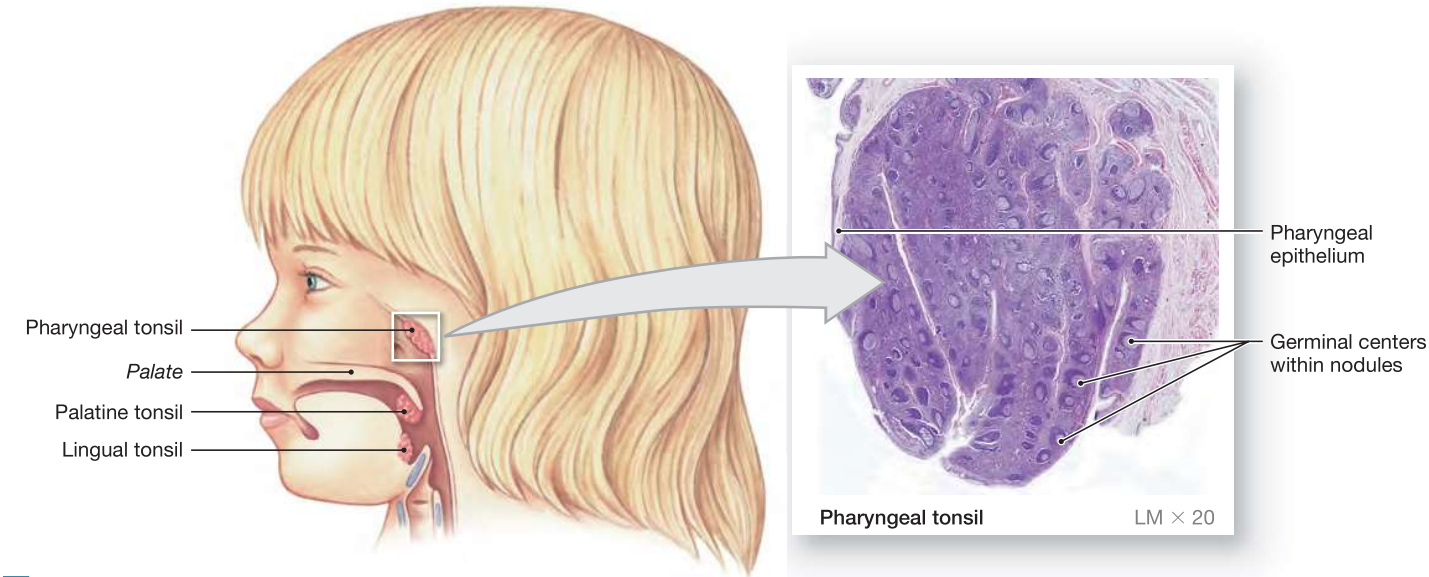
Lymphoid Tissues

Lymphoid tissues are connective tissues dominated by lymphocytes. In a **lymphoid nodule,** or *lymphatic nodule*, the lymphocytes are densely packed in an area of areolar tissue. In many areas, lymphoid nodules form large clusters (Figure 22–7). Lymphoid nodules occur in the connective tissue deep to the epithelia lining the respiratory tract, where they are

Figure 22–7 Lymphoid Nodules.



a Aggregated lymphoid nodules in section



b The positions of the tonsils and a tonsil in section. Notice the pale germinal centers, where lymphocyte cell divisions occur.

Clinical Note

Cancer and the Lymphatic System Metastasizing cancer cells commonly spread along lymphatic vessels. These vessels occur in almost all portions of the body except the central nervous system, and lymphatic capillaries offer little resistance to the passage of cancer cells. As a result, the lymph nodes serve as "way stations" for migrating cancer cells. For this reason, an analysis of lymph nodes can provide information on the spread of cancer cells, and such information helps determine the appropriate therapies. *Lymphomas* are one group of cancers originating in the cells of the lymphatic system.

known as *tonsils*, and along the digestive, respiratory, urinary, and reproductive tracts. They are also found within more complex lymphoid organs, such as lymph nodes or the spleen.

A single nodule averages about a millimeter in diameter. Its boundaries are not distinct, because no fibrous capsule surrounds it. Each nodule often has a central zone called a **germinal center,** which contains dividing lymphocytes (**Figure 22–7b**).

MALT

The collection of lymphoid tissues that protect the epithelia of the digestive, respiratory, urinary, and reproductive systems is called the **mucosa-associated lymphoid tissue (MALT).** Clusters of lymphoid nodules deep to the epithelial lining of the intestine are known as **aggregated lymphoid nodules,** or *Peyer's patches* (**Figure 22–7a**). Other examples of MALT include the appendix and the tonsils.

The *appendix*, or *vermiform* ("worm-shaped") *appendix,* is a blind pouch that originates near the junction between the small and large intestines. Its walls contain a mass of fused lymphoid nodules.

Tonsils

The **tonsils** are large lymphoid nodules in the walls of the pharynx (**Figure 22–7b**). Most people have five tonsils. Left and right **palatine tonsils** are located at the posterior, inferior margin of the oral cavity, along the boundary with the pharynx. A single **pharyngeal tonsil,** often called the *adenoid*, lies in the posterior superior wall of the nasopharynx. A pair of **lingual tonsils** lie deep to the mucous epithelium covering the base (pharyngeal portion) of the tongue. Because of their location, the lingual tonsils are usually not visible unless they become infected and swollen, a condition known as **tonsillitis.**

Lymphoid Organs

A fibrous connective tissue capsule separates lymphoid organs—the *lymph nodes*, the *thymus*, and the *spleen*—from surrounding tissues.

Lymph Nodes

Lymph nodes are small lymphoid organs ranging in diameter from 1 mm to 25 mm (to about 1 in.). The greatest number of lymph nodes is located in the neck, armpits, and groin, where they defend us against bacteria and other invaders. **Figure 22–1** shows the general pattern of lymph node distribution in the body.

A dense connective tissue capsule covers each lymph node (**Figure 22–8**). Bundles of collagen fibers extend from the capsule into the interior of the node. These fibrous partitions are called **trabeculae** (*trabecula*, a beam).

The typical lymph node is shaped like a kidney bean (**Figure 22–8**). Blood vessels and nerves reach the lymph node at a shallow indentation called the **hilum.** Two sets of lymphatic vessels, afferent lymphatics and efferent lymphatics, are connected to each lymph node. **Afferent** (*afferens*, to bring to) **lymphatics** bring lymph to the lymph node from peripheral tissues. The afferent lymphatics penetrate the capsule of the lymph node on the side opposite the hilum. **Efferent** (*efferens*, to bring out) **lymphatics** leave the lymph node at the hilum. These vessels carry lymph away from the lymph node and toward the venous circulation.

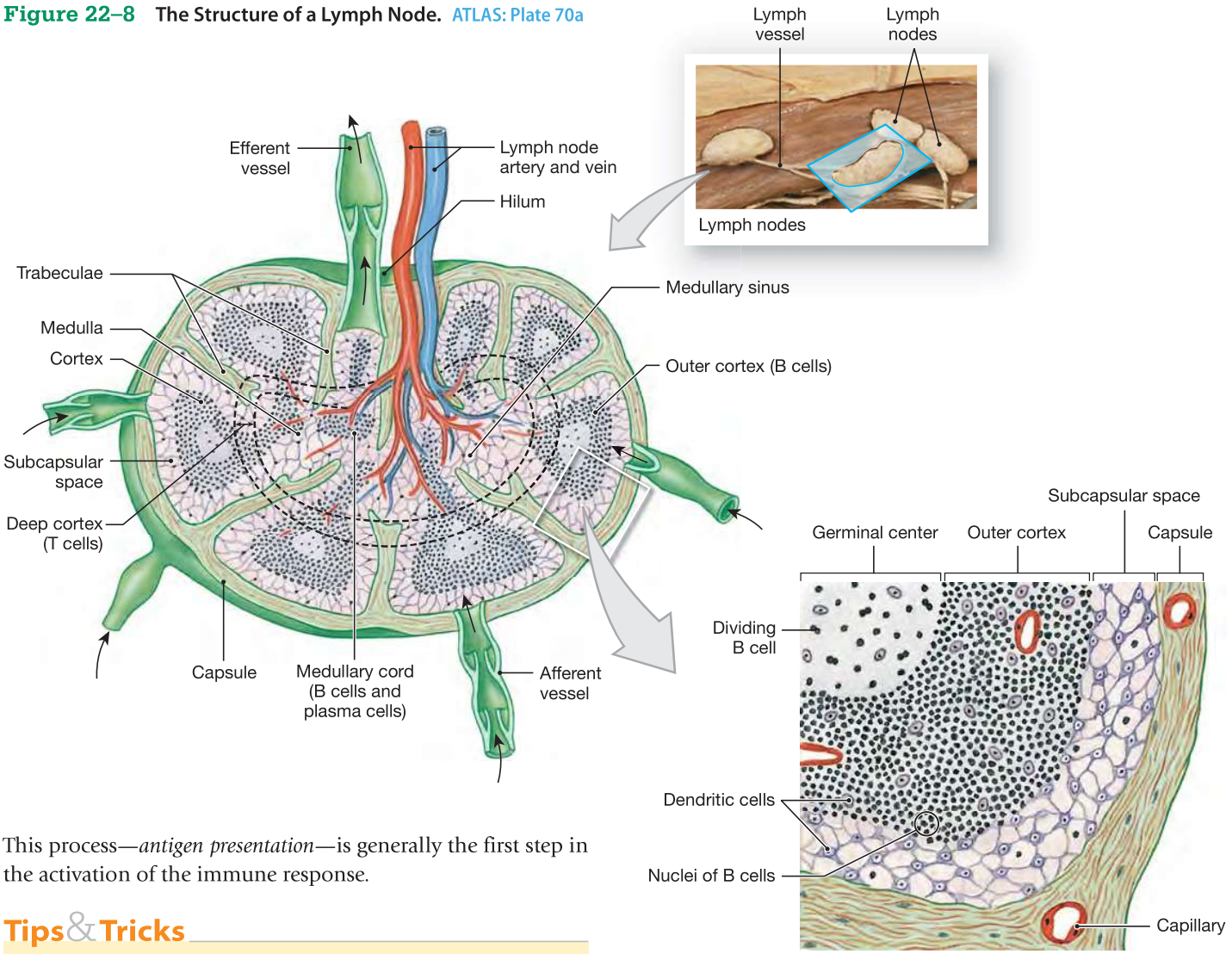
Lymph Flow. Lymph from the afferent lymphatics flows through the lymph node within a network of sinuses, open passageways with incomplete walls (**Figure 22–8**). Lymph first enters a *subcapsular space* (formerly called the *subcapsular sinus*). It contains a meshwork of branching reticular fibers, macrophages, and dendritic cells. **Dendritic cells** are involved in starting an immune response. (We consider their role in a later section.) Lymph passes through the subcapsular space and then flows through the **outer cortex** of the node. The outer cortex contains B cells within germinal centers similar to those of lymphoid nodules.

Lymph then continues through lymph sinuses in the **deep cortex** (*paracortical area*), which is dominated by T cells. Here lymphocytes leave the bloodstream and enter the lymph node by crossing the walls of blood vessels.

After flowing through the sinuses of the deep cortex, lymph continues into the core, or **medulla,** of the lymph node. The medulla contains B cells and plasma cells organized into elongate masses known as **medullary cords.** Lymph passes through a network of sinuses in the medulla and then enters the efferent lymphatics at the hilum.

Lymph Node Function. A lymph node functions like a kitchen water filter. It purifies lymph before it reaches the veins. As lymph flows through a lymph node, at least 99 percent of the antigens in the lymph are removed. Fixed macrophages in the walls of the lymphatic sinuses engulf debris or pathogens in lymph as it flows past. Antigens removed in this way are then processed by the macrophages and "presented" to nearby lymphocytes. Other antigens bind to receptors on the surfaces of dendritic cells, where they can stimulate lymphocyte activity.

Figure 22–8 The Structure of a Lymph Node. ATLAS: Plate 70a



This process—*antigen presentation*—is generally the first step in the activation of the immune response.

Tips & Tricks

Helper T cells "help" translate the message from the antigen-presenting cells of the nonspecific response to the cells of the specific immune responses.

In addition to filtering, lymph nodes function as an early-warning system. Any infection or other abnormality in a peripheral tissue puts antigens into the interstitial fluid, and thus into the lymph leaving the area. These antigens then stimulate macrophages and lymphocytes in nearby lymph nodes.

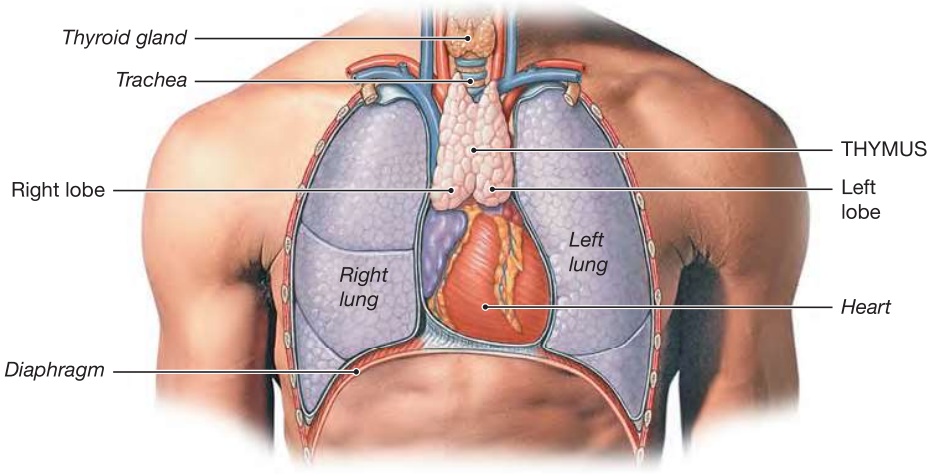
To protect a house against intruders, you might guard all the entrances and exits or place traps by the windows and doors. The distribution of lymphoid tissues and lymph nodes follows such a pattern. The largest lymph nodes are located where peripheral lymphatics connect with the trunk, such as in the groin, the axillae, and the base of the neck. These nodes are often called *lymph glands*. Because lymph is monitored in these nodes, potential problems can be detected and dealt with before they affect the vital organs of the trunk. The mesenteries of the gut also have aggregations of lymph nodes, located near the trachea and passageways leading to the lungs, and in association with the thoracic duct. These lymph nodes protect against pathogens and other antigens within the digestive and respiratory systems.

A minor injury commonly produces a slight enlargement of the nodes along the lymphatic vessels draining the region. This sign is often called "swollen glands." It typically indicates inflammation in peripheral structures. The enlargement generally results from an increase in the number of lymphocytes and phagocytes in the node in response to a minor, localized infection. Chronic or excessive enlargement of lymph nodes is **lymphadenopathy** (lim-fad-e-NOP-a-thē). This condition may occur in response to bacterial or viral infections, endocrine disorders, or cancer.

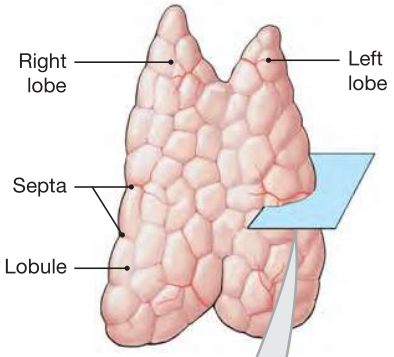
The Thymus

The **thymus** is a pink, grainy organ located in the mediastinum, generally just posterior to the sternum (**Figure 22–9a,b**). In

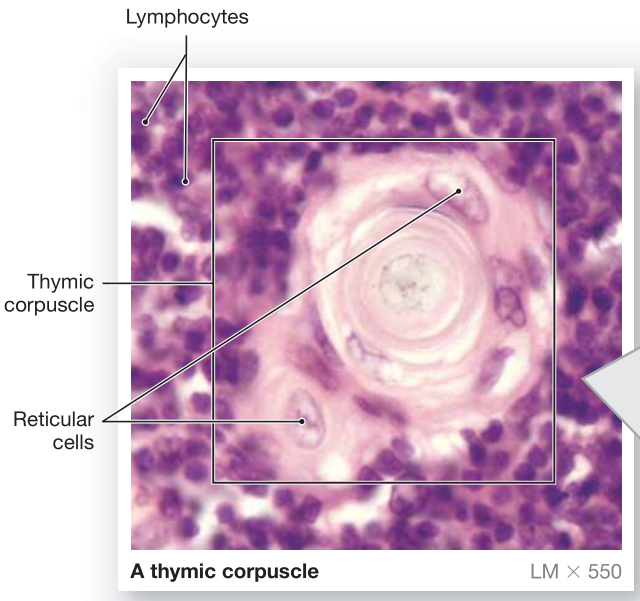
Figure 22–9 The Thymus. ATLAS: Plate 47a



a The appearance and position of the thymus in relation to other organs in the chest.

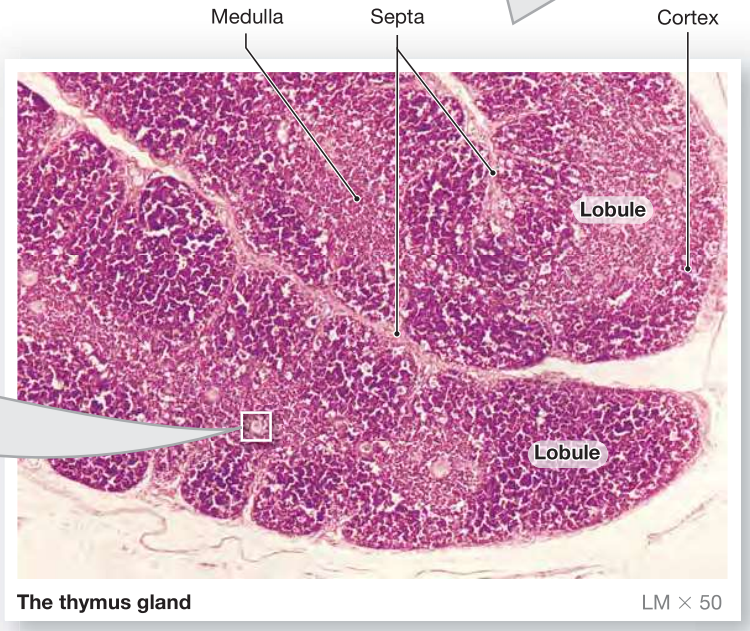


b Anatomical landmarks on the thymus.



A thymic corpuscle LM × 550

d Higher magnification reveals the unusual structure of thymic corpuscles. The small cells are lymphocytes in various stages of development.



The thymus gland LM × 50

c Fibrous septa divide the tissue of the thymus into lobules resembling interconnected lymphoid nodules.

newborn infants and young children, the thymus is relatively large. It commonly extends from the base of the neck to the superior border of the heart. The thymus reaches its greatest size relative to body size in the first year or two after birth. (The organ continues to increase in mass throughout childhood, but the body as a whole grows even faster, so the size of the thymus relative to that of the other organs in the mediastinum gradually decreases.)

The thymus reaches its maximum absolute size, at a weight of about 40 g (1.4 oz), just before puberty. After puberty, it gradually diminishes in size and becomes increasingly fibrous, a process called *involution*. By the time a person reaches age 50, the thymus may weigh less than 12 g (0.3 oz). The gradual decrease in the size and secretory abilities of the thymus may make elderly individuals more susceptible to disease.

The capsule that covers the thymus divides it into two **thymic lobes** (Figure 22–9b). Fibrous partitions called **septa** (singular, *septum*) originate at the capsule and divide the lobes into **lobules** averaging 2 mm in diameter (Figure 22–9b,c). Each lobule consists of a densely packed outer **cortex** and a paler, central **medulla.** Lymphocytes (T cells) in the cortex are actively dividing. As the T cells mature, they migrate into the medulla. After about three weeks, these T cells leave the thymus by entering one of the medullary blood vessels.

Lymphocytes in the cortex are arranged in clusters that are completely surrounded by **reticular epithelial cells.** These cells developed from epithelial cells of the embryo. Reticular epithelial cells also encircle the blood vessels of the cortex. These cells maintain the blood–thymus barrier. They also secrete the thymic hormones that stimulate stem cell divisions and T cell differentiation.

Maturing T cells leave the cortex and enter the medulla of the thymus. The medulla has no blood–thymus barrier. The reticular epithelial cells in the medulla cluster together in concentric layers, forming distinctive structures known as **thymic (Hassall's) corpuscles** (Figure 22–9d). Despite their imposing appearance, the function of thymic corpuscles remains unknown. T cells in the medulla can enter or leave the bloodstream across the walls of blood vessels in this region or within one of the efferent lymphatics that collect lymph from the thymus.

The thymus produces several hormones that are important to the development and maintenance of normal immunological defenses. *Thymosin* (THĪ-mō-sin) is the name originally given to an extract from the thymus that promotes the development and maturation of lymphocytes. This extract actually contains several complementary hormones. They include *thymosin-a*, *thymosin-b*, *thymosin V*, *thymopoietin*, *thymulin*, and others. The plural term, *thymosins,* is now sometimes used to refer to all thymic hormones.

The Spleen

The adult **spleen** contains the largest collection of lymphoid tissue in the body. In essence, the spleen performs the same functions for blood that lymph nodes perform for lymph. Functions of the spleen can be summarized as (1) removing abnormal blood cells and other blood components by phagocytosis, (2) storing iron recycled from red blood cells, and (3) initiating immune responses by B cells and T cells in response to antigens in circulating blood.

Anatomy of the Spleen. The spleen is about 12 cm (5 in.) long and weighs, on average, nearly 160 g (5.6 oz). In gross dissection, the spleen is deep red, due to the blood it contains. The spleen lies along the curving lateral border of the stomach, extending between the 9th and 11th ribs on the left side. It is attached to the lateral border of the stomach by the **gastrosplenic ligament,** a broad band of mesentery (Figure 22–10a).

The spleen has a soft consistency, so its shape primarily reflects the shapes of the structures around it. The spleen is in contact with the muscular diaphragm, the stomach, and the left kidney. The *diaphragmatic surface* is smooth and convex, conforming to the shape of the diaphragm and body wall. The *visceral surface* contains indentations that conform to the shape of the stomach (the *gastric area*) and the kidney (the *renal area*) (Figure 22–10b). Splenic blood vessels (the *splenic artery* and *splenic vein*) and lymphatic vessels communicate with the spleen on the visceral surface at the **hilum,** a groove marking the border between the gastric and renal areas.

Histology of the Spleen. The spleen is surrounded by a capsule containing collagen and elastic fibers.[1] The cellular components within constitute the **pulp** of the spleen (Figure 22–10c). **Red pulp** contains large quantities of red blood cells, and **white pulp** resembles lymphoid nodules.

The splenic artery enters at the hilum and branches to produce a number of arteries that radiate outward toward the capsule. These **trabecular arteries** in turn branch extensively, and their finer branches are surrounded by areas of white pulp. Capillaries then discharge the blood into the red pulp.

The cell population of the red pulp includes all the normal components of circulating blood, plus fixed and free macrophages. The structural framework of the red pulp consists of a network of reticular fibers. The blood passes through this meshwork and enters large sinusoids, also lined by fixed macrophages. The sinusoids empty into small veins, which ultimately collect into **trabecular veins** that continue toward the hilum.

This circulatory arrangement gives the phagocytes in the spleen an opportunity to identify and engulf damaged or infected cells in circulating blood. Lymphocytes are scattered throughout the red pulp, and the area surrounding the white pulp has a high concentration of macrophages and dendritic cells. For this reason, any microorganism or other antigen in the blood quickly comes to the attention of lymphocytes.

