57

The Immune System

Concept Outline

FIGURE 57.1
The influenza epidemic of 1918–1919 killed 22 million people in 18 months. With 25 million Americans infected, the Red Cross often worked around the clock.

When you consider how animals defend themselves, it is natural to think of turtles, armadillos, and other animals covered like tanks with heavy plates of armor. However, armor offers no protection against the greatest dangers vertebrates face—microorganisms and viruses. We live in a world awash with attackers too tiny to see with the naked eye, and no vertebrate could long withstand their onslaught unprotected. We survive because we have evolved a variety of very effective defenses against this constant attack. As we review these defenses, it is important to keep in mind that they are far from perfect. Some 22 million Americans and Europeans died from influenza over an 18-month period in 1918–1919 (figure 57.1), and more than 3 million people will die of malaria this year. Attempts to improve our defenses against infection are among the most active areas of scientific research today.

57.1 Many of the body's most effective defenses are nonspecific.

Skin: The First Line of Defense

The vertebrate is defended from infection the same way knights defended medieval cities. "Walls and moats" make entry difficult; "roaming patrols" attack strangers; and "sentries" challenge anyone wandering about and call patrols if a proper "ID" is not presented.

1. **Walls and moats.** The outermost layer of the vertebrate body, the **skin,** is the first barrier to penetration by microbes. Mucous membranes in the respiratory and digestive tracts are also important barriers that protect the body from invasion.
2. **Roaming patrols.** If the first line of defense is penetrated, the response of the body is to mount a **cellular counterattack,** using a battery of cells and chemicals that kill microbes. These defenses act very rapidly after the onset of infection.
3. **Sentries.** Lastly, the body is also guarded by mobile cells that patrol the bloodstream, scanning the surfaces of every cell they encounter. They are part of the **immune system.** One kind of immune cell aggressively attacks and kills any cell identified as foreign, whereas the other type marks the foreign cell or virus for elimination by the roaming patrols.

The Skin as a Barrier to Infection

The skin is the largest organ of the vertebrate body, accounting for 15% of an adult human's total weight. The skin not only defends the body by providing a nearly impenetrable barrier, but also reinforces this defense with chemical weapons on the surface. Oil and sweat glands give the skin's surface a pH of 3 to 5, acidic enough to inhibit the growth of many microorganisms. Sweat also contains the enzyme **lysozyme,** which digests bacterial cell walls. In addition to defending the body against invasion by viruses and microorganisms, the skin prevents excessive loss of water to the air through evaporation.

The epidermis of skin is approximately 10 to 30 cells thick, about as thick as this page. The outer layer, called the stratum corneum, contains cells that are continuously abraded, injured, and worn by friction and stress during the body's many activities. The body deals with this damage not by repairing the cells, but by replacing them. Cells are shed continuously from the stratum corneum and are replaced by new cells produced in the innermost layer of the epidermis, the stratum basale, which contains some of the most actively dividing cells in the vertebrate body. The cells formed in this layer migrate upward and enter a broad intermediate stratum spinosum layer. As they move upward they form the protein keratin, which makes skin tough and water-resistant. These new cells eventually arrive at the stratum corneum, where they normally remain for about a month before they are shed and replaced by newer cells from below. Psoriasis, which afflicts some 4 million Americans, is a chronic skin disorder in which epidermal cells are replaced every 3 to 4 days, about eight times faster than normal.

The dermis of skin is 15 to 40 times thicker than the epidermis. It provides structural support for the epidermis and a matrix for the many blood vessels, nerve endings, muscles, and other structures situated within skin. The wrinkling that occurs as we grow older takes place in the dermis, and the leather used to manufacture belts and shoes is derived from very thick animal dermis.

The layer of subcutaneous tissue below the dermis contains primarily adipose cells. These cells act as shock absorbers and provide insulation, conserving body heat. Subcutaneous tissue varies greatly in thickness in different parts of the body. It is nonexistent in the eyelids, is a half-centimeter thick or more on the soles of the feet, and may be much thicker in other areas of the body, such as the buttocks and thighs.

Other External Surfaces

In addition to the skin, two other potential routes of entry by viruses and microorganisms must be guarded: the *digestive tract* and the *respiratory tract.* Recall that both the digestive and respiratory tracts open to the outside and their surfaces must also protect the body from foreign invaders. Microbes are present in food, but many are killed by saliva (which also contains lysozyme), by the very acidic environment of the stomach, and by digestive enzymes in the intestine. Microorganisms are also present in inhaled air. The cells lining the smaller bronchi and bronchioles secrete a layer of sticky mucus that traps most microorganisms before they can reach the warm, moist lungs, which would provide ideal breeding grounds for them. Other cells lining these passages have cilia that continually sweep the mucus toward the glottis. There it can be swallowed, carrying potential invaders out of the lungs and into the digestive tract. Occasionally, an infectious agent, called a pathogen, will enter the digestive and respiratory systems and the body will use defense mechanisms such as vomiting, diarrhea, coughing, and sneezing to expel the pathogens.

The surface defenses of the body consist of the skin and the mucous membranes lining the digestive and respiratory tracts, which eliminate many microorganisms before they can invade the body tissues.

Cellular Counterattack: The Second Line of Defense

The surface defenses of the vertebrate body are very effective but are occasionally breached, allowing invaders to enter the body. At this point, the body uses a host of nonspecific cellular and chemical devices to defend itself. We refer to this as the second line of defense. These devices all have one property in common: they respond to *any* microbial infection without pausing to determine the invader's identity.

Although these cells and chemicals of the nonspecific immune response roam through the body, there is a central location for the collection and distribution of the cells of the immune system; it is called the lymphatic system (see chapter 52). The lymphatic system consists of a network of lymphatic capillaries, ducts, nodes and lymphatic organs (figure 57.2), and although it has other functions involved with circulation, it also stores cells and other agents used in the immune response. These cells are distributed throughout the body to fight infections, and also stored in the lymph nodes where foreign invaders can be eliminated as body fluids pass through.

Cells That Kill Invading Microbes

Perhaps the most important of the vertebrate body's nonspecific defenses are white blood cells called leukocytes that circulate through the body and attack invading microbes within tissues. There are three basic kinds of these cells, and each kills invading microorganisms differently.

Macrophages ("big eaters") are large, irregularly shaped cells that kill microbes by ingesting them through *phagocytosis*, much as an amoeba ingests a food particle (figure 57.3). Within the macrophage, the membrane-bound vacuole containing the bacterium fuses with a lysosome. Fusion activates lysosomal enzymes that kill the microbe by liberating large quantities of oxygen free-radicals. Macrophages also engulf viruses, cellular debris, and dust particles in the lungs. Macrophages circulate continuously in the extracellular fluid, and their phagocytic actions supplement those of the specialized phagocytic cells that are part of the structure of the liver, spleen, and bone marrow. In response to an infection, monocytes (an undifferentiated leukocyte) found in the blood squeeze through capillaries to enter the connective tissues. There, at the site of the infection, the monocytes are transformed into additional macrophages.

Neutrophils are leukocytes that, like macrophages, ingest and kill bacteria by phagocytosis. In addition, neutrophils release chemicals (some of which are identical to household bleach) that kill other bacteria in the neighborhood as well as neutrophils themselves.

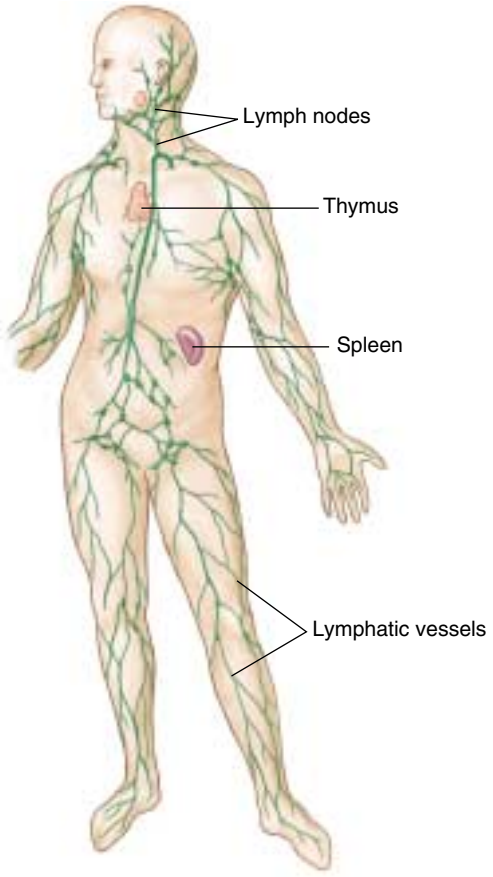


FIGURE 57.2
The lymphatic system. The lymphatic system consists of lymphatic vessels, lymph nodes, and lymphatic organs, including the spleen and thymus gland.