The spleen tears so easily that a seemingly minor hit to the left side of the abdomen can rupture the capsule. The result is serious internal bleeding and eventual circulatory shock. Such an injury is a known risk of contact sports (such as football, hockey, and rugby) and of more individual athletic activities, such as skiing and sledding.

Because the spleen is so fragile, it is very difficult to repair surgically. (Sutures typically tear out before they have been tensed enough to stop the bleeding.) A severely ruptured spleen is removed, a process called a **splenectomy** (splē-NEK-tō-mē). A person can survive without a spleen but lives with an increased risk of bacterial infection (particularly involving pneumococcal bacteria).

The Lymphatic System and Body Defenses

As we have noted, the human body has multiple defense mechanisms. Together they provide *resistance*—the ability to fight infection, illness, and disease. We can sort body defenses into two general categories:

1. **Innate (nonspecific) defenses** do not distinguish one type of threat from another. Their response is the same, regardless of the type of invader. These defenses are present at birth. They include *physical barriers*, *phagocytic cells*,

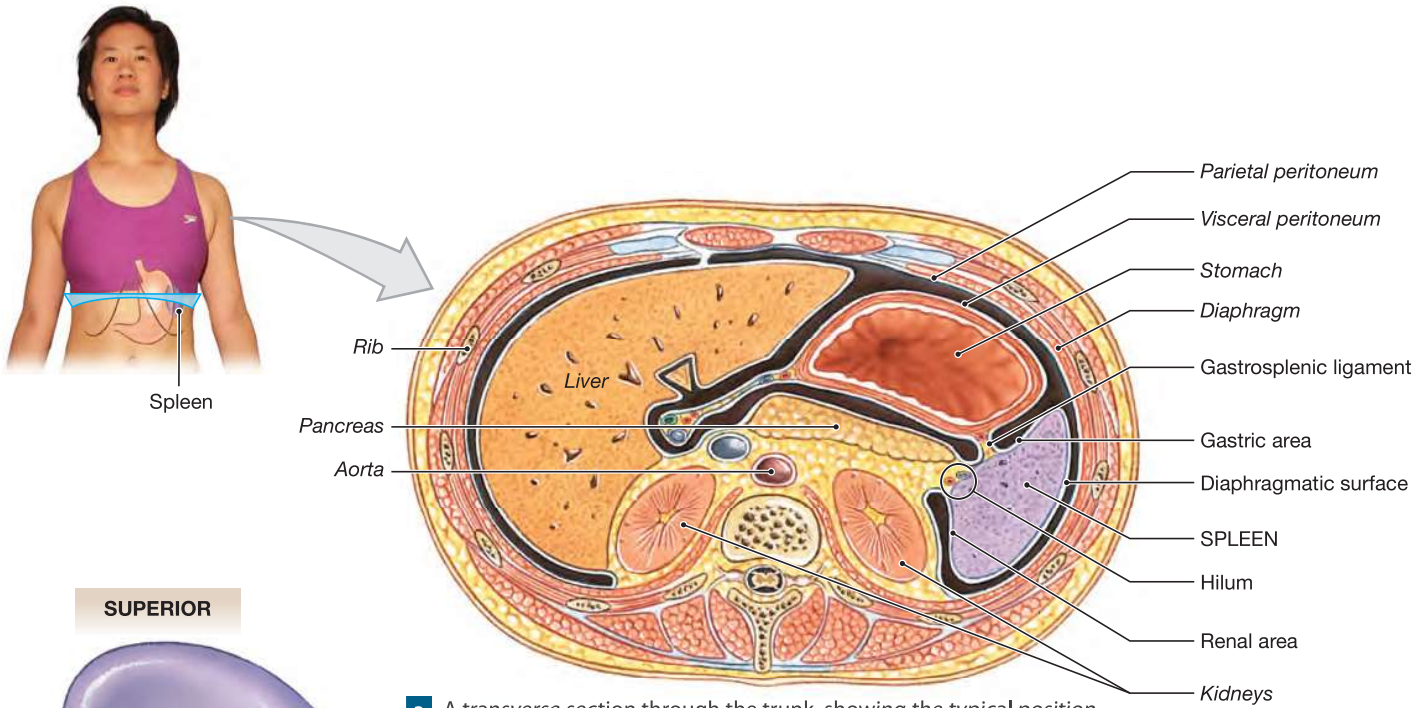
[1]The spleens of dogs, cats, and other mammals of the order *Carnivora* have extensive layers of smooth muscle that can contract to eject blood into the bloodstream. The human spleen lacks those muscle layers and cannot contract.

immunological surveillance, *interferons*, *complement*, *inflammation*, and *fever*. They provide a defensive capability known as **nonspecific resistance.**

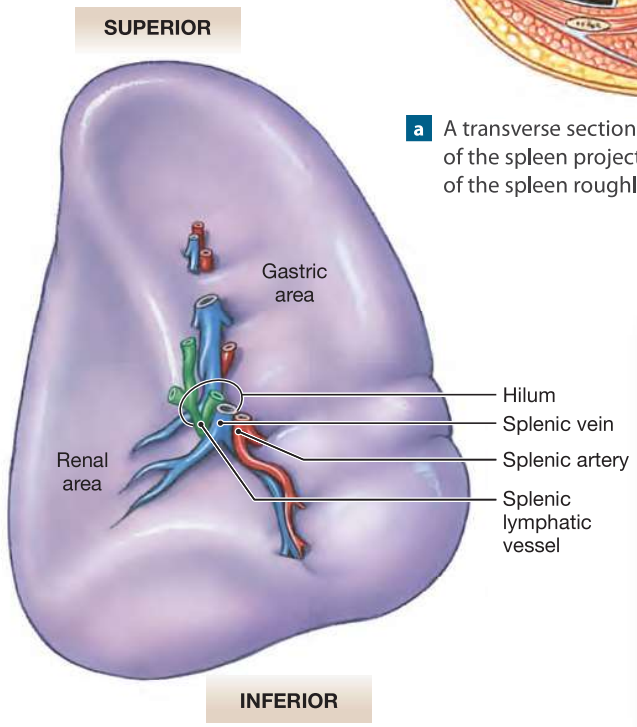
2. **Adaptive (specific) defenses** protect against particular threats. For example, a specific defense may protect against one type of bacterium, but not other bacteria and viruses.

Many specific defenses develop after birth as a result of accidental or deliberate exposure to environmental hazards. *Adaptive defenses depend on the activities of specific lymphocytes*. B cells and T cells are part of our adaptive defenses, which provides protection known as immunity, or **specific resistance.**

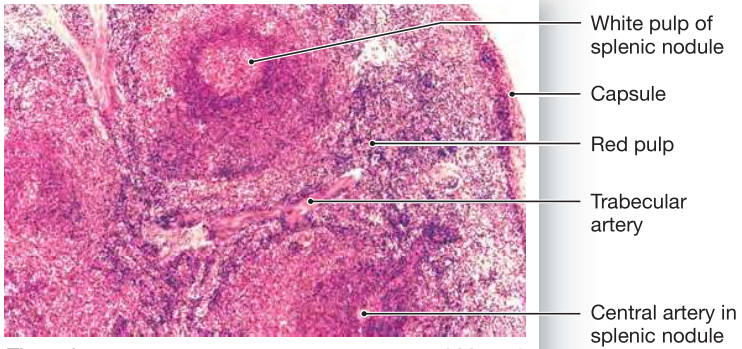
Figure 22–10 The Spleen. ATLAS: Plates 49e; 55; 56e,f; 57a,b



a A transverse section through the trunk, showing the typical position of the spleen projecting into the abdominopelvic cavity. The shape of the spleen roughly conforms to the shapes of adjacent organs.



b A posterior view of the surface of an intact spleen, showing major anatomical landmarks.



c The histological appearance of the spleen. White pulp is dominated by lymphocytes; it appears purple because the nuclei of lymphocytes stain very darkly. Red pulp contains a large number of red blood cells.

22

Innate and adaptive defenses work together. Both must function normally to provide adequate resistance to infection and disease.

Checkpoint

3. List the components of the lymphatic system.
4. How would blockage of the thoracic duct affect the circulation of lymph?
5. If the thymus failed to produce thymic hormones, which population of lymphocytes would be affected?
6. Why do lymph nodes enlarge during some infections?

See the blue Answers tab at the back of the book.

22-3 Innate (nonspecific) defenses do not discriminate between potential threats and respond the same regardless of the invader

Innate (nonspecific) defenses prevent the approach, deny the entry, or limit the spread of microorganisms or other environmental hazards. Seven major categories of innate defenses are summarized in **Figure 22–11**.

1. *Physical barriers* keep hazardous organisms and materials outside the body. For example, a mosquito that lands on your head may be unable to reach the surface of the scalp if you have a full head of hair.
2. *Phagocytes* are cells that engulf pathogens and cell debris. Examples include the macrophages of peripheral tissues and the microphages of blood.
3. *Immunological surveillance* is the destruction of abnormal cells by NK cells in peripheral tissues.
4. *Interferons* are chemical messengers that coordinate the defenses against viral infections.
5. *Complement* is a system of circulating proteins that assists antibodies in the destruction of pathogens.
6. The *inflammatory response* is a localized, tissue-level response that tends to limit the spread of an injury or infection.
7. *Fever* is an elevation of body temperature that accelerates tissue metabolism and the activity of defenses.

Physical Barriers

To cause trouble, an antigenic compound or a pathogen must enter body tissues. In other words, it must cross an epithelium—either at the skin or across a mucous membrane. The epithelial covering of the skin has multiple layers, a keratin coating, and a network of desmosomes that lock adjacent cells together. pp. 147–148 These barriers are very effective in protecting underlying tissues. Even along the more delicate internal passageways of the respiratory, digestive, urinary, and reproductive tracts, epithelial cells are tied together by tight junctions. These cells generally are supported by a dense and fibrous basement membrane.

In addition, specialized accessory structures and secretions protect most epithelia. The hairs on most areas of your body provide some protection against mechanical abrasion, especially on the scalp. They often prevent hazardous materials or insects from contacting your skin. The epidermal surface also receives the secretions of sebaceous and sweat glands. These secretions flush the surface and wash away microorganisms and chemicals. Such secretions may also contain chemicals that kill bacteria, destructive enzymes called *lysozymes*, and antibodies.

The epithelia lining the digestive, respiratory, urinary, and reproductive tracts are more delicate, but they are equally well defended. Mucus bathes most surfaces of your digestive tract. Your stomach contains a powerful acid that can destroy many pathogens. Mucus moves across the respiratory tract lining, urine flushes the urinary passages, and glandular secretions do the same for the reproductive tract. Special enzymes, antibodies, and an acidic pH add to the effectiveness of these secretions.

Phagocytes

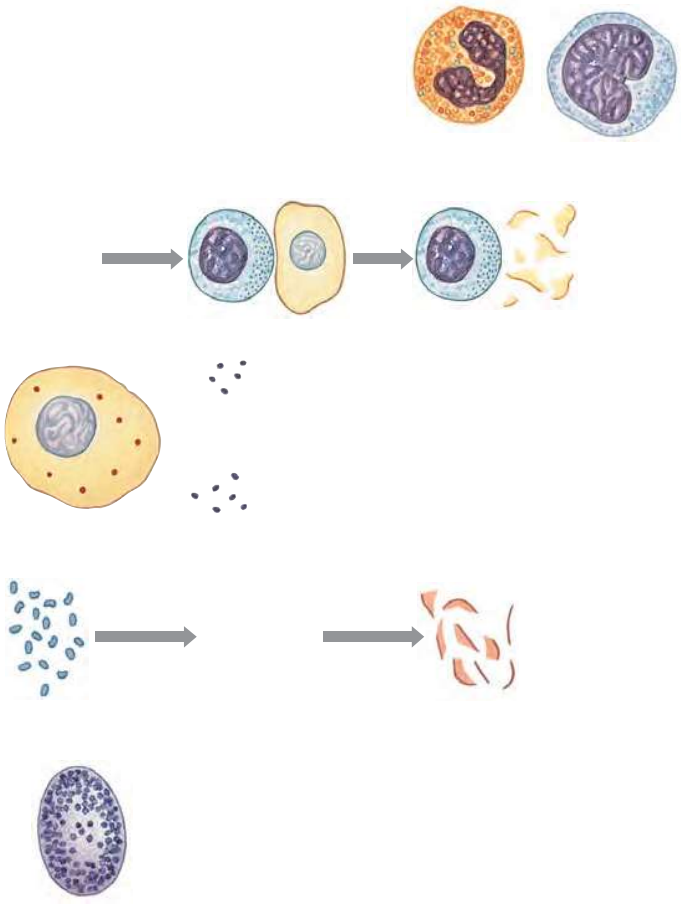
Phagocytes serve as janitors and police in peripheral tissues. They remove cellular debris and respond to invasion by foreign compounds or pathogens. Phagocytes are the "first line of cellular defense" against pathogenic invasion. Many phagocytes attack and remove microorganisms even before lymphocytes detect them. The human body has two general classes of phagocytic cells: *microphages* and *macrophages*.

Microphages

Microphages are the neutrophils and eosinophils that normally circulate in the blood. These phagocytic cells leave the bloodstream and enter peripheral tissues that have been subjected to injury or infection. As noted in Chapter 19, neutrophils are abundant, mobile, and quick to phagocytize cellular debris or invading bacteria. p. 653 Eosinophils are less abundant. They target foreign compounds or pathogens that have been coated with antibodies.

Macrophages

Macrophages are large, actively phagocytic cells. Your body contains several types of macrophages. Most are derived from the monocytes of the circulating blood. Typically, macrophages



How does an activated macrophage respond to a pathogen? It may:

- engulf a pathogen or other foreign object and destroy it with lysosomal enzymes.
- bind to or remove a pathogen from the interstitial fluid, but be unable to destroy the invader until assisted by other cells.
- destroy its target by releasing toxic chemicals, such as *tumor necrosis factor*, nitric oxide, or hydrogen peroxide, into the interstitial fluid.

We consider these responses further in a later section.

Fixed Macrophages. **Fixed macrophages,** or *histiocytes*, reside in specific tissues and organs. These cells are normally incapable of movement, so their targets must diffuse or otherwise move through the surrounding tissue until they are within range. Fixed macrophages are scattered among connective tissues, usually in close association with collagen or reticular fibers. They are found in the papillary and reticular layers of the dermis, in the subarachnoid space of the meninges, and in bone marrow. In some organs, the fixed macrophages have special names. **Microglia** are macrophages in the central nervous system, and **Kupffer cells** are macrophages located in and around the liver sinusoids.

Free Macrophages. **Free macrophages,** or *wandering macrophages*, travel throughout the body. They arrive at the site of an injury by migrating through adjacent tissues or by leaving the circulating blood. Some tissues contain free macrophages with distinctive characteristics. For example, **alveolar macrophages,** also known as *phagocytic dust cells,* monitor the exchange surfaces of the lungs.

Movement and Phagocytosis

Free macrophages and microphages function in similar ways:

- Both can move through capillary walls by squeezing between adjacent endothelial cells. This process is known as *emigration*, or *diapedesis*. ↩ p. 653 The endothelial cells in an injured area develop membrane "markers" that signal passing blood cells that something is wrong. The phagocytic cells then attach to the endothelial lining and migrate into the surrounding tissues.
- Both may be attracted to or repelled by chemicals in the surrounding fluids, a phenomenon called **chemotaxis.** They are particularly sensitive to cytokines released by other body cells and to chemicals released by pathogens.
- For both, phagocytosis begins with **adhesion,** the attachment of the phagocyte to its target. In adhesion, receptors on the plasma membrane of the phagocyte bind to the surface of the target. Adhesion is followed by the formation of a vesicle containing the bound target (**Figure 3-22**, p. 94). The contents of the vesicle are digested once the vesicle fuses with lysosomes or peroxisomes.

All phagocytic cells function in much the same way, although their targets may differ. The life span of an actively phagocytic cell can be rather brief. For example, most neutrophils die before they have engulfed more than 25 bacteria, and during an infection a neutrophil may attack that many in an hour.

Tips & Tricks

Membrane markers and chemotaxis are like putting up the flag on your mailbox: They signal the need for action.

Immunological Surveillance

The immune system generally ignores the body's own cells unless they become abnormal in some way. Natural killer (NK) cells are responsible for recognizing and destroying abnormal cells when they appear in peripheral tissues. The constant monitoring of normal tissues by NK cells is called **immunological surveillance.**

The plasma membrane of an abnormal cell generally contains antigens that are not found on the membranes of normal cells. NK cells recognize an abnormal cell by detecting those antigens. NK cells are much less selective about their targets than are other lymphocytes: They respond to a *variety* of abnormal antigens that may appear anywhere on a plasma membrane. They also attack *any* membrane containing abnormal antigens. As a result, NK cells are highly versatile. A single NK cell can attack bacteria in the interstitial fluid, body cells infected with viruses, or cancer cells.

NK cells respond much more rapidly than T cells or B cells. The activation of T cells and B cells involves a complex and time-consuming sequence of events. NK cells respond immediately on contact with an abnormal cell.

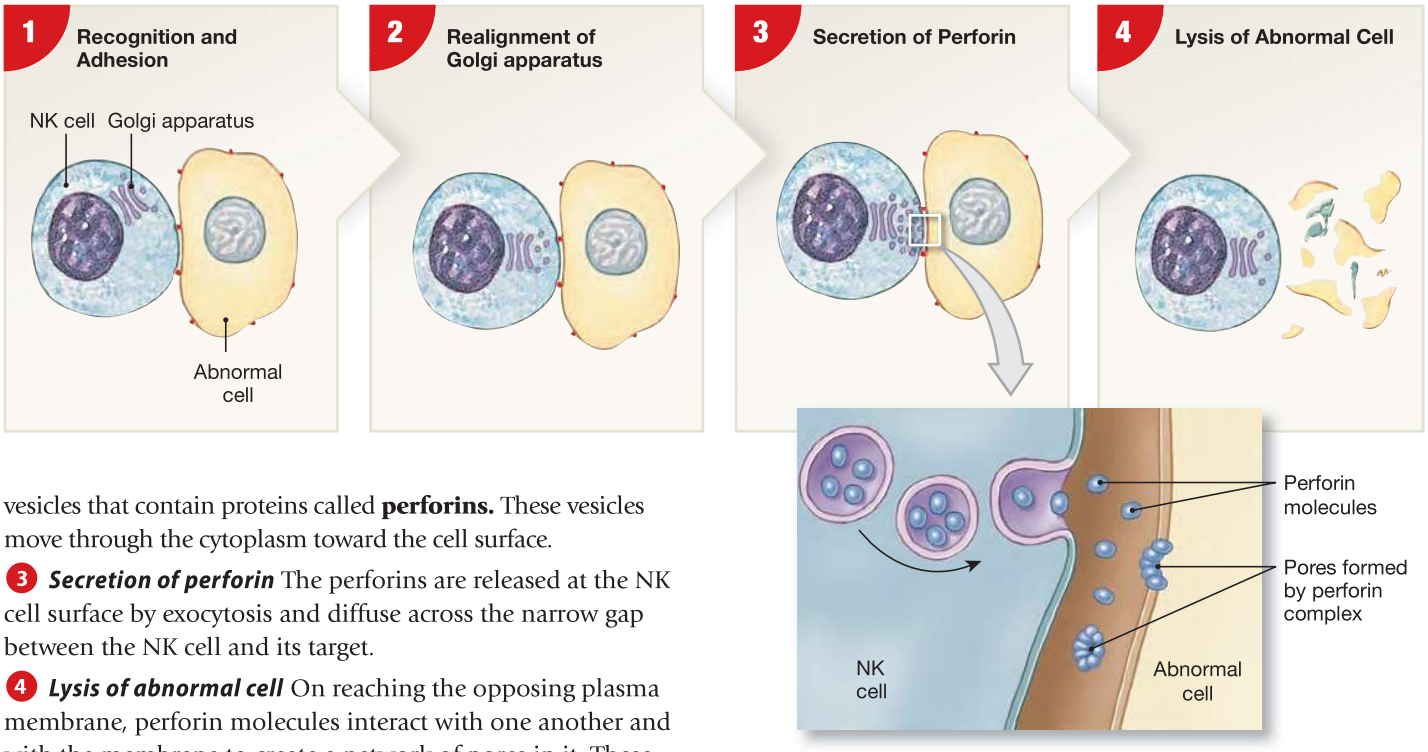
NK Cell Activation

Activated NK cells react in a predictable way (**Figure 22–12**):

1 ***Recognition and adhesion*** If a cell has unusual components in its plasma membrane, an NK cell recognizes that cell as abnormal. This recognition activates the NK cell, which then adheres to its target cell.

2 ***Realignment of Golgi apparatus*** The Golgi apparatus moves around the nucleus until the maturing face points directly toward the abnormal cell. The process might be compared to the rotation of a tank turret to point the cannon toward the enemy. The Golgi apparatus then produces a flood of secretory

Figure 22–12 How Natural Killer Cells Kill Cellular Targets.



vesicles that contain proteins called **perforins.** These vesicles move through the cytoplasm toward the cell surface.

3 ***Secretion of perforin*** The perforins are released at the NK cell surface by exocytosis and diffuse across the narrow gap between the NK cell and its target.

4 ***Lysis of abnormal cell*** On reaching the opposing plasma membrane, perforin molecules interact with one another and with the membrane to create a network of pores in it. These pores are large enough to allow the free passage of ions, proteins, and other intracellular materials. As a result, the target cell can no longer maintain its internal environment, and it quickly disintegrates.

Tips & Tricks

Perforin gets its name because it ***perfor***ates the target cell.

Why doesn't perforin affect the membrane of the NK cell? The answer is not clear, but NK cell membranes contain a second protein, called *protectin*. It may bind and inactivate perforin.

NK cells attack cancer cells and body cells infected with viruses. Cancer cells probably appear throughout life, but their plasma membranes generally contain unusual proteins called **tumor-specific antigens,** which NK cells recognize as abnormal. The NK cells then destroy the cancer cells, preserving tissue integrity. Unfortunately, some cancer cells avoid detection, perhaps because they lack tumor-specific antigens or because these antigens are covered in some way. Other cancer cells are able to destroy the NK cells that detect them. This process of avoiding detection or neutralizing body defenses is called **immunological escape.** Once immunological escape has occurred, cancer cells can multiply and spread without interference by NK cells.

In viral infections, the viruses replicate inside cells, beyond the reach of circulating antibodies. However, infected cells incorporate viral antigens into their plasma membranes, and NK cells recognize these infected cells as abnormal. By destroying them, NK cells can slow or prevent the spread of a viral infection.

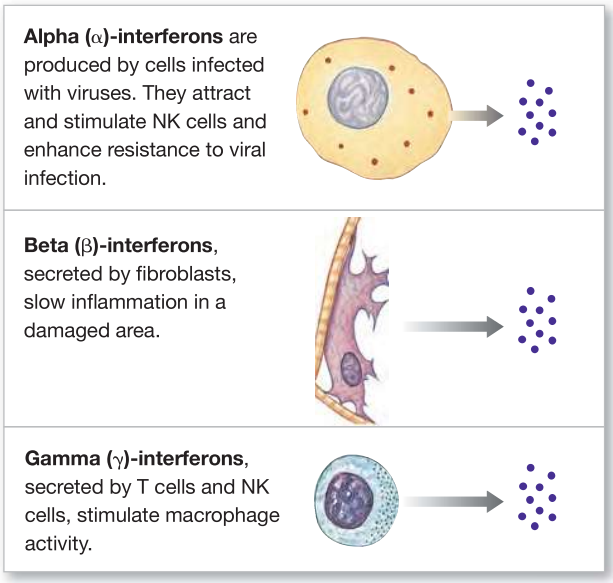
Interferons

Interferons (in-ter-FĒR-onz) are small proteins released by activated lymphocytes and macrophages, and by tissue cells infected with viruses. An interferon binds to surface receptors on the membrane of a normal cell and, via second messengers, triggers the production of **antiviral proteins** in the cytoplasm. Antiviral proteins do not prevent viruses from entering the cell. Instead, they interfere with viral replication inside the cell. In addition to slowing the spread of viral infections, interferons stimulate the activities of macrophages and NK cells.