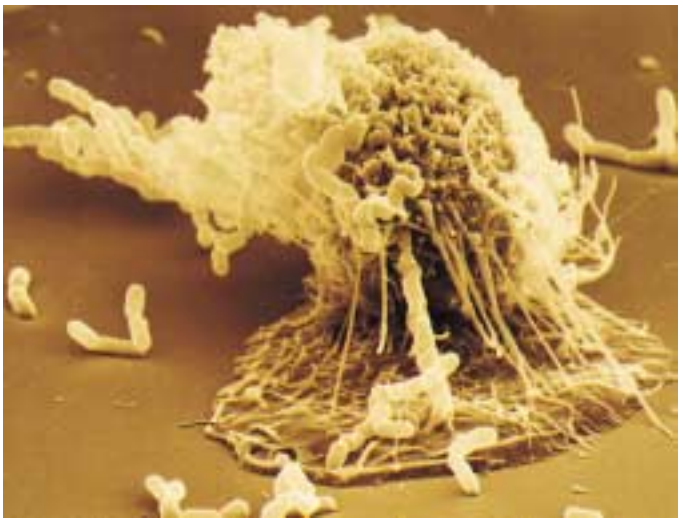


FIGURE 57.3
A macrophage in action (1800×). In this scanning electron micrograph, a macrophage is "fishing" with long, sticky cytoplasmic extensions. Bacterial cells that come in contact with the extensions are drawn toward the macrophage and engulfed.

Natural killer cells do not attack invading microbes directly. Instead, they kill cells of the body that have been infected with viruses. They kill not by phagocytosis, but rather by creating a hole in the plasma membrane of the target cell (figure 57.4). Proteins, called *perforins*, are released from the natural killer cells and insert into the membrane of the target cell, forming a pore. This pore allows water to rush into the target cell, which then swells and bursts. Natural killer cells also attack cancer cells, often before the cancer cells have had a chance to develop into a detectable tumor. The vigilant surveillance by natural killer cells is one of the body's most potent defenses against cancer.

Proteins That Kill Invading Microbes

The cellular defenses of vertebrates are enhanced by a very effective chemical defense called the *complement system*. This system consists of approximately 20 different proteins that circulate freely in the blood plasma. When they encounter a bacterial or fungal cell wall, these proteins aggregate to form a *membrane attack complex* that inserts itself into the foreign cell's plasma membrane, forming a pore like that produced by natural killer cells (figure 57.5). Water enters the foreign cell through this pore, causing the cell to swell and burst. Aggregation of the complement proteins is also triggered by the binding of antibodies to invading microbes, as we will see in a later section.

The proteins of the complement system can augment the effects of other body defenses. Some amplify the inflammatory response (discussed next) by stimulating histamine release; others attract phagocytes to the area of infection; and still others coat invading microbes, roughening the microbes' surfaces so that phagocytes may attach to them more readily.

Another class of proteins that play a key role in body defense are interferons. There are three major categories of interferons: *alpha*, *beta*, and *gamma*. Almost all cells in the body make alpha and beta interferons. These polypeptides act as messengers that protect normal cells in the vicinity of infected cells from becoming infected. Though viruses are still able to penetrate the neighboring cells, the alpha and beta interferons prevent viral replication and protein assembly in these cells. Gamma interferon is produced only by particular lymphocytes and natural killer cells. The secretion of gamma interferon by these cells is part of the immunological defense against infection and cancer, as we will describe later.

A patrolling army of macrophages, neutrophils, and natural killer cells attacks and destroys invading viruses and bacteria and eliminates infected cells. In addition, a system of proteins called complement may be activated to destroy foreign cells, and body cells infected with a virus secrete proteins called interferons that protect neighboring cells.

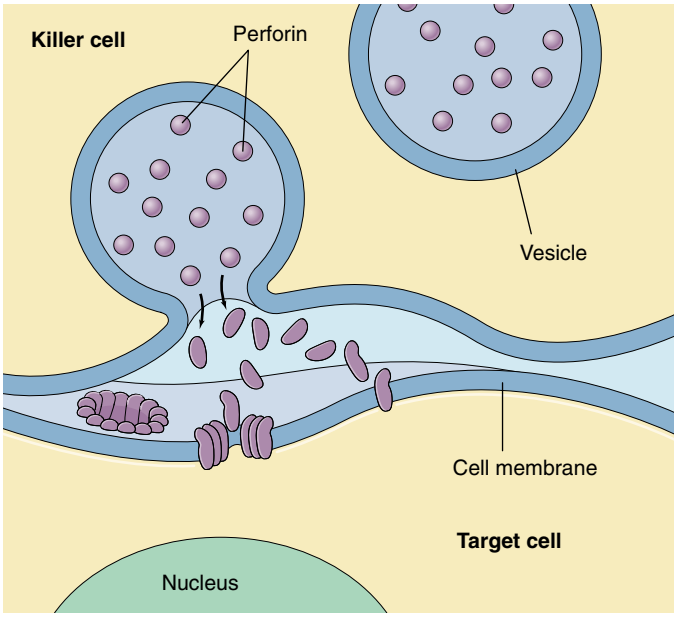


FIGURE 57.4
How natural killer cells kill target cells. The initial event, the tight binding of the killer cell to the target cell, causes vesicles loaded with *perforin* molecules within the killer cell to move to the plasma membrane and disgorge their contents into the intercellular space over the target cell. The perforin molecules insert into the plasma membrane of the target cell like staves of a barrel, forming a pore that admits water and ruptures the cell.

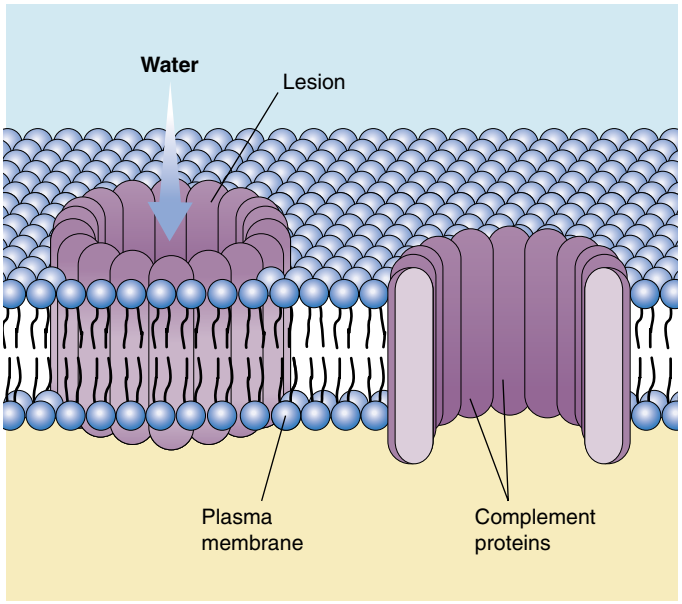


FIGURE 57.5
How complement creates a hole in a cell membrane. As the diagram shows, the complement proteins form a complex transmembrane pore resembling the perforin-lined pores formed by natural killer cells.

The Inflammatory Response

The inflammatory response is a localized, nonspecific response to infection. Infected or injured cells release chemical alarm signals, most notably histamine and prostaglandins. These chemicals promote the dilation of local blood vessels, which increases the flow of blood to the site of infection or injury and causes the area to become red and warm. They also increase the permeability of capillaries in the area, producing the edema (tissue swelling) so often associated with infection. The more permeable capillaries allow phagocytes (monocytes and neutrophils) to migrate from the blood to the extracellular fluid, where they can attack bacteria. Neutrophils arrive first, spilling out chemicals that kill the bacteria in the vicinity (as well as tissue cells and themselves); the *pus* associated with some infections is a mixture of dead or dying pathogens, tissue cells, and neutrophils. Monocytes follow, become macrophages and engulf pathogens and the remains of the dead cells (figure 57.6).

The Temperature Response

Macrophages that encounter invading microbes release a regulatory molecule called interleukin-1, which is carried by the blood to the brain. Interleukin-1 and other pyrogens (Greek *pyr*, "fire") such as bacterial endotoxins cause neurons in the hypothalamus to raise the body's temperature several degrees above the normal value of 37°C (98.6°F). The elevated temperature that results is called a fever.

Experiments with lizards, which regulate their body temperature by moving to warmer or colder locations, demonstrate that infected lizards choose a warmer environment—they give themselves a fever! Further, if lizards are prevented from elevating their body temperature, they have a slower recovery from their infection. Fever contributes to the body's defense by stimulating phagocytosis and causing the liver and spleen to store iron, reducing blood levels of iron, which bacteria need in large amounts to grow. However, very high fevers are hazardous because excessive heat may inactivate critical enzymes. In general, temperatures greater than 39.4°C (103°F) are considered dangerous for humans, and those greater than 40.6°C (105°F) are often fatal.

Inflammation aids the fight against infection by increasing blood flow to the site and raising temperature to retard bacterial growth.