At least three types of interferons exist: alpha (α)-interferons, beta (β)-interferons, and gamma (γ)-interferons (**Figure 22–13**). Most cells other than lymphocytes and macrophages respond to viral infection by secreting beta-interferon.

Interferons are examples of **cytokines** (SĪ-tō-kīnz)—chemical messengers that tissue cells release to coordinate local activities. Most cells produce cytokines only for paracrine communication—that is, cell-to-cell communication within one tissue. However, defense cells release cytokines that also act as hormones, affecting cells and tissues throughout the body. We discuss their role in regulating adaptive (specific) defenses in a later section.

Figure 22–13 Interferons.



Complement System

Plasma contains 11 special **complement (C) proteins** that form the **complement system.** The term *complement* refers to the fact that this system complements the action of antibodies.

The complement proteins interact with one another in chain reactions, or *cascades*, reminiscent of those of the clotting system. **Figure 22–14** provides an overview of the complement system.

The activation of complement can occur by two different routes: the *classical pathway* and the *alternative pathway*.

Complement Activation: The Classical Pathway and the Alternative Pathway

The **classical pathway** activates the complement system most rapidly and effectively. It begins with the binding of complement protein C1 to an antibody already attached to its specific antigen, such as a bacterial cell wall. In the absence of antibody molecules, the **alternative pathway,** or *properdin pathway*, activates the complement system. The alternate pathway is slower and less effective than the classical pathway. This pathway begins when several complement proteins—including **properdin** (*factor P*), *factor B*, and *factor D*—interact in the plasma. Exposure to foreign materials, such as the capsule of a bacterium, can trigger this interaction. Like the classical pathway, the alternative pathway ends with the conversion of inactive C3 protein to the activated C3b protein. Complement activation brings about the following effects: pore formation, enhanced phagocytosis, and histamine release. **Figure 22–14** shows the pathways of complement activation and its effects.

Inflammation

Inflammation, or the *inflammatory response*, is a localized tissue response to injury. ↩ p. 138 Inflammation produces local swelling *(tumor)*, redness *(rubor)*, heat *(calor)*, and pain *(dolor)*. These are known as the *cardinal signs and symptoms of inflammation*.

Many stimuli can produce inflammation. They include impact, abrasion, distortion, chemical irritation, infection by pathogens, and extreme temperatures (hot or cold). Each of these stimuli kills cells, damages connective tissue fibers, or injures the tissue in some other way. The changes alter the chemical composition of the interstitial fluid. Damaged cells release prostaglandins, proteins, and potassium ions. The injury itself may have introduced foreign proteins or pathogens. These changes in the interstitial environment trigger the complex process of inflammation.

Inflammation has several effects:

- The injury is temporarily repaired, and additional pathogens are prevented from entering the wound.
- The spread of pathogens away from the injury is slowed.
- Local, regional, and systemic defenses are mobilized to overcome the pathogens and facilitate permanent repairs. This repair process is called *regeneration*.

The Response to Injury

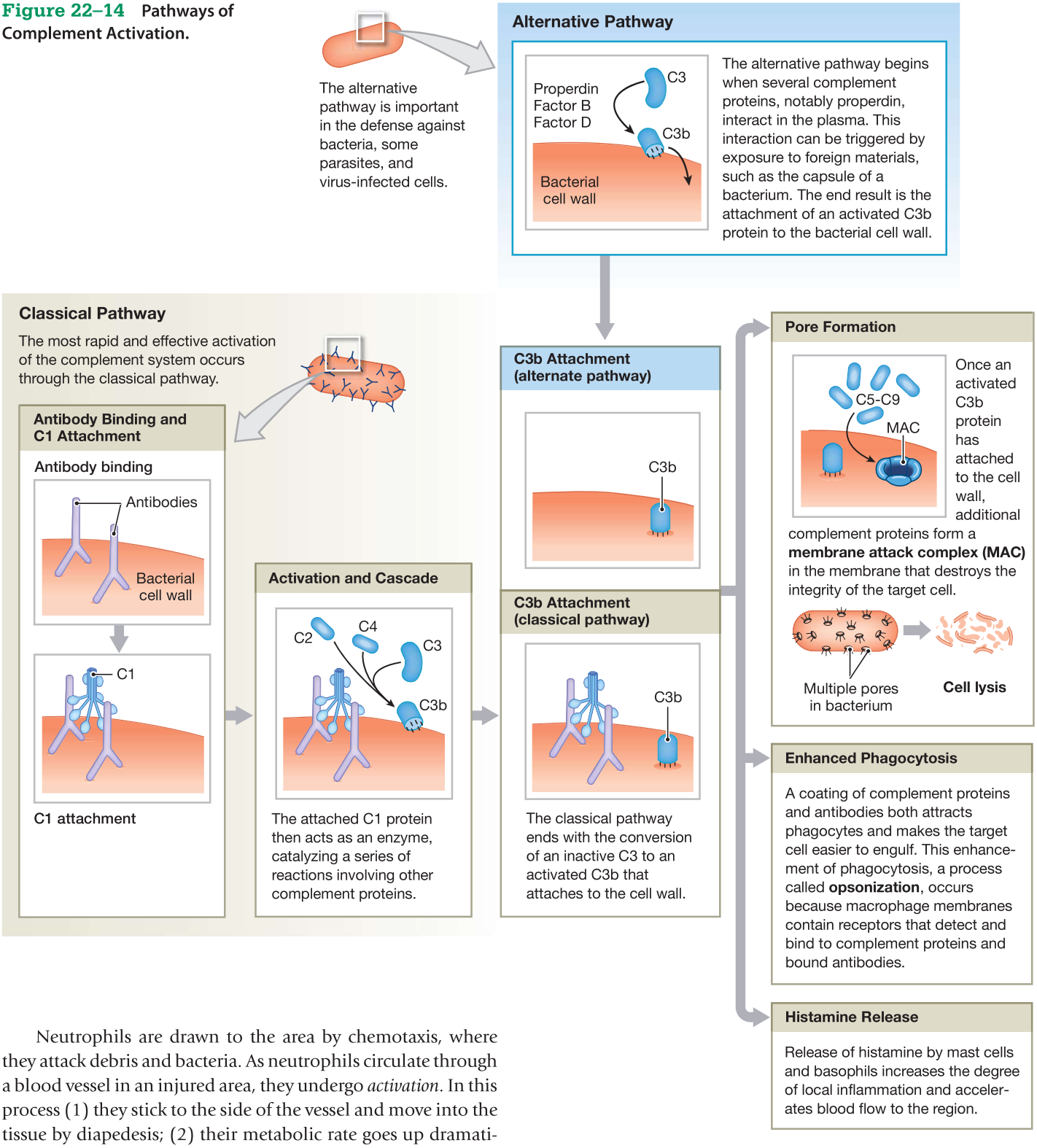
Mast cells play a pivotal role in the inflammatory response. **Figure 22–15** summarizes the events of inflammation in the skin. Comparable events take place in almost any tissue subjected to physical damage or infection.

When stimulated by mechanical stress or chemical changes in the local environment, mast cells release histamine, heparin, prostaglandins, and other chemicals into interstitial fluid. The histamine makes capillaries more permeable and speeds up blood flow through the area. The combination of abnormal tissue conditions and chemicals released by mast cells stimulates local sensory neurons, producing sensations of pain. The person then may take steps to limit the damage, such as removing a splinter or cleaning a wound.

The increased blood flow reddens the area and raises the local temperature. These changes increase the rate of enzymatic reactions and accelerate the activity of phagocytes. The rise in temperature may also denature foreign proteins or vital enzymes of invading microorganisms.

Because vessel permeability has increased, clotting factors and complement proteins can leave the bloodstream and enter the injured or infected area. Clotting does not take place at the actual site of injury, due to the presence of heparin. However, a clot soon forms around the damaged area, both isolating the region and slowing the spread of the chemical or pathogen into healthy tissues. Meanwhile, complement activation through the alternative pathway breaks down bacterial cell walls and attracts phagocytes.

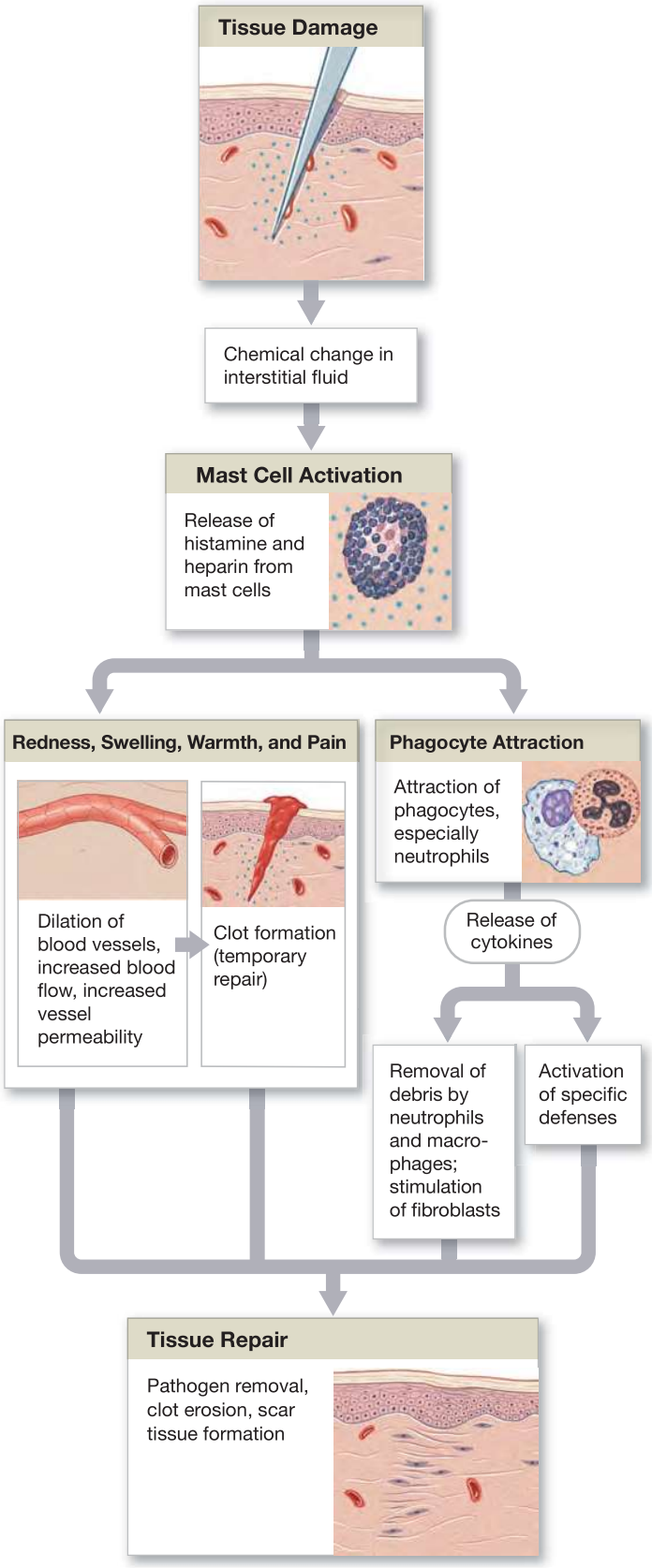
Figure 22–14 Pathways of Complement Activation.



Neutrophils are drawn to the area by chemotaxis, where they attack debris and bacteria. As neutrophils circulate through a blood vessel in an injured area, they undergo *activation*. In this process (1) they stick to the side of the vessel and move into the tissue by diapedesis; (2) their metabolic rate goes up dramatically, and while this *respiratory burst* continues, they generate reactive compounds, such as nitric oxide and hydrogen peroxide, that can destroy engulfed pathogens; and (3) they secrete cytokines that attract other neutrophils and macrophages to the area. As inflammation proceeds, the foreign proteins, toxins, microorganisms, and active phagocytes in the area activate the body's specific defenses.

Fixed and free macrophages engulf pathogens and cell debris. At first, neutrophils outnumber these cells. Then, as the

Figure 22–15 Inflammation and the Steps in Tissue Repair.



macrophages and neutrophils continue to secrete cytokines, the number of macrophages increases rapidly. Eosinophils may get involved if antibodies coat the foreign materials.

The cytokines released by active phagocytes stimulate fibroblasts in the area. The fibroblasts then begin forming scar tissue that reinforces the clot and slows the invasion of adjacent tissues. Over time, the clot is broken down and the injured tissues are either repaired or replaced by scar tissue. The process is essentially complete, although subsequent remodeling may take place over a period of years.

After an injury, tissue conditions generally become even more abnormal before they begin to improve. The tissue destruction that occurs after cells have been injured or destroyed is called **necrosis** (ne-KRŌ-sis). The destruction begins several hours after the initial event, and the damage is due to lysosomal enzymes. Lysosomes break down by autolysis, releasing digestive enzymes that first destroy the injured cells and then attack surrounding tissues. ↩ p. 73 As local inflammation continues, debris, fluid, dead and dying cells, and necrotic tissue components accumulate at the injury site. This viscous fluid mixture is known as **pus.** An accumulation of pus in an enclosed tissue space is called an **abscess.**

Fever

Fever is the maintenance of a body temperature greater than 37.2˚C (99˚F). Recall from Chapter 14 that the preoptic area of the hypothalamus contains a temperature-regulating center. ↩ p. 466 Circulating proteins called **pyrogens** (PĪ-rō-jenz; *pyro-*, fever or heat + *-gen*, substance) can reset this thermostat and raise body temperature.

A variety of stimuli either act as pyrogens themselves or stimulate macrophages to release pyrogens. These stimuli include pathogens, bacterial toxins, and antigen–antibody complexes. Active macrophages release a cytokine called **endogenous pyrogen,** or **interleukin-1** (in-ter-LOO-kin), abbreviated **IL-1.**

Within limits, a fever can be beneficial. High body temperatures may inhibit some viruses and bacteria. The most likely beneficial effect is on body metabolism. For each 1˚C rise in body temperature, metabolic rate increases by 10 percent. Cells can move faster, and enzymatic reactions take place more quickly. As a result, tissue defenses can be mobilized more rapidly and the repair process speeds up.

Checkpoint

7. List the body's nonspecific defenses.
8. What types of cells would be affected by a decrease in the number of monocyte-forming cells in red bone marrow?
9. A rise in the level of interferon in the body suggests what kind of infection?
10. What effects do pyrogens have in the body?

See the blue Answers tab at the back of the book.

22-4 Adaptive (specific) defenses respond to individual threats and are either cell-mediated or antibody-mediated

Adaptive (specific) defenses result from the coordinated activities of T cells and B cells. These cells respond to the presence of specific antigens. In general, T cells bring about **cell-mediated immunity,** or *cellular immunity*, which defends against abnormal cells and pathogens inside cells. B cells provide **antibody-mediated immunity,** or *humoral immunity*, which defends against antigens and pathogens in body fluids.

Both kinds of immunity are important because they come into play under different circumstances. Activated T cells do not respond to antigens in solution, and antibodies (produced by activated B cells) cannot cross plasma membranes. Moreover, helper T cells play a crucial role in antibody-mediated immunity by stimulating the activity of B cells.

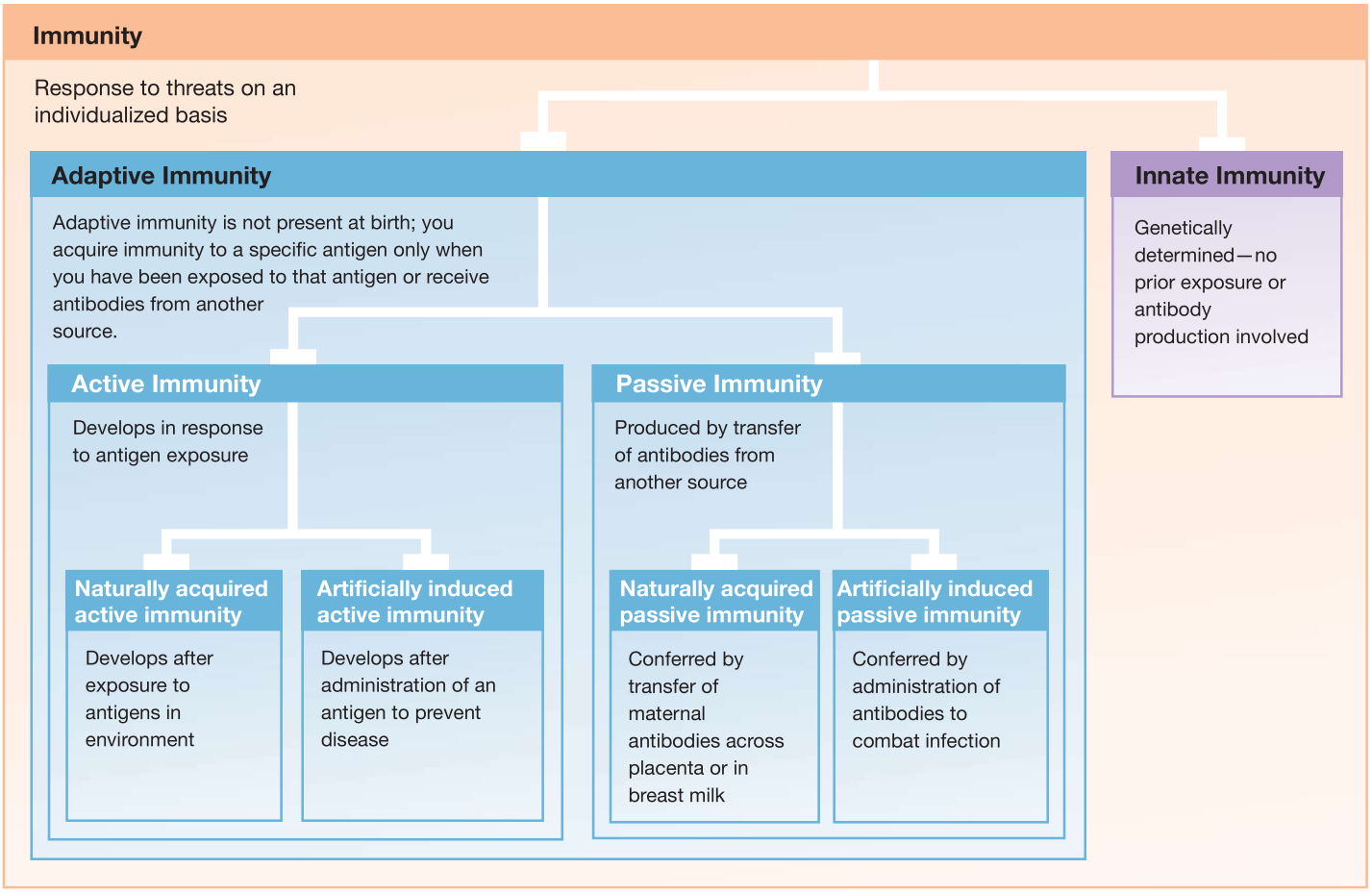
Forms of Immunity

We can classify immunity as either innate or adaptive. (**Figure 22–16**). As we stated earlier, **innate immunity** is genetically determined. It is present at birth and is not related to previous exposures to a particular antigen. For example, people do not get the same diseases that goldfish do. Innate immunity breaks down only in the case of AIDS or other conditions that depress all aspects of specific resistance.

Adaptive immunity is not present at birth. Instead, you develop immunity to a specific antigen only when you have been exposed to that antigen. Adaptive immunity can be *active* or *passive*. These forms of immunity can be either naturally acquired or artificially induced.

Active immunity develops after exposure to an antigen. It is a consequence of the immune response. In active immunity, the body responds to an antigen by making its own antibody. The immune system is *capable* of defending against a huge number of antigens. However, the appropriate defenses are mounted only after you encounter a particular antigen. Active immunity can result from natural exposure to an antigen in the environment

Figure 22–16 Forms of Immunity.



(naturally acquired active immunity) or from deliberate exposure to an antigen *(artificially induced active immunity)*.

- **Naturally acquired active immunity** normally begins to develop after birth. It continues to build as you encounter "new" pathogens or other antigens. You might compare this process to the development of a child's vocabulary: The child begins with a few basic common words and learns new ones as they are encountered.
- **Artificially induced active immunity** stimulates the body to produce antibodies under controlled conditions so that you will be able to overcome natural exposure to the pathogen in the future. This is the basic principle behind *immunization*, or *vaccination*, to prevent disease. A **vaccine** is a preparation designed to induce an immune response. It contains either a dead or an inactive pathogen, or antigens derived from that pathogen.

Passive immunity is produced by transferring antibodies from another source.

- In **naturally acquired passive immunity,** a baby receives antibodies from the mother, either during gestation (by crossing the placenta) or in early infancy (through breast milk).
- In **artificially induced passive immunity,** a person receives antibodies to fight infection or prevent disease. For example, someone who has been bitten by a rabid animal gets injections containing antibodies against the rabies virus.

22

Properties of Immunity

Regardless of the form, immunity has four general properties: (1) *specificity*, (2) *versatility*, (3) *memory*, and (4) *tolerance*.

Specificity

A specific defense is activated by a specific antigen, and the immune response targets that particular antigen and no others. **Specificity** results from the activation of appropriate lymphocytes and the production of antibodies with targeted effects. Specificity occurs because T cells and B cells respond to the molecular structure of an antigen. The shape and size of the antigen determine which lymphocytes will respond to it. Each T cell or B cell has receptors that will bind to one specific antigen, ignoring all others. The response of an activated T cell or B cell is equally specific. Either lymphocyte will destroy or inactivate that antigen without affecting other antigens or normal tissues.

Versatility

Millions of antigens in the environment can pose a threat to health. Over a normal lifetime, you encounter only a fraction of that number—perhaps tens of thousands of antigens. Your immune system, however, has no way of anticipating which antigens it will encounter. It must be ready to confront *any* antigen at *any* time. **Versatility** results in part from the large diversity of lymphocytes present in the body, and in part from variability in the structure of synthesized antibodies.

During development, cells in the lymphatic system differentiate to produce a huge number of lymphocytes with varied antigen sensitivities. The trillion or more T cells and B cells in your body include millions of different lymphocyte populations, distributed throughout the body. Each population contains several thousand cells with receptors in their membranes that differ from the receptors of other lymphocyte populations. As a result, each population of lymphocytes responds to a different antigen.

Several thousand lymphocytes are not enough to overcome a pathogenic invasion. However, when activated by an appropriate antigen, a lymphocyte begins to divide, producing more lymphocytes with the same specificity. All the cells produced by these divisions make up a **clone,** and all the members of that clone are sensitive to the same specific antigen.

To understand how this system works, think about running a commercial kitchen with only samples on display. You can display a wide selection because the samples don't take up much space, and you don't have to expend energy now preparing food that might never be eaten. When a customer selects one of your samples and places an order for several dozen, you prepare them on the spot.

The same principle applies to the lymphatic system. Your body contains a small number of many different kinds of lymphocytes. When an antigen arrives, lymphocytes sensitive to it are "selected." These lymphocytes divide to generate a large number of additional lymphocytes of the same type.