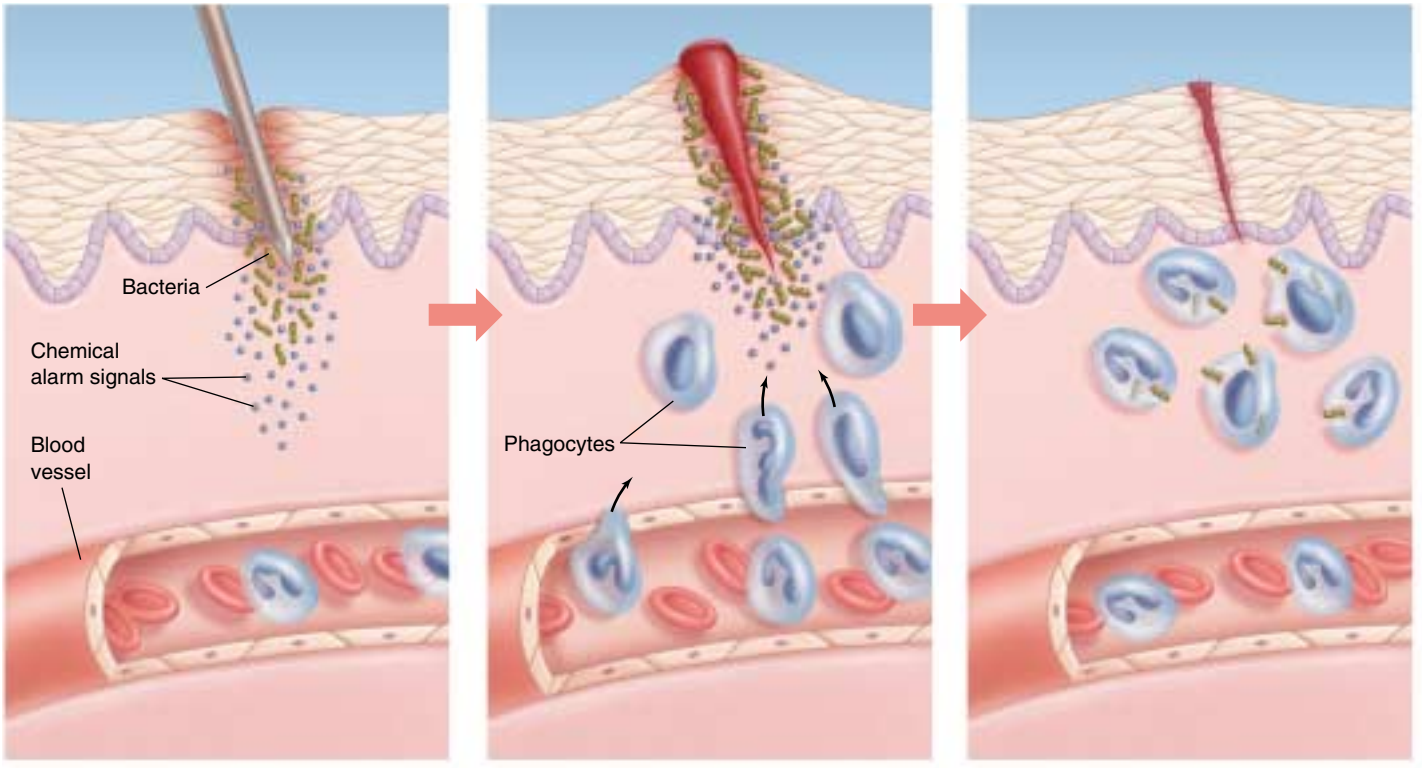


FIGURE 57.6
The events in a local inflammation. When an invading microbe has penetrated the skin, chemicals, such as histamine and prostaglandins, cause nearby blood vessels to dilate. Increased blood flow brings a wave of phagocytic cells, which attack and engulf invading bacteria.

57.2 Specific immune defenses require the recognition of antigens.

The Immune Response: The Third Line of Defense

Few of us pass through childhood without contracting some sort of infection. Chicken pox, for example, is an illness that many of us experience before we reach our teens. It is a disease of childhood, because most of us contract it as children and *never catch it again.* Once you have had the disease, you are usually immune to it. Specific immune defense mechanisms provide this immunity.

Discovery of the Immune Response

In 1796, an English country doctor named Edward Jenner carried out an experiment that marks the beginning of the study of immunology. Smallpox was a common and deadly disease in those days. Jenner observed, however, that milkmaids who had caught a much milder form of "the pox" called cowpox (presumably from cows) rarely caught smallpox. Jenner set out to test the idea that cowpox conferred protection against smallpox. He infected people with cowpox (figure 57.7), and as he had predicted, many of them became immune to smallpox.

FIGURE 57.7
The birth of immunology. This famous painting shows Edward Jenner inoculating patients with cowpox in the 1790s and thus protecting them from smallpox.