Memory

As we just saw, during the initial response to an antigen, lymphocytes that are sensitive to it undergo repeated cycles of cell division. Immunologic **memory** exists because those cell divisions produce two groups of cells. One group attacks the invader immediately. Another group remains inactive unless it meets the same antigen at a later date. This inactive group is made up of *memory cells* that enable your immune system to "remember" an antigen it has previously encountered, and to launch a faster, stronger, and longer-lasting counterattack if such an antigen appears again.

Tolerance

The immune system does not respond to all antigens. All cells and tissues in the body, for example, contain antigens that normally do not stimulate an immune response. We say that the immune system exhibits **tolerance** toward such antigens.

The immune response targets foreign cells and compounds, but it generally ignores normal tissues. During their differentiation in the red bone marrow (B cells) and thymus (T cells), any cells that react to antigens that are normally present in the body are destroyed. As a result, mature B cells and T cells ignore normal antigens, also called *self-antigens*, but attack foreign antigens, or *nonself antigens*. Tolerance can also develop over time in response to chronic exposure to an antigen in the environment. Such tolerance lasts only as long as the exposure continues.

An Introduction to the Immune Response

Figure 22–17 provides an overview of the immune response. When an antigen triggers an immune response, it usually activates both T cells and B cells. The activation of T cells generally occurs first, but only after phagocytes have been exposed to the antigen. Once activated, T cells attack the antigen and stimulate the activation of B cells. Activated B cells mature into cells that produce antibodies. Antibodies in the bloodstream then bind to and attack the antigen. We examine these processes more closely in the sections that follow.

Checkpoint

11. **Distinguish between cell-mediated (cellular) immunity and antibody-mediated (humoral) immunity.**
12. **Identify the two forms of active immunity and the two forms of passive immunity.**
13. **List the four general properties of immunity.**

See the blue Answers tab at the back of the book.

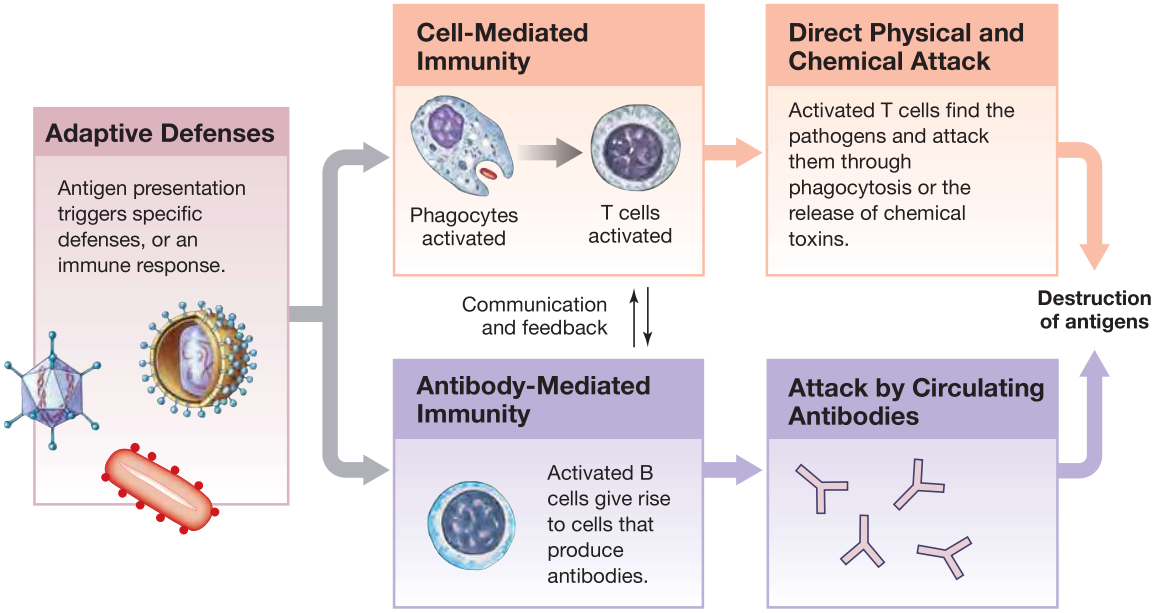
22-5 T cells play a role in initiating, maintaining, and controlling the immune response

The role of T cells in the immune response is varied and important in resisting pathogens. We have already noted four major types of T cells:

1. *Cytotoxic T* (T_C) *cells* are responsible for cell-mediated immunity. These cells enter peripheral tissues and directly attack antigens physically and chemically.
2. *Memory T cells* respond to antigens they have already encountered by cloning more lymphocytes to ward off the invader.
3. *Helper T* (T_H) *cells* stimulate the responses of both T cells and B cells. Helper T cells are absolutely vital to the immune response, because they must activate B cells before the B cells can produce antibodies. The reduction in the helper T cell population that occurs in AIDS is largely responsible for the loss of immunity. (We discuss AIDS on p. 805.)
4. *Suppressor T* (T_S) *cells* inhibit T cell and B cell activities and moderate the immune response.

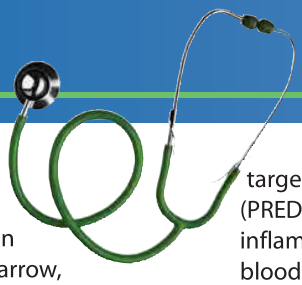
Before an immune response can begin, T cells must be activated by exposure to an antigen. This activation seldom occurs through direct interaction between a T cell and the antigen. Foreign compounds or pathogens entering a tissue commonly fail to stimulate an immediate immune response.

Figure 22–17 An Overview of the Immune Response.



Clinical Note

Graft Rejection and Immunosuppression



Rejection hurts

Organ transplantation may be a treatment option for patients with severe disorders of the bone marrow, kidneys, liver, heart, lungs, or pancreas. Finding a suitable donor is the first major problem. In the United States, each day many people die while awaiting an organ transplant, and dozens are added to the transplant waiting list.

After surgery, the major problem is **graft rejection.** In graft rejection, T cells are activated by contact with MHC proteins on plasma membranes in the donated tissues. The cytotoxic T cells that develop then attack and destroy the foreign cells.

Transplant success can be improved by *immunosuppression*, a reduction in the sensitivity of the immune system. Until recently, the drugs used to produce immunosuppression did not selectively target the immune response. For example, **prednisone** (PRED-ni-sōn), a corticosteroid, was used because it has anti-inflammatory effects that reduce the number of circulating white blood cells and depress the immune response. Unfortunately, corticosteroid use also causes undesirable side effects in systems other than the immune system.

An understanding of the communication among T cells, macrophages, and B cells has now led to the development of drugs with more selective effects. **Cyclosporin A,** a compound derived from a fungus, was the most important *immunosuppressive drug* developed in the 1980s. This compound suppresses all aspects of the immune response. It acts primarily by suppressing helper T cell activity while leaving suppressor T cells relatively unaffected. Even more narrowly focused drugs are available, including monoclonal antibodies that prevent antigen recognition by T cell receptors.

Antigen Presentation

For T cells to recognize an antigen, the antigen must be bound to glycoproteins in the plasma membranes of another cell. Recall that glycoproteins are integral membrane components. ↩ p. 67 **Antigen presentation** occurs when an antigen–glycoprotein combination capable of activating T cells appears in a plasma membrane.

The structure of these glycoproteins is genetically determined. The genes controlling their synthesis are located along one portion of chromosome 6, in a region called the **major histocompatibility complex (MHC).** These membrane glycoproteins are called **MHC proteins,** or *human leukocyte antigens (HLAs)*.

The amino acid sequences and the shapes of MHC proteins differ among individuals. Each MHC molecule has a distinct three-dimensional shape with a relatively narrow central groove. An antigen that fits into this groove can be held in position by hydrogen bonding.

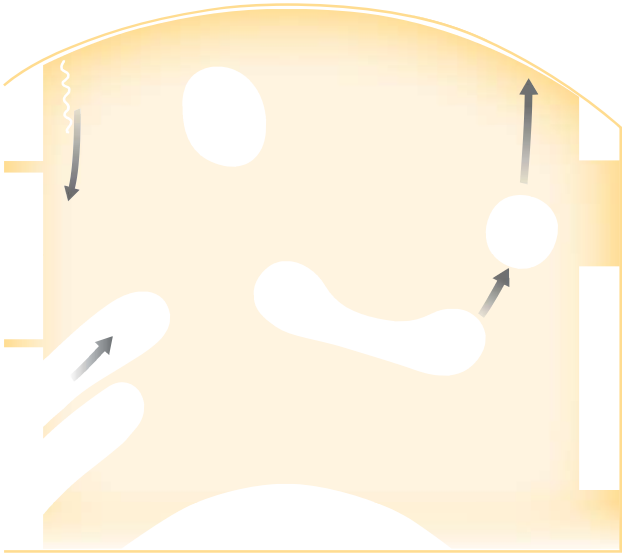
Two major classes of MHC proteins are known: *Class I* and *Class II*. An antigen bound to a Class I MHC protein acts like a red flag that in effect tells the immune system "Hey, I'm an abnormal cell—kill me!" An antigen bound to a Class II MHC protein tells the immune system "Hey, this antigen is dangerous—get rid of it!"

Class I MHC proteins are in the plasma membranes of all nucleated cells. These proteins are continuously synthesized and exported to the plasma membrane in vesicles created at the Golgi apparatus. As they form, Class I proteins pick up small peptides from the surrounding cytoplasm and carry them to the cell surface. If the cell is healthy and the peptides are normal, T cells ignore them. If the cytoplasm contains abnormal (nonself) peptides or viral proteins (**Figure 22–18a**), they soon appear in the plasma membrane, and T cells will recognize them as foreign and be activated. Ultimately, their activation leads to the destruction of the abnormal cells. This is the primary reason that donated organs are commonly rejected by the recipient. Despite preliminary cross-match testing, the recipient's T cells recognize the transplanted tissue as foreign.

Class II MHC proteins are present only in the plasma membranes of antigen-presenting cells and lymphocytes. **Antigen-presenting cells (APCs)** are specialized cells responsible for activating T cell defenses against foreign cells (including bacteria) and foreign proteins. Antigen-presenting cells include all the phagocytic cells of the monocyte–macrophage group discussed in other chapters, including (1) free and fixed macrophages in connective tissues, (2) the Kupffer cells of the liver, and (3) the microglia in the central nervous system (Chapter 12). ↩ pp. 122, 183 The dendritic (Langerhans) cells of the skin and the dendritic cells of the lymph nodes and spleen are APCs that are not phagocytic. ↩ p. 148

Phagocytic APCs engulf and break down pathogens or foreign antigens. This **antigen processing** creates fragments of the antigen, which are then bound to Class II MHC proteins and inserted into the plasma membrane (**Figure 22–18b**). *Class II MHC proteins appear in the plasma membrane only when the cell is processing antigens*. Exposure to an APC membrane containing a processed antigen can stimulate appropriate T cells.

The dendritic cells remove antigenic materials from their surroundings via pinocytosis rather than phagocytosis. However, their plasma membranes still present antigens bound to Class II MHC proteins.



Antigen Recognition

How do T cells recognize antigens? Inactive T cells have receptors that can bind either Class I or Class II MHC proteins. These receptors also have binding sites for a specific target antigen. If an MHC protein contains any antigen other than the specific target of a particular kind of T cell, the T cell remains inactive. If the MHC protein contains the antigen that the T cell is programmed to detect, binding occurs. This process is called **antigen recognition,** because the T cell recognizes that it has found an appropriate target.

Some T cells can recognize antigens bound to Class I MHC proteins, whereas others can recognize antigens bound to Class II MHC proteins. Whether a T cell responds to antigens held by one class or the other depends on a type of protein in the T cell's own plasma membrane. The membrane proteins involved are

members of a larger group of proteins called **CD** (*cluster of differentiation*) **markers**.

Lymphocytes, macrophages, and other related cells have CD markers. More than 70 types of CD markers exist, and each type is designated by a number. All T cells have a **CD3 receptor complex** in their plasma membranes, and this complex ultimately activates the T cell. Either of two other CD markers may be bound to the CD3 receptor complex, and these two CD markers are especially important in specific groups of T cells:

1. **CD8** markers are found on cytotoxic T cells and suppressor T cells, which together are often called *CD8 T cells* or *CD8+ T cells*. CD8 T cells respond to antigens presented by Class I MHC proteins.
2. **CD4** markers are found on helper T cells, often called *CD4 T cells* or *CD4+ T cells*. CD4 T cells respond to antigens presented by Class II MHC proteins.

T cells are not usually activated upon their first encounter with the antigen. Antigen recognition simply prepares the cell for activation.

Costimulation

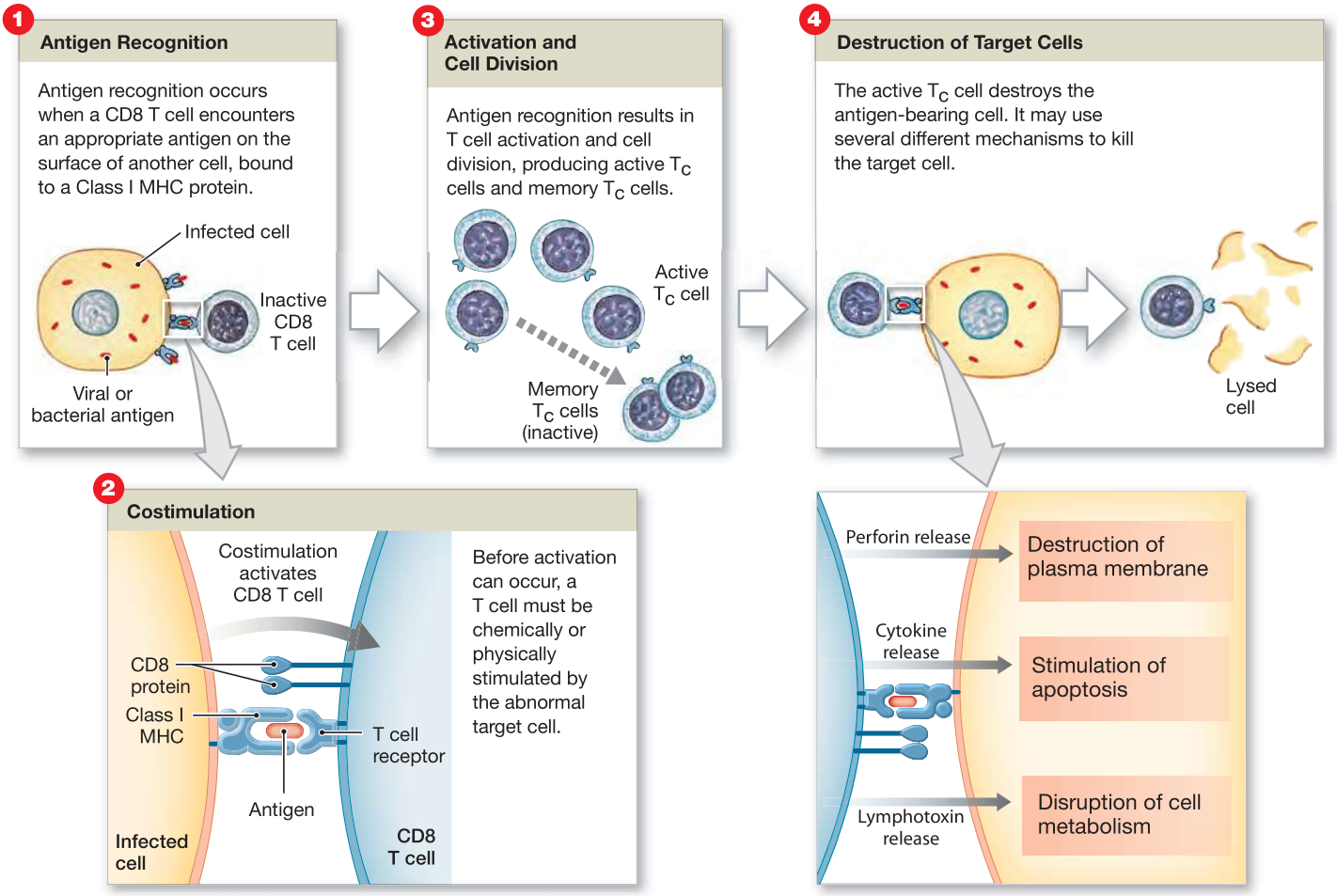
In order to proceed from recognition to activation, a T cell must also bind to the stimulating cell at a second site. This vital secondary binding process, called *costimulation*, essentially confirms the initial activation signal.

Costimulation is like the safety on a gun: It helps prevent T cells from mistakenly attacking normal (self) tissues. If a cell displays an unusual antigen but does not display the "I am an active phagocyte" or "I am infected" signal, T cell activation will not occur. Costimulation is important only in determining whether a T cell will become activated. Once activation has occurred, the "safety" is off and the T cell will attack any cells that carry the target antigens.

Activation of CD8 T Cells

Two different types of CD8 T cells are activated by exposure to antigens bound to Class I MHC proteins. One type responds quickly, giving rise to large numbers of *cytotoxic T cells* and *memory T cells* (**Figure 22–19**). The other type responds

Figure 22–19 Antigen Recognition by and Activation of Cytotoxic T Cells.



more slowly and produces relatively small numbers of *suppressor T cells*.

Cytotoxic T Cells

Cytotoxic T (T_C) cells seek out and destroy abnormal and infected cells. They are highly mobile cells that roam throughout injured tissues. When a cytotoxic T cell encounters its target antigen bound to Class I MHC proteins, it immediately destroys the target cell (**Figure 22–19**). The T cell may (1) release perforin to destroy the target cell's plasma membrane, (2) secrete a poisonous **lymphotoxin** (lim-fō-TOK-sin) to kill the target cell, or (3) activate genes in the target cell's nucleus that tell that cell to die. (We introduced genetically programmed cell death, called *apoptosis*, in Chapter 3.) p. 96

The entire sequence of events, from the appearance of the antigen in a tissue to cell destruction by cytotoxic T cells, takes a significant amount of time. After the first exposure to an antigen, two days or more may pass before the concentration of cytotoxic T cells reaches effective levels at the site of injury or infection. Over this period, the damage or infection may spread, making it more difficult to control.

Memory T_C Cells

The same cell divisions that produce cytotoxic T cells also produce thousands of **memory T_C cells.** These cells do not differentiate further the first time the antigen triggers an immune response. However, if the same antigen appears a second time, memory T cells *immediately* differentiate into cytotoxic T cells. They produce a prompt, effective cellular response that can overwhelm the invader before it becomes well established in the tissues.

Suppressor T Cells

Suppressor T (T_S) cells suppress the responses of other T cells and of B cells by secreting inhibitory cytokines called *suppression factors*. Suppression does not take place right away, because activation takes much longer for suppressor T cells than for other types of T cells. In addition, upon activation, most of the CD8 T cells in the bloodstream produce cytotoxic T cells rather than suppressor T cells. As a result, suppressor T cells act *after* the initial immune response. In effect, these cells limit the degree of immune system activation from a single stimulus.

Activation of CD4 T Cells

Upon activation, helper T cells with CD4 T markers undergo a series of divisions that produce both active helper T cells and **memory helper T cells,** also called **memory T_H cells** (**Figure 22–20**). The memory helper T cells remain in reserve. The active helper T cells secrete a variety of cytokines that coordinate specific and nonspecific defenses and stimulate cell-mediated and antibody-mediated immunities. These cytokines do the following:

1. stimulate the T cell divisions that produce memory helper T cells and speed the maturation of cytotoxic T cells;
2. enhance nonspecific defenses by attracting macrophages to the affected area, preventing their departure, and stimulating their phagocytic activity and effectiveness;
3. attract and stimulate the activity of cytotoxic T cells, providing another means of destroying abnormal cells and pathogens; and
4. promote the activation of B cells, leading ultimately to antibody production.

Figure 22–20 Antigen Recognition and Activation of Helper T Cells. Inactive CD4 T cells (T_H cells) must be exposed to appropriate antigens bound to Class II MHC proteins. The T_H cells then undergo activation, dividing to produce active T_H cells and memory T_H cells.

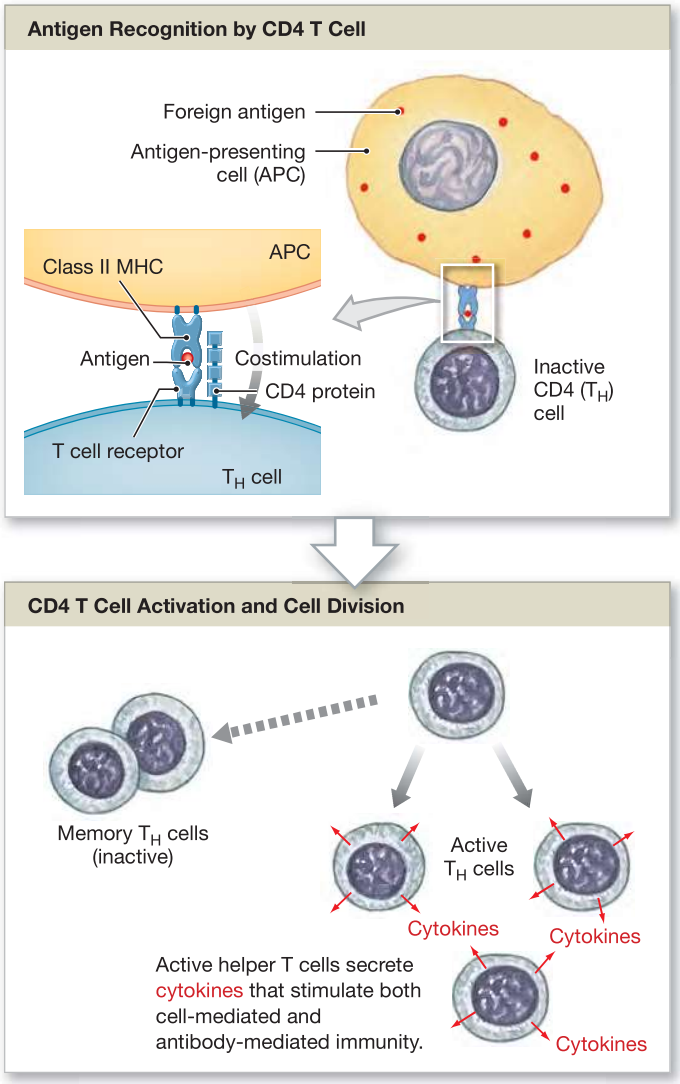


Figure 22–21 A Summary of the Pathways of T Cell Activation.

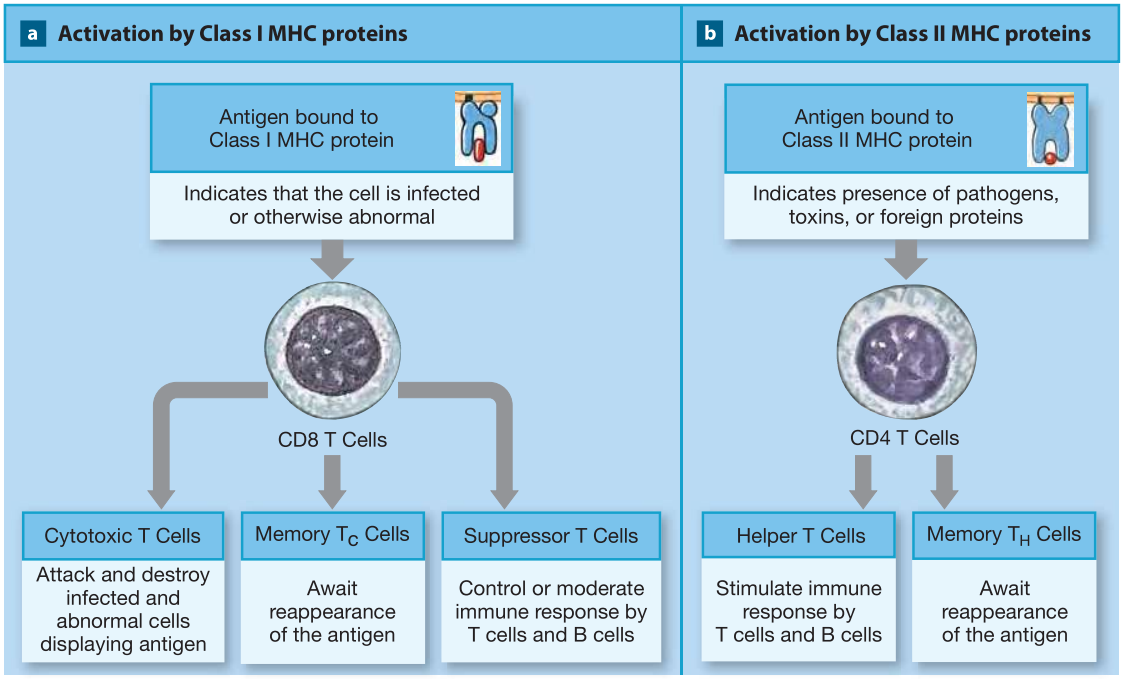


Figure 22–21 provides a review of the methods of antigen presentation and T cell stimulation. The plasma membranes of infected or otherwise abnormal cells trigger an immune response when CD8 T cells recognize antigens bound to Class I MHC proteins. Extracellular pathogens or foreign proteins trigger an immune response when CD4 T cells recognize antigens displayed by Class II MHC proteins. In the next section, we will see how the helper T cells derived from activated CD4 T cells in turn activate B cells that are sensitive to the specific antigen involved.

22

Checkpoint

14. **Identify the four major types of T cells.**
15. **How can the presence of an abnormal peptide in the cytoplasm of a cell initiate an immune response?**
16. **A decrease in the number of cytotoxic T cells would affect which type of immunity?**
17. **How would a lack of helper T cells affect the antibody-mediated immune response?**

See the blue Answers tab at the back of the book.

22-6 B cells respond to antigens by producing specific antibodies

B cells are responsible for launching a chemical attack on antigens. They produce appropriate specific *antibodies*.

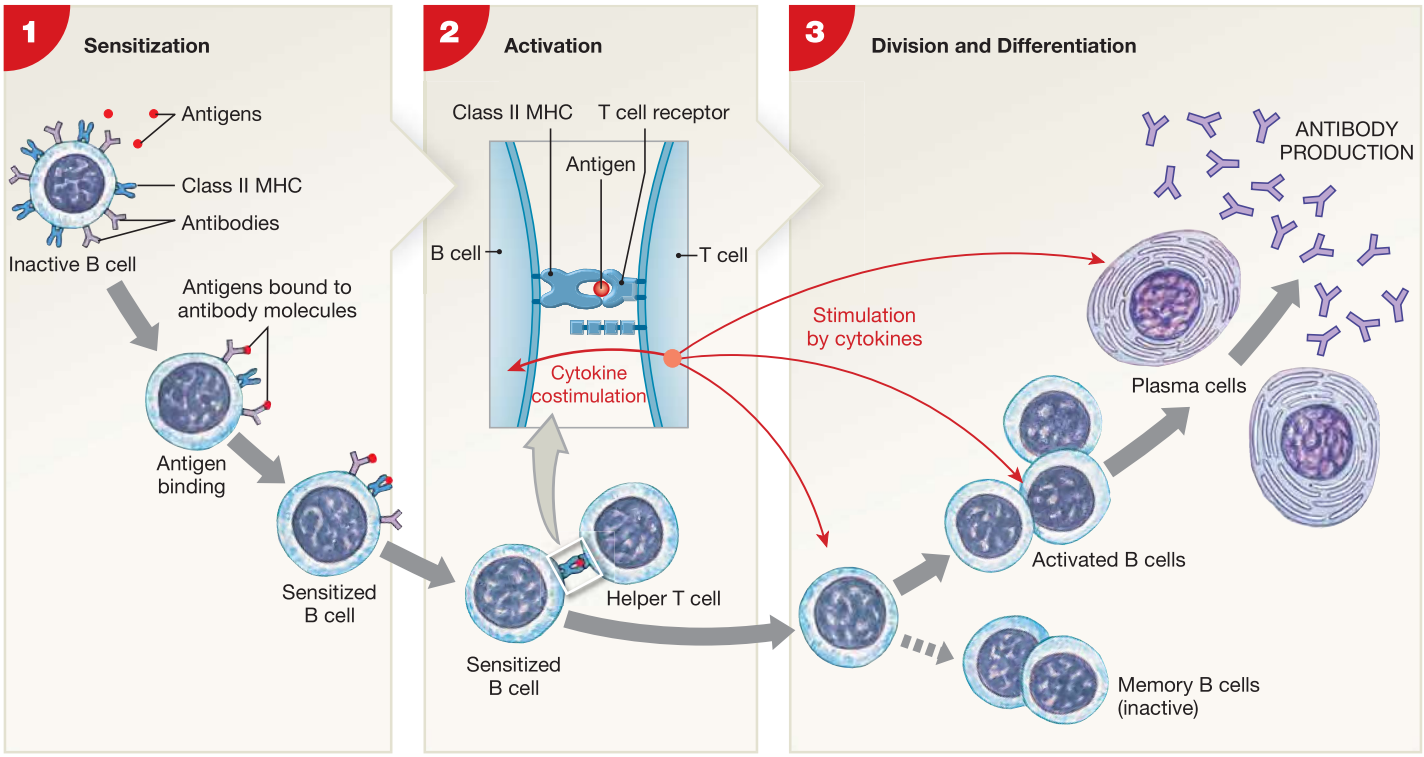
B Cell Sensitization and Activation

As noted earlier, the body has millions of B cell populations. Each kind of B cell carries its own particular antibody molecules in its plasma membrane. If corresponding antigens appear in the interstitial fluid, they interact with these superficial antibodies. When binding occurs, the B cell prepares to undergo activation. This preparatory process is called **sensitization.** Because B cells migrate throughout the body, pausing briefly in one lymphoid tissue or another, sensitization typically takes place within the lymph node nearest the site of infection or injury.

Recall that B cell plasma membranes contain Class II MHC proteins. During sensitization, antigens are brought into the cell by endocytosis. The antigens subsequently appear on the surface of the B cell, bound to Class II MHC proteins. (The mechanism is comparable to that shown in **Figure 22–18b**). The sensitized B cell is then on "standby" but generally does not undergo activation unless it receives the "OK" from a helper T cell (**Figure 22–22**). The need for activation by a helper T cell helps prevent inappropriate activation, the same way that costimulation acts as a "safety" in cell-mediated immunity.

What happens when a sensitized B cell meets a helper T cell that has already been activated via antigen presentation? The helper T cell binds to the B cell's MHC complex, recognizes the antigen, and begins secreting cytokines that promote B cell activation. After activation of the B cell, these same cytokines stimulate B cell division, speed plasma cell formation, and enhance antibody production.

Figure 22–22 The Sensitization and Activation of B Cells. A B cell is sensitized by exposure to antigens. Once antigens are bound to antibodies in the B cell membrane, the B cell displays those antigens in its plasma membrane. Activated helper T cells encountering the antigens release cytokines that costimulate the sensitized B cell and trigger its activation. The activated B cell then divides, producing memory B cells and plasma cells that secrete antibodies.



The activated B cell typically divides several times, producing daughter cells that differentiate into plasma cells and *memory B cells*. The plasma cells begin synthesizing and secreting large quantities of antibodies into the interstitial fluid. These antibodies have the same target as the antibodies on the surface of the sensitized B cell. When stimulated by cytokines from helper T cells, a plasma cell can secrete up to 100 million antibody molecules each hour.

Memory B cells perform the same role in antibody-mediated immunity that memory T cells perform in cell-mediated immunity. Memory B cells do not respond to a threat on first exposure. Instead, they remain in reserve to deal with subsequent injuries or infections that involve the same antigens. On subsequent exposure, the memory B cells divide and differentiate into plasma cells that secrete antibodies in massive quantities.

Antibody Structure

A Y-shaped antibody molecule consists of two pairs of polypeptide chains: one pair of **heavy chains** and one pair of **light chains** (Figure 22–23). Each chain contains both *constant segments* and *variable segments*.

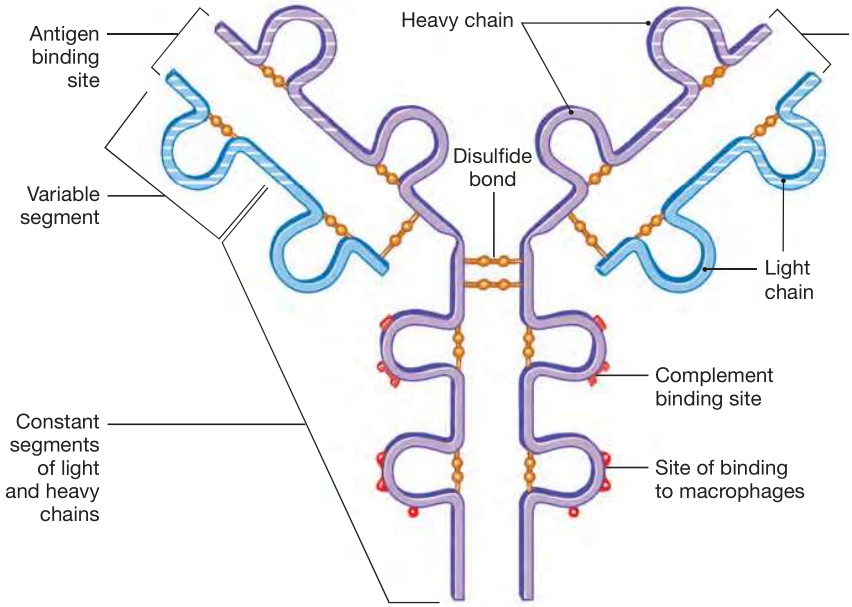
The constant segments of the heavy chains form the base of the antibody molecule (Figure 22–23a,b). B cells produce only five types of constant segments. These are the basis of a classification scheme that identifies antibodies as *IgG*, *IgE*, *IgD*, *IgM*, or *IgA*, as we discuss in the next section. The structure of the constant segments of the heavy chains determines the way the antibody is secreted and how it is distributed within the body. For example, antibodies in one class circulate in body fluids, whereas those of another class bind to the membranes of basophils and mast cells.

The heavy-chain constant segments, which are bound to constant segments of the light chains, also contain binding sites that can activate the complement system. These binding sites are covered when the antibody is secreted but become exposed when the antibody binds to an antigen.

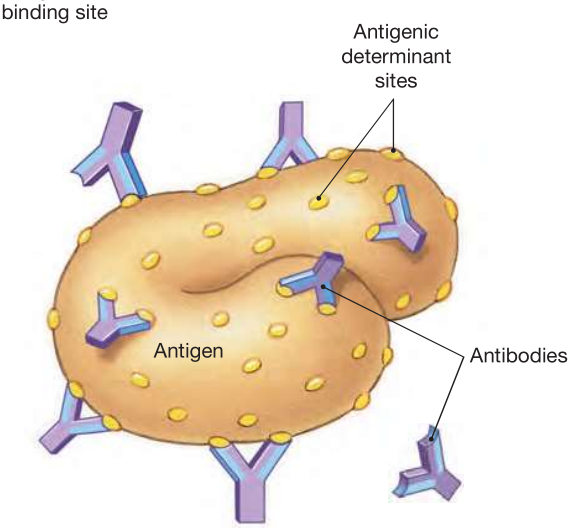
The specificity of an antibody molecule depends on the amino acid sequence of the variable segments of the light and heavy chains. The free tips of the two variable segments form the **antigen binding sites** of the antibody molecule (Figure 22–23a). These sites can interact with an antigen in the same way that the active site of an enzyme interacts with a substrate molecule. p. 53

Small differences in the structure of the variable segments affect the precise shape of the antigen binding site. These differences make antibodies specific for different antigens. The distinctions are the result of minor genetic variations that occur during the production, division, and differentiation of B cells.

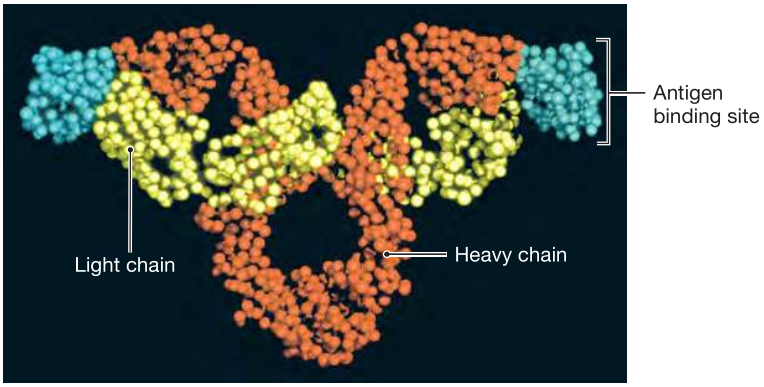
Figure 22–23 Antibody Structure and Function.



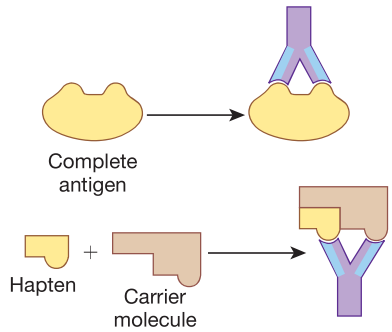
a A diagrammatic view of the structure of an antibody.



c Antibodies bind to portions of an antigen called antigenic determinant sites, or epitopes.



b A computer-generated image of a typical antibody.



d Antibody molecules can bind a hapten (partial antigen) once it has become a complete antigen by combining with a carrier molecule.

A normal adult body contains roughly 10 trillion B cells, which can produce an estimated 100 million types of antibodies, each with a different specificity.

The Antigen–Antibody Complex

An **antigen–antibody complex** forms when an antibody molecule binds to its corresponding antigen molecule. Once the two molecules are in position, hydrogen bonding and other weak chemical forces lock them together.

Antibodies do not bind to the entire antigen. Instead, they bind to specific portions of its exposed surface—regions called **antigenic determinant sites,** or **epitopes** (Figure 22–23c). The specificity of the binding depends initially on the three-dimensional "fit" between the variable segments of the antibody molecule and the corresponding antigenic determinant sites. A **complete antigen** has at least two antigenic determinant sites, one for each of the antigen binding sites on an antibody molecule. Exposure to a complete antigen can lead to B cell sensitization and a subsequent immune response. Most environmental antigens have multiple antigenic determinant sites, and entire microorganisms may have thousands.

Haptens, or *partial antigens,* do not ordinarily cause B cell activation and antibody production. Haptens include short peptide chains, steroids and other lipids, and several drugs, including antibiotics such as *penicillin*. However, haptens may become attached to carrier molecules, forming combinations that can function as complete antigens (Figure 22–23d). In some cases, the carrier contributes an antigenic determinant site. Antibodies will then attack both the hapten and the carrier molecule. If the carrier molecule is normally present in the tissues, the antibodies may begin attacking and destroying normal cells. This process is the basis for several drug reactions, including allergies to penicillin.

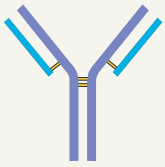
Classes and Actions of Antibodies

Body fluids may contain five classes of antibodies, or **immunoglobulins (Igs):** *IgG*, *IgE*, *IgD*, *IgM*, and *IgA* (Table 22–1). The classes are determined by differences in the structure of the heavy-chain constant segments. For this reason, the classes have no effect on the antibody's specificity, which is determined by the antigen binding sites.

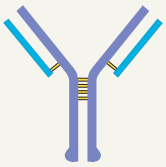
The formation of an antigen–antibody complex may cause the elimination of the antigen in seven ways:

1. *Neutralization.* Both viruses and bacterial toxins have specific sites that must bind to target regions on body cells before they can enter or injure those cells. Antibodies may bind to those sites, making the virus or toxin incapable of attaching itself to a cell. This mechanism is known as **neutralization.**
2. *Precipitation and Agglutination.* Each antibody molecule has two antigen binding sites, and most antigens have many antigenic determinant sites. If individual antigens (such as macromolecules or bacterial cells) are far apart, an antibody molecule will necessarily bind to two antigenic sites on the same antigen. However, if antigens are close together, an antibody can bind to antigenic determinant sites on two separate antigens. In this way, antibodies can link large numbers of antigens together. The three-dimensional structure created by such binding is known as an **immune complex.** When the antigen is a soluble molecule, such as a toxin, this process may create complexes that are too large to remain in solution. The formation of insoluble immune complexes is called **precipitation.** When the target antigen is on the surface of a cell or virus, the formation of large complexes is called **agglutination.** For example, the clumping of erythrocytes that takes place when incompatible blood types are mixed is an agglutination reaction. p. 652
3. *Activation of the Complement System.* When an antibody molecule binds to an antigen, portions of the antibody molecule change shape. This change exposes areas that bind complement proteins. The bound complement molecules then activate the complement system, which destroys the antigen (as discussed previously).
4. *Attraction of Phagocytes.* Antigens covered with antibodies attract eosinophils, neutrophils, and macrophages. These cells phagocytize pathogens and destroy foreign or abnormal plasma membranes.
5. *Opsonization.* A coating of antibodies and complement proteins increases the effectiveness of phagocytosis. This effect is called *opsonization* (p. 783). Some bacteria have slick plasma membranes or capsules, but opsonization makes it easier for phagocytes to hang onto their prey before they engulf it. Phagocytes can bind more easily to antibodies and complement proteins than they can to the bare surface of a pathogen.
6. *Stimulation of Inflammation.* Antibodies may promote inflammation by stimulating basophils and mast cells.

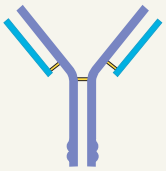
Table 22–1 Classes of Antibodies



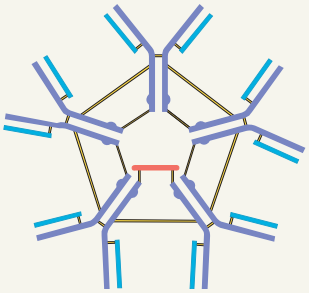
IgG is the largest and most diverse class of antibodies. They account for 80 percent of all antibodies. IgG antibodies are responsible for resistance against many viruses, bacteria, and bacterial toxins. These antibodies can cross the placenta, and maternal IgG provides passive immunity to the fetus during embryological development. However, the anti-Rh antibodies produced by Rh-negative mothers are also IgG antibodies and produce *hemolytic disease of the newborn.*



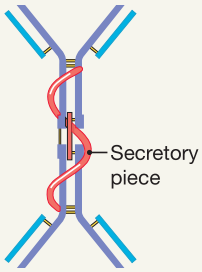
IgE attaches as an individual molecule to the exposed surfaces of basophils and mast cells. When a suitable antigen is bound by IgE molecules, the cell is stimulated to release histamine and other chemicals that accelerate inflammation in the immediate area. IgE is also important in the allergic response.



IgD is an individual molecule on the surfaces of B cells, where it can bind antigens in the extracellular fluid. This binding can play a role in the sensitization of the B cell involved.



IgM is the first class of antibody secreted after an antigen is encountered. IgM concentration declines as IgG production accelerates. Although plasma cells secrete individual IgM molecules, IgM circulates as a five-antibody starburst. The anti-A and anti-B antibodies responsible for the agglutination of incompatible blood types are IgM antibodies. IgM antibodies may also attack bacteria that are insensitive to IgG.



IgA is found primarily in glandular secretions such as mucus, tears, saliva, and semen. These antibodies attack pathogens before they gain access to internal tissues. IgA antibodies circulate in blood as individual molecules or in pairs. Epithelial cells absorb them from the blood and attach a *secretory piece*, which confers solubility, before secreting the IgA molecules onto the epithelial surface.

7. *Prevention of Bacterial and Viral Adhesion.* Antibodies dissolved in saliva, mucus, and perspiration coat epithelia, adding an additional layer of defense. A covering of antibodies makes it difficult for pathogens to attach to and penetrate body surfaces.

Tips & Tricks

The classes of immunoglobulins—Ig***M***, Ig***A***, Ig***D***, Ig***G***, Ig***E***—spell ***MADGE***.

Primary and Secondary Responses to Antigen Exposure

The initial immune response to an antigen is called the **primary response.** When the antigen appears again, it triggers a more extensive and prolonged **secondary response.** This response is due to the presence of large numbers of memory cells that are primed for the arrival of the antigen. Primary and secondary responses occur in both cell-mediated and antibody-mediated immunities. Let's look at the pattern of antibody production over time to see the differences between the primary and secondary responses.

The Primary Response

The primary response takes time to develop because the antigen must activate the appropriate B cells. These cells must then differentiate into plasma cells. As plasma cells differentiate and begin secreting, the concentration of circulating antibodies makes a gradual, sustained rise (**Figure 22–24a**).

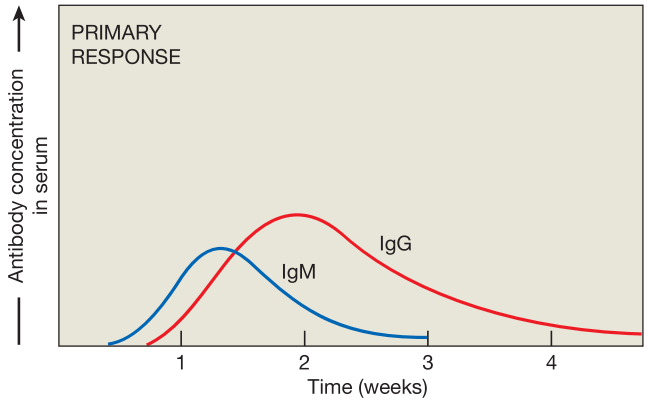
During the primary response, the **antibody titer,** or level of antibody activity, in the plasma does not peak until one to two weeks after the initial exposure. If the individual is no longer exposed to the antigen, the antibody concentration then declines. The antibody titer declines because (1) plasma cells have very high metabolic rates and survive for only a short time, and (2) suppressor T cells release suppression factors that inhibit further production of plasma cells. However, suppressor T cell activity does not begin immediately after exposure to the antigen. Also, under normal conditions helper T cells outnumber suppressor T cells by more than 3 to 1. As a result, many B cells are activated before suppressor T cell activity has a noticeable effect.

Activated B cells start dividing immediately. At each cycle of division, some of the daughter cells differentiate into plasma cells, while others continue to divide. Molecules of *immunoglobulin M*, or *IgM*, are the first to appear in the bloodstream. The plasma cells that produce IgM differentiate after only a few cycles of B cell division. Levels of *immunoglobulin G*, or *IgG*, rise more slowly, because the plasma cells responsible differentiate only after repeated cell divisions that also generate large numbers of memory B cells. In general, IgM is less effective as a defense than IgG. However, IgM provides an immediate defense that can fight the infection until massive quantities of IgG can be produced.