We now know that smallpox and cowpox are caused by two different viruses with similar surfaces. Jenner's patients who were injected with the cowpox virus mounted a defense that was also effective against a later infection of the smallpox virus. Jenner's procedure of injecting a harmless microbe in order to confer resistance to a dangerous one is called **vaccination.** Modern attempts to develop resistance to malaria, herpes, and other diseases often involve delivering antigens via a harmless vaccinia virus related to cowpox virus.

Many years passed before anyone learned how exposure to an infectious agent can confer resistance to a disease. A key step toward answering this question was taken more than a half-century later by the famous French scientist Louis Pasteur. Pasteur was studying fowl cholera, and he isolated a culture of bacteria from diseased chickens that would produce the disease if injected into healthy birds. Before departing on a two-week vacation, he accidentally left his bacterial culture out on a shelf. When he returned, he injected this old culture into healthy birds and found that it had been weakened; the injected birds became only slightly ill and then recovered. Surprisingly, however, those birds did not get sick when subsequently infected with fresh fowl cholera. They remained healthy even if given massive doses of active fowl cholera bacteria that did produce the disease in control chickens. Clearly, something about the bacteria could elicit immunity as long as the bacteria did not kill the animals first. We now know that molecules protruding from the surfaces of the bacterial cells evoked active immunity in the chickens.

Key Concepts of Specific Immunity

An **antigen** is a molecule that provokes a specific immune response. Antigens are large, complex molecules such as proteins; they are generally foreign to the body, usually present of the surface of pathogens. A large antigen may have several parts, and each stimulate a different specific immune response. In this case, the different parts are known as **antigenic determinant sites,** and each serves as a different antigen. Particular lymphocytes have receptor proteins on their surfaces that recognize an antigen and direct a specific immune response against either the antigen or the cell that carries the antigen.

Lymphocytes called B cells respond to antigens by producing proteins called **antibodies.** Antibody proteins are secreted into the blood and other body fluids and thus provide **humoral immunity.** (The term *humor* here is used in its ancient sense, referring to a body fluid.) Other lymphocytes called T cells do not secrete antibodies but instead directly attack the cells that carry the specific antigens. These cells are thus described as producing **cell-mediated immunity.**

The specific immune responses protect the body in two ways. First, an individual can gain immunity by being exposed to a *pathogen* (disease-causing agent) and perhaps getting the disease. This is *acquired immunity*, such as the resistance to the chicken pox that you acquire after having the disease in childhood. Another term for this process is **active immunity.** Second, an individual can gain immunity by obtaining the antibodies from another individual. This happened to you before you were born, with antibodies made by your mother being transferred to you across the placenta. Immunity gained in this way is called **passive immunity.**

Antigens are molecules, usually foreign, that provoke a specific immune attack. This immune attack may involve secreted proteins called antibodies, or it may invoke a cell-mediated attack.

Cells of the Specific Immune System

The immune defense mechanisms of the body involve the actions of white blood cells, or leukocytes. Leukocytes include neutrophils, eosinophils, basophils, and monocytes, all of which are phagocytic and are involved in the second line of defense, as well as two types of lymphocytes (*T cells* and *B cells*), which are not phagocytic but are critical to the specific immune response (table 57.1), the third line of defense. T cells direct the cell-mediated response, B cells the humoral response.

After their origin in the bone marrow, T cells migrate to the thymus (hence the designation "T"), a gland just above the heart. There they develop the ability to identify microorganisms and viruses by the antigens exposed on their surfaces. Tens of millions of different T cells are made, each specializing in the recognition of one particular antigen. No invader can escape being recognized by at least a few T cells. There are four principal kinds of T cells: inducer T cells oversee the development of T cells in the thymus; helper T cells (often symbolized T_H) initiate the immune response; cytotoxic ("cell-poisoning") T cells (often symbolized T_C) lyse cells that have been infected by viruses; and suppressor T cells terminate the immune response.

Unlike T cells, B cells do not travel to the thymus; they complete their maturation in the bone marrow. (B cells are so named because they were originally characterized in a region of chickens called the bursa.) From the bone marrow, B cells are released to circulate in the blood and lymph. Individual B cells, like T cells, are specialized to recognize particular foreign antigens. When a B cell encounters the antigen to which it is targeted, it begins to divide rapidly, and its progeny differentiate into plasma cells and memory cells. Each plasma cell is a miniature factory producing antibodies that stick like flags to that antigen wherever it occurs in the body, marking any cell bearing the antigen for destruction. The immunity that Pasteur observed resulted from such antibodies and from the continued presence of the B cells that produced them.

The lymphocytes, T cells and B cells, are involved in the specific immune response. T cells develop in the thymus while B cells develop in the bone marrow.