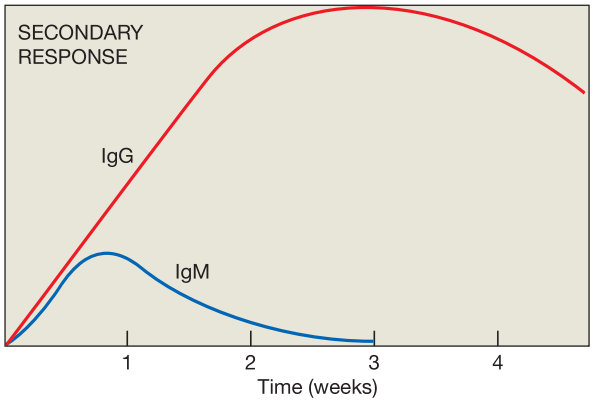
The Secondary Response

Unless memory B cells are exposed to the same antigen a second time, they do not differentiate into plasma cells. If and when that exposure occurs, the memory B cells respond right away—faster than the B cells stimulated during the initial exposure. This response is immediate in part because memory B cells are activated at relatively low antigen concentrations. In addition, these cells synthesize more effective and destructive antibodies. Activated memory B cells divide and differentiate into plasma cells that

Figure 22–24 The Primary and Secondary Responses in Antibody-Mediated Immunity.



a The primary response, which takes about two weeks to develop peak antibody levels and activities (titers). IgM and IgG antibody concentrations do not remain elevated.



b The secondary response, which is characterized by a very rapid increase in IgG antibody concentration and titer, rises to levels much higher than those of the primary response. Antibody activity remains elevated for an extended period after the second exposure to the antigen.

secrete these antibodies in massive quantities. This secretion is the secondary response to antigen exposure.

During the secondary response, antibody concentrations and titers increase more rapidly and reach levels many times higher than they did in the primary response (**Figure 22–24b**). The secondary response appears even if the second exposure occurs years after the first. The reason is that memory cells may survive for 20 years or more.

The primary response develops slowly and does not produce antibodies in massive quantities. For these reasons, it may not prevent an infection the first time a pathogen appears in the body. However, a person who survives the first infection will probably be resistant to that pathogen in the future, thanks to a rapid and overwhelming secondary response. The effectiveness of the secondary response is one of the basic principles behind the use of immunization to prevent disease.

Tips & Tricks

The antibody response is like ordering a custom suit. The first suit (the primary antibody response) takes time to make because the tailor (an activated B cell) must first make a pattern (a clone of memory cells). Subsequent suits (secondary responses) are made much more quickly because the pattern already exists.

Summary of the Immune Response

We have now examined the basic cellular and chemical interactions that follow the appearance of a foreign antigen in the body. **Table 22–2** reviews the cells that participate in tissue defenses and **Figure 22–25** provides a timeline for their appearance at the site of a bacterial infection.

In the early stages of infection, neutrophils and NK cells migrate into the threatened area and destroy bacteria. Over time, cytokines draw increasing numbers of phagocytes into the region. Cytotoxic T cells appear as arriving T cells are activated by antigen presentation. Last of all, the population of plasma cells rises as activated B cells differentiate. This rise is followed by a gradual, sustained increase in the activity (titer) of circulating antibodies.

Figure 22–26 provides an integrated view of the immune response and its relationship to nonspecific defenses. The basic

Figure 22–25 The Course of the Body's Response to a Bacterial Infection. The basic sequence of events, which begins with the appearance of bacteria in peripheral tissues at time 0.

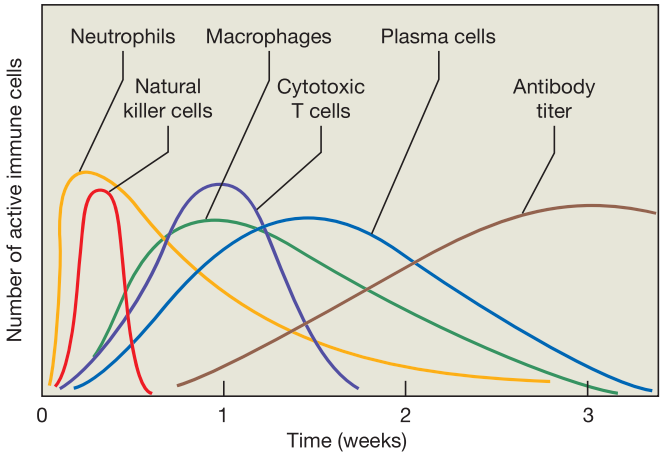
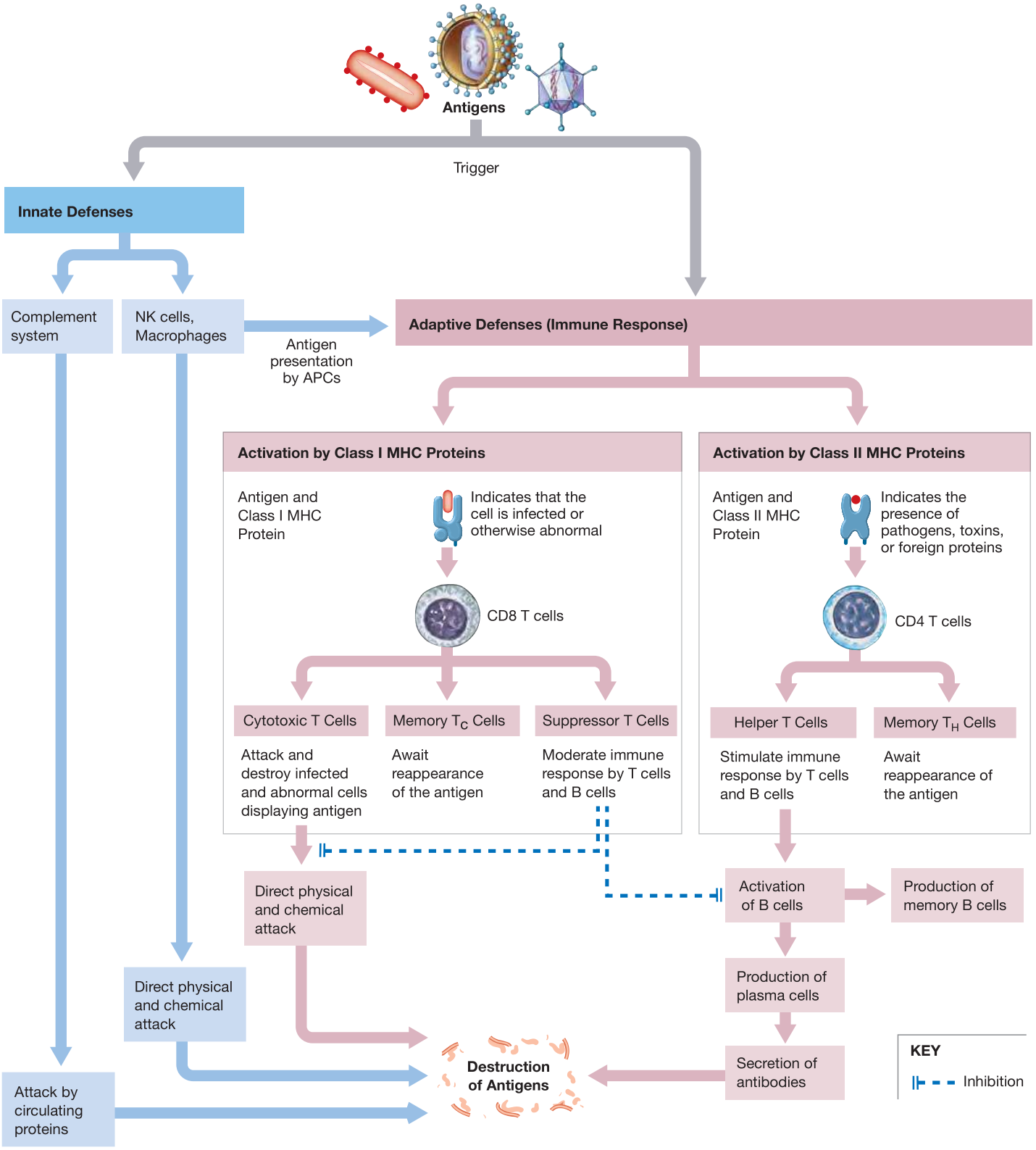


Table 22–2 Cells That Participate in Tissue Defenses

Cell	Functions
Neutrophils	Phagocytosis; stimulation of inflammation
Eosinophils	Phagocytosis of antigen–antibody complexes; suppression of inflammation; participation in allergic response
Mast cells and basophils	Stimulation and coordination of inflammation by release of histamine, heparin, leukotrienes, prostaglandins
ANTIGEN-PRESENTING CELLS	
Macrophages (free and fixed macrophages, Kupffer cells, microglia, etc.)	Phagocytosis; antigen processing; antigen presentation with Class II MHC proteins; secretion of cytokines, especially interleukins and interferons
Dendritic (Langerhans) cells	Pinocytosis; antigen processing; antigen presentation bound to Class II MHC proteins
LYMPHOCYTES	
NK cells	Destruction of plasma membranes containing abnormal antigens
Cytotoxic T cells (T_C, CD8 marker)	Lysis of plasma membranes containing antigens bound to Class I MHC proteins; secretion of perforins, defensins, lymphotoxins, and other cytokines
Helper T cells (T_H, CD4 marker)	Secretion of cytokines that stimulate cell-mediated and antibody-mediated immunity; activation of sensitized B cells
B cells	Differentiation into plasma cells, which secrete antibodies and provide antibody-mediated immunity
Suppressor T cells (T_S, CD8 marker)	Secretion of suppression factors that inhibit the immune response
Memory cells (T_S, T_H, B)	Produced during the activation of T cells and B cells; remain in tissues awaiting rearrival of antigens

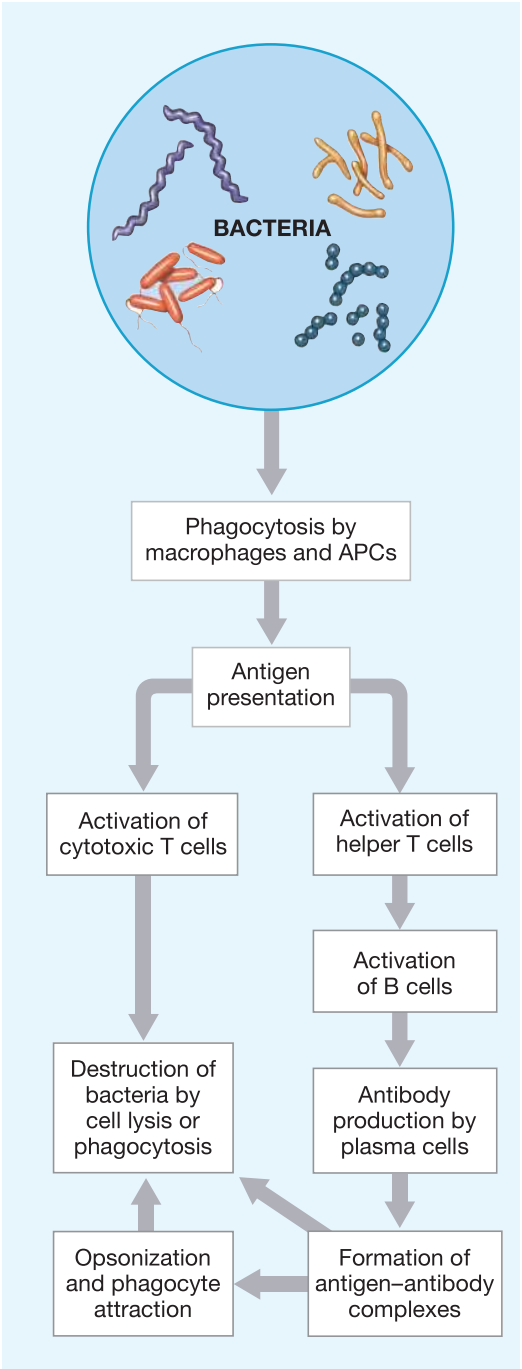
Figure 22–26 An Integrated Summary of the Immune Response.



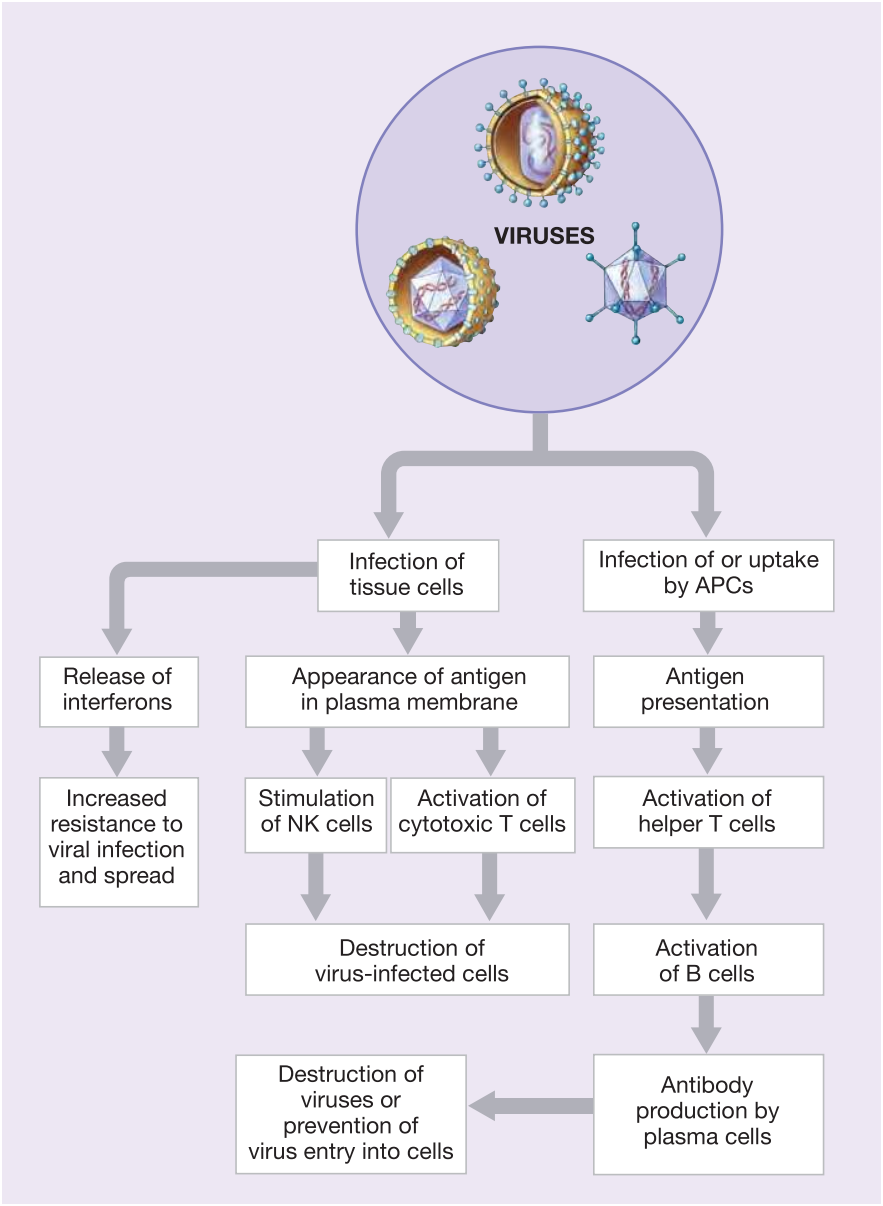
sequence of events is similar when a viral infection occurs. The initial steps are different, however, because cytotoxic T cells and NK cells can be activated by contact with virus-infected cells.

Figure 22–27 contrasts the events involved in defending against bacterial infection with those involved in defending against viral infection.

Figure 22–27 **Defenses against Bacterial and Viral Pathogens.**



a Defenses against bacteria involve phagocytosis and antigen presentation by APCs.



b Defenses against viruses involves direct contact with virus-infected cells and antigen presentation by APCs.

Checkpoint

18. Define sensitization.
19. Describe the structure of an antibody.
20. A sample of lymph contains an elevated number of plasma cells. Would you expect the number of antibodies in the blood to be increasing or decreasing? Why?
21. Which would be more negatively affected—the primary response or the secondary response—by a lack of memory B cells for a particular antigen?

See the blue Answers tab at the back of the book.

22-7 Immunological competence enables a normal immune response; abnormal responses result in immune disorders

We begin this section by exploring **immunological competence,** the ability to produce an immune response after exposure to an antigen. Then we consider some of the disorders that result when immune responses go wrong. Finally, we examine the role of stress in immune responses.

The Development of Immunological Competence

Cell-mediated immunity can be demonstrated as early as the third month of fetal development. Active antibody-mediated immunity follows about one month later.

The first cells that leave the fetal thymus migrate to the skin and into the epithelia lining the mouth, the digestive tract, and the uterus and vagina in females. These cells take up residence in these tissues as antigen-presenting cells, such as the dendritic cells of the skin, whose primary function will be to help activate T cells. T cells that leave the thymus later in development populate lymphoid organs throughout the body.

The plasma membranes of the first B cells produced in the liver and bone marrow carry IgM antibodies. Sometime after the fourth month the fetus may produce IgM antibodies if exposed to specific pathogens. It is uncommon for the fetus to produce antibodies, however, because the developing fetus has naturally acquired passive immunity due to IgG antibodies from the mother's bloodstream. These are the only antibodies that can cross the placenta. They include the antibodies responsible for the clinical problems due to Rh incompatibility, discussed in Chapter 19. ↩ p. 654 Problems with incompatibilities involving the ABO blood groups rarely occur. The reason is that anti-A and anti-B antibodies are IgM antibodies, which cannot cross the placenta.

The natural immunity provided by maternal IgG may not be enough to protect the fetus if the maternal defenses are overwhelmed by a bacterial or viral infection. For example, the microorganisms responsible for syphilis and rubella ("German measles") can cross from the maternal to the fetal bloodstream, producing a congenital infection that leads to the production of fetal antibodies. IgM provides only a partial defense, and these infections can result in severe developmental problems for the fetus.

Delivery eliminates the maternal supply of IgG. Although the mother provides IgA antibodies in breast milk, the infant gradually loses its passive immunity. The amount of maternal IgG in the infant's bloodstream declines rapidly over the first two months after birth. During this period, the infant becomes vulnerable to infection by bacteria or viruses that were previously overcome by maternal antibodies. The infant's immune system begins to respond to infections, environmental antigens, and vaccinations. As a result, the infant begins producing its own IgG. It has been estimated that, from birth to age 12, children encounter a "new" antigen every six weeks. (This fact explains why most parents, who were exposed to the same antigens when they were children, remain healthy while their children develop runny noses and colds.) Over this period, the concentration of circulating antibodies gradually rises toward normal adult levels. Populations of memory B cells and T cells also increase.

Skin tests are sometimes used to determine whether an individual has been exposed to a particular antigen. In these procedures, small quantities of antigen are injected into the skin, generally on the anterior surface of the forearm. If resistance has developed, the region becomes inflamed over the next two to four days. Many states require a tuberculosis test, called a *tuberculin skin test*, before children enter public school. If the test is positive, further tests must then be performed to determine whether an infection is currently under way. Skin tests are also used to check for allergies to environmental antigens.

Cytokines of the Immune System

Cytokines are chemical messengers involved in cellular immunity. They include hormones and paracrine-like glycoproteins important to the immune response. Interferons, interleukins,

and tumor necrosis factors are examples of cytokines (Spotlight Figure 22–28).

Immune Disorders

Because the immune response is so complex, many opportunities exist for things to go wrong. A variety of clinical conditions result from disorders of the immune function. **Autoimmune disorders** develop when the immune response inappropriately targets normal body cells and tissues. In an **immunodeficiency disease,** either the immune system fails to develop normally or the immune response is blocked in some way. Autoimmune disorders and immunodeficiency diseases are fairly rare—clear evidence of the effectiveness of the immune system's control mechanisms. A far more common (and generally far less dangerous) class of immune disorders is **allergies.** Next we consider examples of each type of immune disorder.

Autoimmune Disorders

Autoimmune disorders affect an estimated 5 percent of adults in North America and Europe. In previous chapters we have cited many examples of the effects of autoimmune disorders on the function of major systems.

The immune system usually recognizes but ignores antigens normally found in the body—self-antigens. When the recognition system does not work correctly, however, activated B cells make antibodies against other body cells and tissues. These "misguided" antibodies are called **autoantibodies.** The trigger may be a reduction in suppressor T cell activity, the excessive stimulation of helper T cells, tissue damage that releases large quantities of antigenic fragments, haptens bound to compounds normally ignored, viral or bacterial toxins, or a combination of factors.

The resulting condition depends on the antigen that the autoantibodies attack. For example:

- The inflammation of *thyroiditis* is due to autoantibodies against thyroglobulin.
- *Rheumatoid arthritis* occurs when autoantibodies form immune complexes in connective tissues around the joints.
- *Insulin-dependent diabetes mellitus (IDDM)* develops when autoantibodies attack cells in the pancreatic islets.

Many autoimmune disorders appear to be cases of mistaken identity. For example, proteins associated with the measles, Epstein–Barr, influenza, and other viruses contain amino acid sequences that are similar to those of myelin proteins. As a result, antibodies that target these viruses may also attack myelin sheaths. This accounts for the neurological complications that sometimes follow a vaccination or a viral infection. It also may be responsible for *multiple sclerosis*.

For unknown reasons, the risk of autoimmune problems increases if an individual has an unusual type of MHC protein. At least 50 clinical conditions have been linked to specific variations in MHC structure.

Immunodeficiency Diseases

Immunodeficiency diseases result from (1) problems with the embryological development of lymphoid organs and tissues; (2) an infection with a virus, such as HIV, that depresses immune function; or (3) treatment with, or exposure to, immunosuppressive agents, such as radiation or drugs.

Individuals born with **severe combined immunodeficiency disease (SCID)** fail to develop either cell-mediated or antibody-mediated immunity. Their lymphocyte populations are low, and normal B cells and T cells are absent. Such infants cannot produce an immune response, so even a mild infection can prove fatal. Total isolation offers protection but at great cost—extreme restrictions on lifestyle. Bone marrow transplants from a compatible donor, normally a close relative, have been used to colonize lymphoid tissues with functional lymphocytes. Gene-splicing techniques have led to therapies that can treat at least one form of SCID.

AIDS is an immunodeficiency disease that results from a viral infection that targets helper T cells. As the number of T cells declines, normal immune control breaks down. When a subsequent infection occurs, suppressor factors from suppressor T cells inhibit an immune response before the few surviving helper T cells can stimulate the formation of cytotoxic T cells or plasma cells in adequate numbers. We consider AIDS further on page 805.

Immunosuppressive drugs have been used for many years to prevent graft rejection after transplant surgery. Unfortunately, immunosuppressive agents can destroy stem cells and lymphocytes and lead to a complete failure of the immune response.

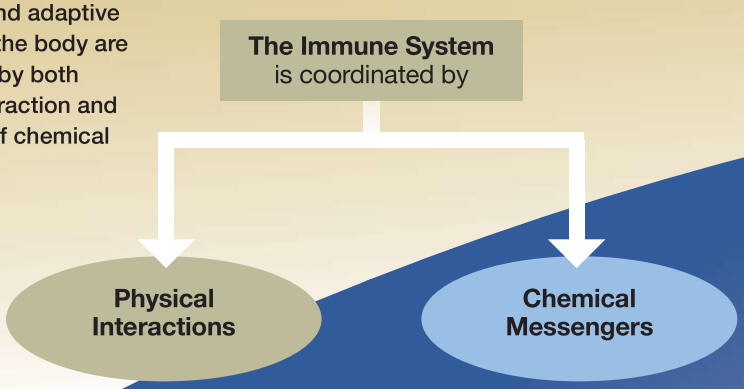
Allergies

Allergies are inappropriate or excessive immune responses to antigens. The sudden increase in cellular activity or antibody titers can have several unpleasant side effects. For example, neutrophils or cytotoxic T cells may destroy normal cells while they are attacking an antigen. Or the antigen–antibody complex may trigger massive inflammation. Antigens that set off allergic reactions are often called **allergens.**

Spotlight

Figure 22–28
Cytokines of the Immune System

The innate and adaptive defenses of the body are coordinated by both physical interaction and the release of chemical messengers.