Table 57.1 Cells of the Immune System

Cell Type	Function
Helper T cell	Commander of the immune response; detects infection and sounds the alarm, initiating both T cell and B cell responses
Inducer T cell	Not involved in the immediate response to infection; mediates the maturation of other T cells in the thymus
Cytotoxic T cell	Detects and kills infected body cells; recruited by helper T cells
Suppressor T cell	Dampens the activity of T and B cells, scaling back the defense after the infection has been checked
B cell	Precursor of plasma cell; specialized to recognize specific foreign antigens
Plasma cell	Biochemical factory devoted to the production of antibodies directed against specific foreign antigens
Mast cell	Initiator of the inflammatory response, which aids the arrival of leukocytes at a site of infection; secretes histamine and is important in allergic responses
Monocyte	Precursor of macrophage
Macrophage	The body's first cellular line of defense; also serves as antigen-presenting cell to B and T cells and engulfs antibody-covered cells
Natural killer cell	Recognizes and kills infected body cells; natural killer (NK) cell detects and kills cells infected by a broad range of invaders; killer (K) cell attacks only antibody-coated cells

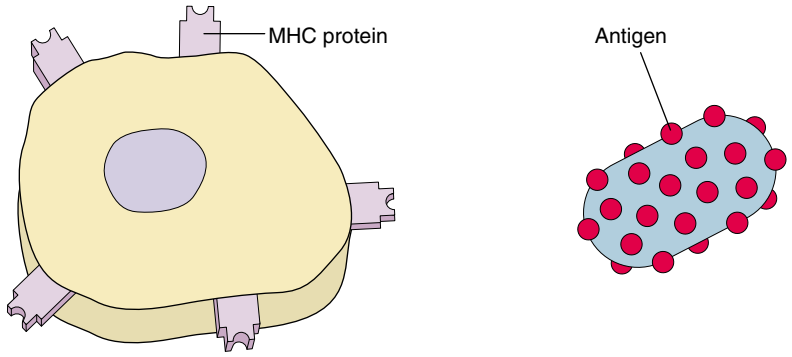
Initiating the Immune Response

To understand how the third line of defense works, imagine you have just come down with the flu. Influenza viruses enter your body in small water droplets inhaled into your respiratory system. If they avoid becoming ensnared in the mucus lining the respiratory membranes (first line of defense), and avoid consumption by macrophages (second line of defense), the viruses infect and kill mucous membrane cells.

At this point macrophages initiate the immune defense. Macrophages inspect the surfaces of all cells they encounter. The surfaces of most vertebrate cells possess glycoproteins produced by a group of genes called the **major histocompatibility complex (MHC).** These glycoproteins are called **MHC proteins** or, specifically in humans, **human leukocyte antigens (HLA).** The genes encoding the MHC proteins are highly polymorphic (have many forms); for example, the human MHC proteins are specified by genes that are the most polymorphic known, with nearly 170 alleles each. Only rarely will two individuals have the same combination of alleles, and the MHC proteins are thus different for each individual, much as fingerprints are. As a result, the MHC proteins on the tissue cells serve as self markers that enable the individual's immune system to distinguish its cells from foreign cells, an ability called **self-versus-nonself recognition.** T cells of the immune system will recognize a cell as self or nonself by the MHC proteins present on the cell surface.

When a foreign particle, such as a virus, infects the body, it is taken in by cells and partially digested. Within the cells, the viral antigens are processed and moved to the surface of the plasma membrane. The cells that perform this function are known as **antigen-presenting cells** (figure 57.8). At the membrane, the processed antigens are complexed with the MHC proteins. This enables T cells to recognize antigens presented to them associated with the MHC proteins.

There are two classes of MHC proteins. MHC-I is present on every nucleated cell of the body. MHC-II, however, is found only on macrophages, B cells, and a subtype of T cells called $CD4^+$ T cells (table 57.2). These three cell types work together in one form of the immune response, and their MHC-II markers permit them to recognize one another. Cytotoxic T lymphocytes, which act to destroy infected cells as previously described, can only interact with antigens presented to them with MHC-I proteins. Helper T lymphocytes, whose functions will soon be described, can interact only with antigens presented with MHC-II proteins. These restrictions result from the presence of coreceptors, which are proteins associated with the T cell receptors. The coreceptor known as CD8 is associated with the cytotoxic T cell receptor (these cells can therefore be indicated as $CD8^+$). The CD8 coreceptor can interact only with the MHC-I proteins of an infected cell. The coreceptor known as CD4 is associated with the helper T cell receptor (these cells can thus be indicated as $CD4^+$) and interacts only with the MHC-II proteins of another lymphocyte (figure 57.9).