CYTOKINES

An example of the release of chemical messengers is the secretion of cytokines by many cell types involved in the immune response. The six groups of cytokines shown here merit special attention.

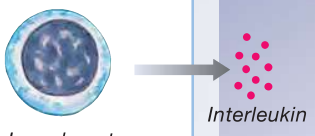
Interleukins

Interleukins may be the most diverse and important chemical messengers in the immune system. Nearly 20 types of interleukins have been identified. Lymphocytes and macrophages are the primary sources of interleukins, but endothelial cells, fibroblasts, and astrocytes also produce certain interleukins, such as interleukin-1 (IL-1).

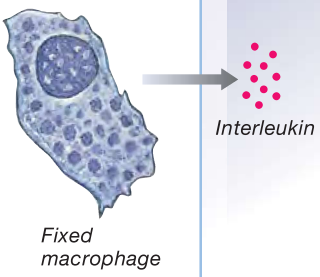
The functions of interleukins include the following:

1. **Increasing T Cell Sensitivity to Antigens Exposed on Macrophage Membranes.** Heightened sensitivity speeds up the production of cytotoxic and regulatory T cells.
2. **Stimulating B Cell Activity, Plasma Cell Formation, and Antibody Production.** These events promote the production of antibodies and the development of antibody-mediated immunity.
3. **Enhancing Nonspecific Defenses.** Known effects of interleukin production include (a) stimulation of inflammation, (b) formation of scar tissue by fibroblasts, (c) elevation of body temperature via the preoptic nucleus of the hypothalamus, (d) stimulation of mast cell formation, and (e) promotion of adrenocorticotropic hormone (ACTH) secretion by the anterior lobe of the pituitary gland.
4. **Moderating the Immune Response.** Some interleukins help suppress immune function and shorten the immune response.

Two interleukins, IL-1 and IL-2, are important in stimulating and maintaining the immune response. When released by activated macrophages and lymphocytes, these cytokines stimulate the activities of other immune cells and of the secreting cell. The result is a positive feedback loop that helps to recruit additional immune cells.



Although mechanisms exist to control the degree of stimulation, the regulatory process sometimes breaks down. Massive production of interleukins can cause problems at least as severe as those of the primary infection. For example, in *Lyme disease*, activated macrophages release IL-1 in response to a localized bacterial infection. This release produces fever, pain, skin rash, and arthritis throughout the entire body.

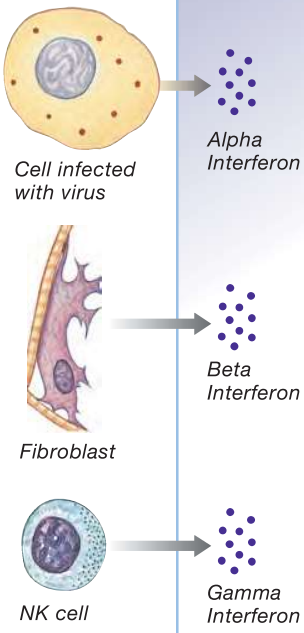


Some interleukins enhance the immune response, while others suppress it. The quantities secreted at any moment affect the nature and intensity of the response to an antigen. During a typical infection, the pattern of interleukin secretion changes constantly. Whether stimulatory or suppressive interleukins predominate plays a part in determining whether the individual overcomes the infection. For this reason, interleukins and their interactions are now the focus of intensive research.

Interferons

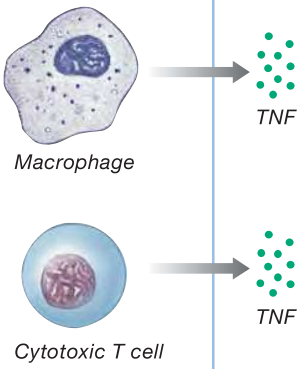
Interferons make the cell that synthesizes them, and that cell's neighbors, resistant to viral infection. In this way, interferons slow the spread of a virus. They may have other beneficial effects as well. For example, alpha-interferons and gamma-interferons attract and stimulate NK cells. Beta-interferons slow the progress of inflammation associated with viral infection. Gamma-interferons also stimulate macrophages, making them more effective at killing bacterial or fungal pathogens.

Because they stimulate NK cell activity, interferons can be used to fight some cancers. For example, alpha-interferons have been used to treat malignant melanoma, bladder cancer, ovarian cancer, and some forms of leukemia. Alpha- or gamma-interferons may be used to treat Kaposi's sarcoma, a cancer that typically develops in patients with AIDS.



Tumor Necrosis Factors

Tumor necrosis factors (TNFs) slow the growth of a tumor and kill sensitive tumor cells. Activated macrophages secrete one type of TNF and carry the molecules in their plasma membranes. Cytotoxic T cells produce a different type of TNF. In addition to their effects on tumor cells, TNFs stimulate granular leukocyte production, promote eosinophil activity, cause fever, and increase T cell sensitivity to interleukins.



Phagocyte-Activating Chemicals

Several cytokines coordinate immune defenses by adjusting the activities of phagocytic cells. These cytokines include factors that attract free macrophages and microphages and prevent their premature departure from the site of an injury.

Colony-Stimulating Factors

Colony-stimulating factors (CSFs) were introduced in Chapter 19. ↩ p. 658 These factors are produced by active T cells, cells of the monocyte–macrophage group, endothelial cells, and fibrocytes. CSFs stimulate the production of blood cells in red bone marrow and lymphocytes in lymphoid tissues and organs.

Miscellaneous Cytokines

This general category includes many chemicals discussed in earlier chapters. Examples include leukotrienes, lymphotoxins, perforin, hemopoiesis-stimulating factor, and suppression factors.

NOTE: Cytokines are often classified according to their origins. For example, *lymphokines* are produced by lymphocytes. *Monokines* are secreted by active macrophages and other antigen-presenting cells. These terms are misleading, however, because lymphocytes and macrophages may secrete the same cytokines. In addition, cells involved in adaptive defenses and tissue repair can also secrete cytokines.

There are several types of allergies. A complete classification has four categories. They include *immediate hypersensitivity (Type I)*, *cytotoxic reactions (Type II)*, *immune complex disorders (Type III)*, and *delayed hypersensitivity (Type IV)*. In Chapter 19 we discussed one example of a cytotoxic (Type II) reaction: the cross-reaction that follows the transfusion of an incompatible blood type. ↩ p. 650 Here we focus on immediate (Type I) hypersensitivity. It is probably the most common type of allergy.

Immediate hypersensitivity is a rapid and especially severe response to an antigen. One form, *allergic rhinitis*, includes hay fever and environmental allergies. This form may affect 15 percent of the U.S. population. Sensitization to an allergen during the initial exposure leads to the production of large quantities of IgE. Genes may determine a person's tendency to produce IgE in response to particular allergens.

Due to the lag time needed to activate B cells, produce plasma cells, and synthesize antibodies, the first exposure to an allergen does not produce signs and symptoms. Instead, it sets the stage for the next encounter. After sensitization, the IgE molecules become attached to basophils and mast cells throughout the body. When the individual meets the same allergen again, the bound antibodies stimulate these cells to release histamine, heparin, several cytokines, prostaglandins, and other chemicals into the surrounding tissues. A sudden, massive inflammation of the affected tissues results.

The cytokines and other mast cell secretions draw basophils, eosinophils, T cells, and macrophages into the area. These cells release their own chemicals, extending and intensifying the responses initiated by mast cells. The severity of the allergic reaction depends on the individual's sensitivity and on the location involved. If allergen exposure occurs at the body surface, the response may be restricted to that area. If the allergen enters the bloodstream, the response could be lethal.

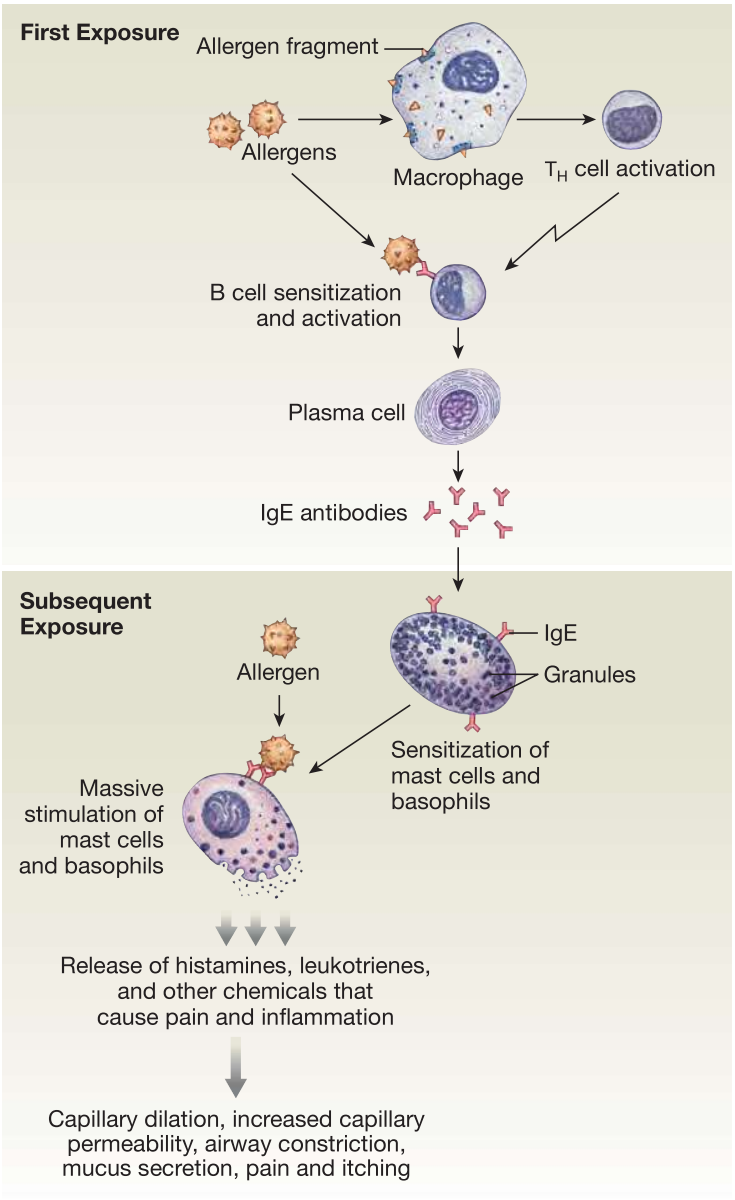
In **anaphylaxis** (an-a-fi-LAK-sis; *ana-*, again + *phylaxis*, protection), a circulating allergen affects mast cells throughout the body (**Figure 22–29**). (In drug reactions, such as allergies to penicillin, IgE antibodies are produced in response to a hapten [partial antigen] bound to a larger molecule that is widely distributed within the body because the combination acts as an allergen.) A wide range of signs and symptoms can develop within minutes. Changes in capillary permeabilities produce swelling and edema in the dermis, and raised welts, or *hives*, appear on the skin. Smooth muscles along the respiratory passageways contract, and the narrowed passages make breathing extremely difficult. In severe cases, an extensive peripheral vasodilation occurs, producing a drop in blood pressure that can lead to a circulatory collapse. This response is **anaphylactic shock.**

The prompt administration of drugs that block the action of histamine, known as **antihistamines** (an-tē-HIS-ta-mēnz), can prevent many of the signs and symptoms of immediate hypersensitivity. *Benadryl (diphenhydramine hydrochloride)* is a popular antihistamine that is available over the counter. Severe anaphylaxis is treated with injections of antihistamines, corticosteroids, and epinephrine.

Stress and the Immune Response

One of the normal effects of interleukin-1 secretion is the stimulation of adrenocorticotropic hormone (ACTH) production

Figure 22–29 The Mechanism of Anaphylaxis.



Clinical Note

AIDS

It's a **pandemic** disease

Acquired immune deficiency syndrome (AIDS), or *late-stage HIV disease*, is caused by the **human immunodeficiency virus (HIV).** This virus is a *retrovirus*: It carries its genetic information in RNA rather than in DNA. The virus enters human leukocytes by receptor-mediated endocytosis. ↩ p. 92 Specifically, the virus binds to CD4 cells, the membrane protein characteristic of helper T cells. HIV also infects several types of antigen-presenting cells, including those of the monocyte–macrophage line. It is the infection of helper T cells that leads to clinical problems.

Once the virus is inside a cell, the viral enzyme *reverse transcriptase* synthesizes a complementary strand of DNA. This strand is then incorporated into the cell's genetic material. When these inserted viral genes are activated, the infected cell begins synthesizing viral proteins. In effect, the viral genes take over the cell's synthetic machinery and force the cell to produce additional viruses. These new viruses are then shed at the cell surface.

Cells infected with HIV are ultimately destroyed by (1) formation of pores in the plasma membrane as the viruses are shed, (2) cessation of cell maintenance due to the continuing synthesis of viral components, (3) autolysis, or (4) stimulation of programmed cell death, or apoptosis.

The gradual destruction of helper T cells impairs the immune response, because these cells play a central role in coordinating cell-mediated and antibody-mediated responses to antigens. To make matters worse, suppressor T cells are relatively unaffected by the virus. Over time the excess of suppressing factors "turns off" the normal immune response. Circulating antibody levels decline and cell-mediated immunity is reduced. The body is left with impaired defenses against a wide variety of microbial invaders. Microorganisms that would ordinarily be harmless can now initiate lethal *opportunistic infections*. The risk of cancer also increases because immune surveillance is depressed.

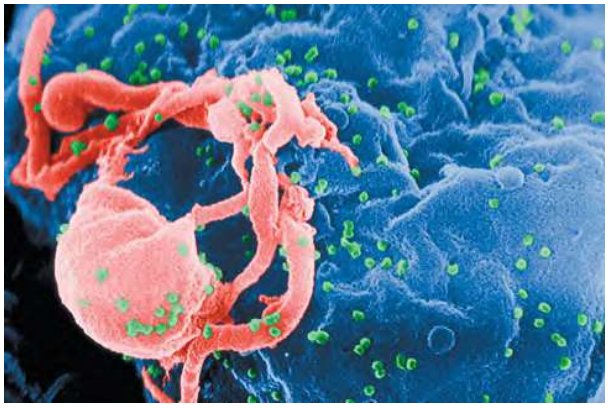
Infection with HIV occurs through intimate contact with the body fluids of infected individuals. The major routes of transmission involve contact with blood, semen, or vaginal secretions, although all body fluids may contain the virus. Worldwide, most individuals with AIDS become infected through sexual contact with an HIV-infected person (who may *not* necessarily show clinical signs of AIDS). The next largest group of infected individuals is intravenous drug users who shared contaminated needles. Relatively few individuals have become infected with the virus after receiving a transfusion of contaminated blood or blood products. Finally, an increasing number of infants are born with AIDS acquired from infected mothers.

AIDS continues to be a public health problem of massive proportions. Through 2008, there have been over 550,000 total deaths from AIDS in the United States. Currently about 15,000 deaths and 37,000 new diagnoses occur in the U.S. each year. Worldwide statistics are staggering. According to 2009 reports from the World Health Organization (WHO), 33.4 million people are living with HIV-AIDS, and over 27 million deaths have occurred to date. About two million people die each year—or one every 16 seconds—yet only 42% of infected people receive antiretroviral therapy.

The most effective ways to prevent HIV infection include abstinence, mutual monogamy of uninfected partners, male circumcision (to reduce the risk of transmission), and the avoidance of needle sharing. Circumcised men are up to 70% less likely to become infected than uncircumcised men. They are also less likely to infect their female partners. The use of latex condoms labeled "for the prevention of disease" has been shown to prevent the passage of HIV and the hepatitis and herpes viruses. Natural condoms, also called lambskin condoms, are made from the intestinal membrane of a lamb and are not effective against disease transmission because infectious agents can pass through the naturally occurring pores. (The pores are too small for sperm to pass through, so they are effective as a contraceptive.) Synthetic condoms, usually made of polyurethane, are considered to offer similar protection as latex, but differences in their manufacture cause variable reliability.

Clinical signs and symptoms of AIDS may not appear until 5–10 years or more after infection. When they do appear, they are commonly mild, consisting of lymphadenopathy and chronic, but nonfatal, infections. So far as is known, however, AIDS is almost always fatal. Most people who carry the virus will eventually die from complications of the disease. (A handful of infected individuals have been able to tolerate the virus without apparent illness for many years.)

Despite intensive efforts, a vaccine has yet to be developed that prevents HIV infection in an uninfected person exposed to the virus. The survival rate for AIDS patients has been steadily increasing. That is, more people are living longer before dying of AIDS or its complications. New drugs and drug combinations slow the progression of the disease, and improved antibiotic therapies help combat secondary infections.



HIV (green) budding from an infected T_H cell (blue) SEM × 40,000

by the anterior lobe of the pituitary gland. This hormone in turn prompts the secretion of glucocorticoids by the adrenal cortex. p. 617 The anti-inflammatory effects of the glucocorticoids may help control the extent of the immune response.

It is clear, however, that chronic stress depresses the immune system and can be a serious threat to health. The long-term secretion of glucocorticoids, as in the resistance phase of the *stress response*, can inhibit the immune response and lower a person's resistance to disease. p. 630 The effects of glucocorticoids that alter the effectiveness of innate and adaptive defenses include the following:

- *Depression of the Inflammatory Response.* Glucocorticoids inhibit mast cells and make capillaries less permeable. Inflammation becomes less likely. When it does occur, the reduced permeability of the capillaries slows the entry of fibrinogen, complement proteins, and cellular defenders into tissues.
- *Reduction in the Abundance and Activity of Phagocytes in Peripheral Tissues.* This reduction further impairs innate defense mechanisms. It also interferes with the processing and presentation of antigens to lymphocytes.
- *Inhibition of Interleukin Secretion.* A reduction in interleukin production depresses the response of lymphocytes, even to antigens bound to MHC proteins.

The mechanisms that bring about these changes are still under investigation.

Checkpoint

22. **Which kind of immunity protects a developing fetus, and how is that immunity produced?**
23. **What is an autoimmune disorder?**
24. **How does increased stress reduce the effectiveness of the immune response?**

See the blue Answers tab at the back of the book.

22-8 The immune response diminishes with advancing age

With advancing age, the immune system becomes less effective at combating disease. T cells become less responsive to antigens, so fewer cytotoxic T cells respond to an infection. This effect may be due to the gradual shrinking of the thymus and to lower circulating levels of thymic hormones. Because the number of helper T cells is also reduced, B cells are less responsive, so antibody levels do not rise as quickly after antigen exposure. The net result is an increased susceptibility to viral and bacterial infections. For this reason, vaccinations for acute viral diseases such as the flu (influenza), and for pneumococcal pneumonia, are strongly recommended for elderly individuals. The increased incidence of cancer in the elderly reflects the fact that immune surveillance declines, so tumor cells are not eliminated as effectively.

Checkpoint

25. **Why are the elderly more susceptible to viral and bacterial infections?**
26. **What may account for the increased incidence of cancer among the elderly?**

See the blue Answers tab at the back of the book.

22-9 The nervous and endocrine systems influence the immune response

Figure 22–30 summarizes the interactions between the lymphatic system and other physiological systems we have studied so far. Interactions among elements of the immune response and the nervous and endocrine systems are now the focus of intense research. For example,

- The thymus secretes oxytocin, ADH, and endorphins as well as thymic hormones. The effects on the CNS are not known, but removal of the thymus lowers brain endorphin levels.
- Both thymic hormones and cytokines help establish the normal levels of CRH and TRH produced by the hypothalamus.
- Other thymic hormones affect the anterior lobe of the pituitary gland directly, stimulating the secretion of prolactin and GH.

Conversely, the nervous system can apparently adjust the sensitivity of the immune response:

- The PNS innervates dendritic cells in the lymph nodes, spleen, skin, and other antigen-presenting cells. The nerve endings release neurotransmitters that heighten local immune responses. For this reason, some skin conditions, such as *psoriasis*, worsen when a person is under stress.
- Neuroglia in the CNS produce cytokines that promote an immune response.
- A sudden decline in immune function can occur after even a brief period of emotional distress.

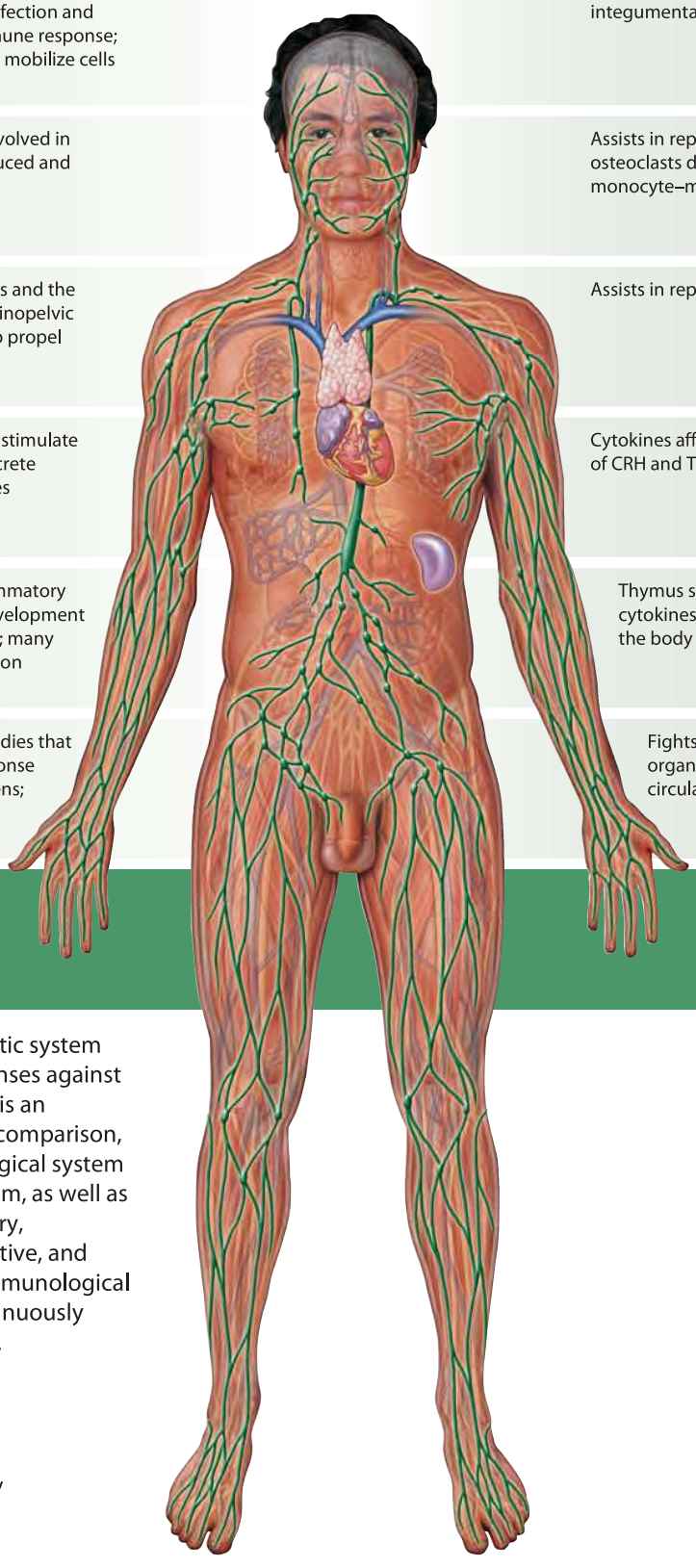
Checkpoint

27. **What is the relationship between the endocrine system and the lymphatic system?**
28. **Identify the role of the lymphatic system for all body systems.**

See the blue Answers tab at the back of the book.

SYSTEM INTEGRATOR

Body System → Lymphatic System	Lymphatic System → Body System
Integumentary — Provides physical barriers to pathogen entry; macrophages in dermis resist infection and present antigens to trigger immune response; mast cells trigger inflammation, mobilize cells of lymphatic system	Provides IgA antibodies for secretion onto integumentary surfaces — **Integumentary** Page 165
Skeletal — Lymphocytes and other cells involved in the immune response are produced and stored in red bone marrow	Assists in repair of bone after injuries; osteoclasts differentiate from monocyte–macrophage cell line — **Skeletal** Page 275
Muscular — Protects superficial lymph nodes and the lymphatic vessels in the abdominopelvic cavity; muscle contractions help propel lymph along lymphatic vessels	Assists in repair after injuries — **Muscular** Page 369
Nervous — Microglia present antigens that stimulate adaptive defenses; glial cells secrete cytokines; innervation stimulates antigen-presenting cells	Cytokines affect hypothalamic production of CRH and TRH — **Nervous** Page 543
Endocrine — Glucocorticoids have anti-inflammatory effects; thymosins stimulate development and maturation of lymphocytes; many hormones affect immune function	Thymus secretes thymosins; cytokines affect cells throughout the body — **Endocrine** Page 632
Cardiovascular — Distributes WBCs; carries antibodies that attack pathogens; clotting response helps restrict spread of pathogens; granulocytes and lymphocytes produced in bone marrow	Fights infections of cardiovascular organs; returns tissue fluid to circulation — **Cardiovascular** Page 759



The LYMPHATIC System

For all body systems, the lymphatic system provides adaptive (specific) defenses against infection. The lymphatic system is an anatomically distinct system. In comparison, the immune system is a physiological system that includes the lymphatic system, as well as components of the integumentary, cardiovascular, respiratory, digestive, and other body systems. Through immunological surveillance, pathogens are continuously eliminated throughout the body.

Figure 22–30 diagrams the functional relationships between the lymphatic system and the other body systems we have studied so far.

Respiratory Page 857
Digestive Page 910
Urinary Page 992
Reproductive Page 1072

Related Clinical Terms

adenitis: Inflammation of the adenoid (pharyngeal tonsil).
allograft: Transplant between compatible recipient and donor of the same species.
anamnestic response: An immune response that is initiated by memory cells.
autograft: A transplant of tissue that is taken from the same person.
Burkitt's lymphoma: A malignant cancer of B lymphocytes.
chronic fatigue syndrome: A complicated disorder most often characterized by extreme fatigue that does not improve with rest, and which may worsen with physical activity.
congenital thymic aplasia: Congenital (present at birth) absence of the thymus and parathyroid glands and a deficiency of immunity.
Coombs test: A medical test to detect antibodies or complement in the blood.
dermatomyositis: An autoimmune disease characterized by inflammation of the skin and muscles.
eczema: A genetic inflammatory skin disorder, often with crusts, papules, and leaky eruptions.
Hodgkin's lymphoma: A malignant lymphoma affecting lymph nodes and lymph organs.
host versus graft disease: A pathological condition in which cells from the transplanted tissue of a donor initiate an immunological response, attacking the cells and tissue of the recipient.
hybridoma: A tissue culture composed of cancer cells fused to lymphocytes to mass-produce a specific antibody.
immunology: Branch of biomedicine concerned with the structure and function of the immune system.
infectious mononucleosis: An acute disease caused by the Epstein–Barr virus, producing fever, swelling of the lymph nodes, sore throat, and increased lymphocytes in the bloodstream.
latex allergy: Hypersensitivity to products made of the sap of the rubber plant.
polymyositis: An autoimmune disease characterized by inflammation and atrophy of muscles.
sentinel node: The first lymph node to receive drainage from a tumor. It is used to determine if there is lymphatic metastasis in some types of cancer.
splenomegaly: Enlargement of the spleen.
systemic lupus erythematosus (SLE): An autoimmune disease in which a person's immune system attacks and injures its own organs and tissues in virtually every system of the body.
xenograft: A transplant that is made between two different species.

Chapter Review

Study Outline

22-1 Surface barriers and internal defenses constitute innate defenses, and lymphocytes provide adaptive defenses p. 765

1. The cells, tissues, and organs of the **lymphatic system** play a central role in the body's defenses against a variety of **pathogens,** or disease-causing organisms.
2. *Lymphocytes*, the primary cells of the lymphatic system, are central to an **immune response** against specific threats to the body. **Immunity** is the ability to resist infection and disease through the activation of adaptive (specific) defenses.

22-2 Lymphatic vessels, lymphocytes, lymphoid tissues, and lymphoid organs function in body defenses p. 765

3. The lymphatic system includes a network of **lymphatic vessels,** or **lymphatics,** that carry **lymph** (a fluid similar to plasma, but with a lower concentration of proteins). An array of **lymphoid tissues** and **lymphoid organs** is connected to lymphatics. *(Figure 22–1)*
4. The lymphatic system produces, maintains, and distributes lymphocytes (which attack invading organisms, abnormal cells, and foreign proteins); it also helps maintain blood volume and eliminate local variations in the composition of interstitial fluid.
5. Lymph flows along a network of lymphatic vessels, the smallest of which are the **lymphatic capillaries** *(terminal lymphatics)*. The lymphatic vessels empty into the **thoracic duct** and the **right lymphatic duct.** *(Figures 22–2 to 22–4)*
6. The three classes of lymphocytes are **T** (**t**hymus-dependent) **cells, B** (**b**one marrow–derived) **cells,** and **NK** (**n**atural **k**iller) **cells.** *(Figure 22–5)*
7. **Cytotoxic T cells** attack foreign cells or body cells infected by viruses and provide **cell-mediated (cellular) immunity.** *Regulatory T cells* (**helper T cells** and **suppressor T cells**) regulate and coordinate the immune response.
8. B cells can differentiate into **plasma cells,** which produce and secrete *antibodies* that react with specific chemical targets called **antigens.** Antibodies in body fluids are called *immunoglobulins*. B cells are responsible for **antibody-mediated (humoral) immunity.**
9. NK cells (also called **large granular lymphocytes**) attack foreign cells, normal cells infected with viruses, and cancer cells. NK cells provide *immunological surveillance*.
10. Lymphocytes continuously migrate into and out of the blood through the lymphoid tissues and organs. **Lymphopoiesis** (lymphocyte production) involves the red bone marrow, thymus, and peripheral lymphoid tissues. *(Figure 22–6)*
11. **Lymphoid tissues** are connective tissues dominated by lymphocytes. In a **lymphoid nodule,** the lymphocytes are densely packed in an area of loose connective tissue. The lymphoid tissue that protects the epithelia of the digestive, respiratory, urinary, and reproductive tracts is called **mucosa-associated lymphoid tissue (MALT).** *(Figure 22–7)*

12. Important lymphoid organs include the **lymph nodes,** the **thymus,** and the **spleen.** Lymphoid tissues and organs are distributed in areas that are especially vulnerable to injury or invasion.
13. Lymph nodes are encapsulated masses of lymphoid tissue. The **deep cortex** is dominated by T cells; the **outer cortex** and **medulla** contain B cells. *(Figure 22–8)*
14. The thymus lies behind the sternum, in the anterior mediastinum. **Reticular epithelial cells** scattered among the lymphocytes maintain the blood–thymus barrier and secrete thymic hormones. *(Figure 22–9)*
15. The adult spleen contains the largest mass of lymphoid tissue in the body. The cellular components form the **pulp** of the spleen. **Red pulp** contains large numbers of red blood cells, and **white pulp** resembles lymphoid nodules. *(Figure 22–10)*
16. The lymphatic system is a major component of the body's defenses, which are classified as either (1) **innate (nonspecific) defenses,** which protect without distinguishing one threat from another, or (2) **adaptive (specific) defenses,** which protect against particular threats only.

22-3 Innate (nonspecific) defenses do not discriminate between potential threats and respond the same regardless of the invader p. 778

17. Innate (nonspecific) defenses prevent the approach, deny the entry, or limit the spread of living or nonliving hazards. *(Figure 22–11)*
18. Physical barriers include skin, mucous membranes, hair, epithelia, and various secretions of the integumentary and digestive systems.
19. The two types of phagocytic cells are **microphages** and **macrophages** (cells of the **monocyte–macrophage system**). Microphages are neutrophils and eosinophils in circulating blood.
20. **Phagocytes** leave the bloodstream by *emigration*, or *diapedesis* (migration between adjacent endothelial cells), and exhibit **chemotaxis** (sensitivity and orientation to chemical stimuli).
21. **Immunological surveillance** involves constant monitoring of normal tissues by NK cells that are sensitive to abnormal antigens on the surfaces of otherwise normal cells. NK cells kill cancer cells that have **tumor-specific antigens** on their surfaces. *(Figure 22–12)*
22. **Interferons**—small proteins released by cells infected with viruses—trigger the production of **antiviral proteins,** which interfere with viral replication inside the cell. Interferons are **cytokines**—chemical messengers released by tissue cells to coordinate local activities. *(Figure 22–13)*
23. At least 11 **complement proteins** make up the **complement system.** These proteins interact with each other in cascades to destroy target plasma membranes, stimulate inflammation, attract phagocytes, or enhance phagocytosis. The complement system can be activated by either the **classical pathway** or the **alternative pathway.** *(Figure 22–14)*
24. **Inflammation** is a localized tissue response to injury. *(Figure 22–15)*
25. A **fever** (body temperature greater than 37.2°C [99°F]) can inhibit pathogens and accelerate metabolic processes. **Pyrogens** can reset the body's thermostat and raise the temperature.

22-4 Adaptive (specific) defenses respond to individual threats and are either cell-mediated or antibody-mediated p. 785

26. T cells are responsible for **cell-mediated (cellular) immunity.** B cells provide **antibody-mediated (humoral) immunity.**
27. Forms of immunity include **innate immunity** (genetically determined and present at birth) or **adaptive immunity** (produced by prior exposure to an antigen or antibody production). The two types of adaptive immunity are **active immunity** (which appears after exposure to an antigen) and **passive immunity** (produced by the transfer of antibodies from another source). *(Figure 22–16)*
28. Immunity exhibits four general properties: **specificity, versatility, memory,** and **tolerance.** *Memory cells* enable the immune system to "remember" previous target antigens. Tolerance is the ability of the immune system to ignore some antigens, such as those of normal body cells.
29. The immune response is triggered by the presence of an antigen and includes cell-mediated and antibody-mediated defenses. *(Figure 22–17)*

22-5 T cells play a role in initiating, maintaining, and controlling the immune response p. 787

30. **Antigen presentation** occurs when an antigen–glycoprotein combination appears in a plasma membrane (typically of a macrophage). T cells sensitive to this antigen are activated if they contact the membrane of the antigen-presenting cell.
31. All body cells have plasma membrane glycoproteins. The genes controlling their synthesis make up a chromosomal region called the **major histocompatibility complex (MHC).** The membrane glycoproteins are called **MHC proteins. APCs (antigen-presenting cells)** are involved in antigen stimulation.
32. Lymphocytes are not activated by lone antigens, but respond instead to an antigen bound to either a **Class I** or a **Class II** MHC protein in a process called **antigen recognition.** *(Figure 22–18)*
33. Class I MHC proteins are in all nucleated body cells. Class II MHC proteins are only in antigen-presenting cells (APCs) and lymphocytes.
34. Whether a T cell responds to antigens held in Class I or Class II MHC proteins depends on the structure of the T cell plasma membrane. T cell plasma membranes contain proteins called **CD** (**c***luster of* **d***ifferentiation*) **markers. CD3 markers** are present on all T cells. **CD8 markers** are on cytotoxic and suppressor T cells. **CD4 markers** are on all helper T cells.
35. One type of CD8 cell responds quickly, giving rise to large numbers of cytotoxic T cells and memory T cells. The other type of CD8 cell responds more slowly, giving rise to small numbers of suppressor T cells.
36. Cytotoxic T cells seek out and destroy abnormal and infected cells, using three different methods, including the secretion of **lymphotoxin.** *(Figure 22–19)*
37. Cell-mediated immunity (cellular immunity) results from the activation of CD8 T cells by antigens bound to Class I MHCs. When activated, most of these T cells divide to generate cytotoxic T cells and **memory T_C cells,** which remain in reserve to guard against future such attacks. Suppressor T cells depress the responses of other T cells and of B cells. *(Figures 22–19, 22–21)*

38. Helper, or CD4, T cells respond to antigens presented by Class II MHC proteins. When activated, helper T cells secrete cytokines that aid in coordinating adaptive and innate defenses, and regulate cell-mediated and antibody-mediated immunity. *(Figures 22–20, 22–21)*

22-6 B cells respond to antigens by producing specific antibodies p. 792

39. B cells become **sensitized** when antibody molecules in their membranes bind antigens. The antigens are then displayed on the Class II MHC proteins of the B cells, which become activated by helper T cells activated by the same antigen. *(Figure 22–22)*
40. An active B cell may differentiate into a plasma cell or produce daughter cells that differentiate into plasma cells and **memory B cells.** Antibodies are produced by plasma cells. *(Figure 22–22)*
41. A Y-shaped antibody molecule consists of two parallel pairs of polypeptide chains containing *constant* and *variable segments*. *(Figure 22–23)*
42. When antibody molecules bind to an antigen, they form an **antigen–antibody complex.** Effects that appear after binding include **neutralization** (antibody binding that prevents viruses or bacterial toxins from binding to body cells); **precipitation** (formation of an insoluble **immune complex**) and **agglutination** (formation of large complexes); *opsonization* (coating of pathogens with antibodies and complement proteins to enhance phagocytosis); stimulation of inflammation; and prevention of bacterial or viral adhesion. *(Figure 22–23)*
43. The five classes of antibodies **(immunoglobulins, Ig)** in body fluids are (1) **IgG,** responsible for resistance against many viruses, bacteria, and bacterial toxins; (2) **IgE,** which releases chemicals that accelerate local inflammation; (3) **IgD,** located on the surfaces of B cells; (4) **IgM,** the first type of antibody secreted after an antigen arrives; and (5) **IgA,** found in glandular secretions. *(Table 22–1)*
44. In humoral immunity, the antibodies first produced by plasma cells are the agents of the **primary response.** The maximum antibody level and **antibody titer** appears during the **secondary response** to antigen exposure. *(Figure 22–24)*
45. The initial steps in the immune responses to viral and bacterial infections differ. *(Figures 22–25 to 22–27; Table 22–2)*
46. Cytokines are chemical messengers coordinated by the immune system. **Interleukins** increase T cell sensitivity to antigens exposed on macrophage membranes; stimulate B cell activity, plasma cell formation, and antibody production; enhance innate defenses; and moderate the immune response. *(Spotlight Figure 22–28)*
47. Interferons slow the spread of a virus by making the synthesizing cell and its neighbors resistant to viral infections. *(Spotlight Figure 22–28)*
48. **Tumor necrosis factors (TNFs)** slow tumor growth and kill tumor cells. *(Spotlight Figure 22–28)*
49. Several cytokines adjust the activities of phagocytic cells to coordinate innate and adaptive defenses. *(Spotlight Figure 22–28)*
50. **Colony-stimulating factors (CSFs)** are factors produced by active T cells, cells of the monocyte–macrophage group, endothelial cells, and fibroblasts. *(Spotlight Figure 22–28)*

22-7 Immunological competence enables a normal immune response; abnormal responses result in immune disorders p. 800

51. **Immunological competence** is the ability to produce an immune response after exposure to an antigen. A developing fetus receives passive immunity from the maternal bloodstream. After delivery, the infant begins developing active immunity following exposure to environmental antigens.
52. **Autoimmune disorders** develop when the immune response inappropriately targets normal body cells and tissues.
53. In an **immunodeficiency disease,** either the immune system does not develop normally or the immune response is blocked.
54. **Allergies** are inappropriate or excessive immune responses to **allergens** (antigens that trigger allergic reactions). The four types of allergies are *immediate hypersensitivity (Type I)*, *cytotoxic reactions (Type II)*, *immune complex disorders (Type III)*, and *delayed hypersensitivity (Type IV)*.
55. In **anaphylaxis,** a circulating allergen affects mast cells throughout the body. *(Figure 22–29)*
56. Interleukin-1 released by active macrophages triggers the release of ACTH by the anterior pituitary gland. Glucocorticoids produced by the adrenal cortex moderate the immune response, but their long-term secretion can lower a person's resistance to disease.

22-8 The immune response diminishes with advancing age p. 806

57. With aging, the immune system becomes less effective at combating disease.

22-9 The nervous and endocrine systems influence the immune response p. 806

58. The lymphatic system has extensive interactions with the nervous and endocrine systems. *(Figure 22–30)*.

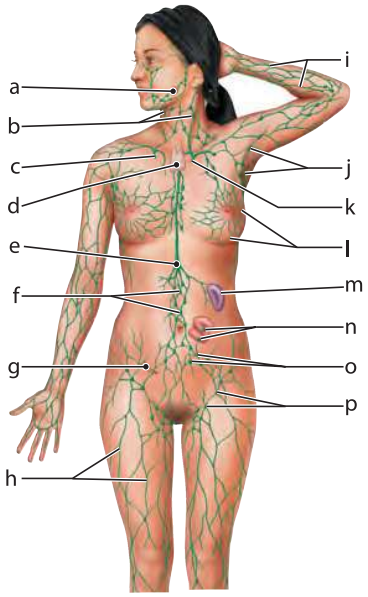
Review Questions

See the blue Answers tab at the back of the book.

LEVEL 1 Reviewing Facts and Terms

1. Identify the structures of the lymphatic system in the following diagram.

(a) _____
(b) _____
(c) _____
(d) _____
(e) _____
(f) _____
(g) _____
(h) _____
(i) _____
(j) _____
(k) _____
(l) _____
(m) _____
(n) _____
(o) _____
(p) _____



2. Lymph from the right arm, the right half of the head, and the right chest is received by the
   (a) cisterna chyli.
   (b) right lymphatic duct.
   (c) right thoracic duct.
   (d) aorta.
3. Anatomically, lymph vessels resemble
   (a) elastic arteries.
   (b) muscular arteries.
   (c) arterioles.
   (d) medium veins.
   (e) the venae cavae.
4. The specificity of an antibody is determined by the
   (a) fixed segment.
   (b) antigenic determinants.
   (c) variable region.
   (d) size of the antibody.
   (e) antibody class.
5. The major histocompatibility complex (MHC)
   (a) is responsible for forming lymphocytes.
   (b) produces antibodies in lymph glands.
   (c) is a group of genes that codes for human leukocyte antigens.
   (d) is a membrane protein that can recognize foreign antigens.
   (e) is the antigen found on bacteria that stimulates an immune response.
6. Red blood cells that are damaged or defective are removed from the bloodstream by the
   (a) thymus.
   (b) lymph nodes.
   (c) spleen.
   (d) tonsils.
7. Phagocytes move through capillary walls by squeezing between adjacent endothelial cells, a process known as
   (a) diapedesis.
   (b) chemotaxis.
   (c) adhesion.
   (d) perforation.
8. Perforins are proteins associated with the activity of
   (a) T cells.
   (b) B cells.
   (c) NK cells.
   (d) plasma cells.
9. Complement activation
   (a) stimulates inflammation.
   (b) attracts phagocytes.
   (c) enhances phagocytosis.
   (d) achieves a, b, and c.
10. The most beneficial effect of fever is that it
    (a) inhibits the spread of some bacteria and viruses.
    (b) increases the metabolic rate by up to 10 percent.
    (c) stimulates the release of pyrogens.
    (d) achieves a and b.
11. CD4 markers are associated with
    (a) cytotoxic T cells.
    (b) suppressor T cells.
    (c) helper T cells.
    (d) a, b, and c.
12. List the specific functions of each of the body's lymphoid tissues and organs.
13. Give a function for each of the following:
    (a) cytotoxic T cells
    (b) helper T cells
    (c) suppressor T cells
    (d) plasma cells
    (e) NK cells
    (f) stromal cells
    (g) reticular epithelial cells
    (h) interferons
    (i) pyrogens
    (j) T cells
    (k) B cells
    (l) interleukins
    (m) tumor necrosis factor
    (n) colony-stimulating factors
14. What are the three classes of lymphocytes, and where does each class originate?
15. What seven defenses, present at birth, provide the body with the defensive capability known as innate (nonspecific) resistance?

LEVEL 2 Reviewing Concepts

16. Compared with innate defenses, adaptive defenses
    (a) do not distinguish between one threat and another.
    (b) are always present at birth.
    (c) protect against threats on an individual basis.
    (d) deny the entry of pathogens to the body.
17. Blocking the antigen receptors on the surface of lymphocytes would interfere with
    (a) phagocytosis of the antigen.
    (b) that lymphocyte's ability to produce antibodies.
    (c) antigen recognition.
    (d) the ability of the lymphocyte to present antigen.
    (e) opsonization of the antigen.

18. A *decrease* in which population of lymphocytes would impair all aspects of an immune response?
    (a) cytotoxic T cells
    (b) helper T cells
    (c) suppressor T cells
    (d) B cells
    (e) plasma cells
19. Skin tests are used to determine if a person
    (a) has an active infection.
    (b) has been exposed to a particular antigen.
    (c) carries a particular antigen.
    (d) has measles.
    (e) can produce antibodies.
20. Compare and contrast the effects of complement with those of interferon.
21. How does a cytotoxic T cell destroy another cell displaying antigens bound to Class I MHC proteins?
22. How does the formation of an antigen–antibody complex cause the elimination of an antigen?
23. Give one example of each type of immunity: innate immunity, naturally acquired active immunity, artificially induced active immunity, artificially induced passive immunity, and naturally acquired passive immunity.
24. An anesthesia technician is advised that she should be vaccinated against hepatitis B, which is caused by a virus. She is given one injection and is told to come back for a second injection in a month and a third injection after six months. Why is this series of injections necessary?

LEVEL 3 Critical Thinking and Clinical Applications

25. An investigator at a crime scene discovers some body fluid on the victim's clothing. The investigator carefully takes a sample and sends it to the crime lab for analysis. On the basis of the analysis of antibodies, could the crime lab determine whether the sample is blood plasma or semen? Explain.
26. Ted finds out that he has been exposed to measles. He is concerned that he might have contracted the disease, so he goes to see his physician. The physician takes a blood sample and sends it to a lab for antibody levels and titers. The results show an elevated level and activity of IgM antibodies to rubella (measles) virus but very few IgG antibodies to the virus. Has Ted contracted the disease?
27. While walking along the street, you and your friend see an elderly woman whose left arm appears to be swollen to several times its normal size. Your friend remarks that the woman must have been in the tropics and contracted a form of filariasis that produces elephantiasis. You disagree, saying that it is more likely that the woman had a radical mastectomy (the removal of a breast because of cancer). Explain the rationale behind your answer.
28. Paula's grandfather is diagnosed as having lung cancer. His physician takes biopsies of several lymph nodes from neighboring regions of the body, and Paula wonders why, since his cancer is in the lungs. What would you tell her?
29. Willy is allergic to ragweed pollen and tells you that he read about a medication that can help his condition by blocking certain antibodies. Do you think that this treatment could help Willy? Explain.

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Animated tutorials in *Interactive Physiology*® (IP) help you understand difficult physiological concepts in this chapter.

Go to Immune System and find the following topics:

- Immune System Overview
- Anatomy Review
- Innate Host Defenses
- Common Characteristics of B and T Lymphocytes
- Humoral Immunity
- Cellular Immunity