(a) **Body cell**

(b) **Foreign microbe**

(c) **Antigen-presenting cell**

FIGURE 57.8
Antigens are presented on MHC proteins. (*a*) Cells of the body have MHC proteins on their surfaces that identify them as "self" cells. Immune system cells do not attack these cells. (*b*) Foreign cells or microbes have antigens on their surfaces. B cells are able to bind directly to free antigens in the body and initiate an attack on a foreign invaded. (*c*) T cells can bind to antigens only after the antigens are processed and complexed with MHC proteins on the surface of an antigen-presenting cell.

Table 57.2 Key Cell Surface Proteins of the Immune System

	Immune Receptors		MHC Proteins	
Cell Type	**T Receptor**	**B Receptor**	**MHC-I**	**MHC-II**
B cell	–	+	+	+
$CD4^+$ T cell	+	–	+	+
$CD8^+$ T cell	+	–	+	–
Macrophage	–	–	+	+

Note: $CD4^+$ T cells include inducer T cells and helper T cells; $CD8^+$ T cells include cytotoxic T cells and suppressor T cells. + means present; – means absent.

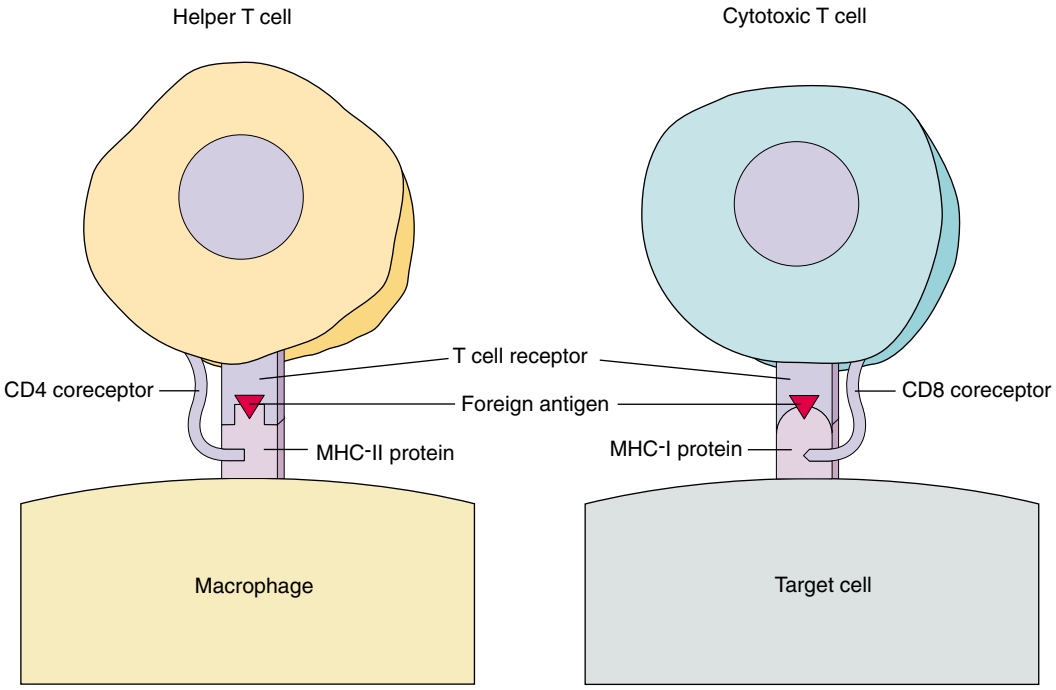


FIGURE 57.9
T cells bind to foreign antigens in conjunction with MHC proteins. The CD4 coreceptor on helper T cells requires that these cells interact with class-2 MHC (or MHC-II) proteins. The CD8 coreceptor on cytotoxic T cells requires that these cells interact only with cells bearing class-1 MHC (or MHC-I) proteins.

Macrophages encounter foreign particles in the body, partially digest the virus particles, and present the foreign antigens in a complex with the MHC-II proteins on its membrane. This combination of MHC-II proteins and foreign antigens is required for interaction with the receptors on the surface of helper T cells. At the same time, macrophages that encounter antigens or antigen-presenting cells release a protein called **interleukin-1** that acts as a chemical alarm signal (discussed in the next section). Helper T cells respond to interleukin-1 by simultaneously initiating two parallel lines of immune system defense: the cell-mediated response carried out by T cells and the humoral response carried out by B cells.

Antigen-presenting cells must present foreign antigens together with MHC-II proteins in order to activate helper T cells, which have the CD4 coreceptor. Cytotoxic T cells use the CD8 coreceptor and must interact with foreign antigens presented on MHC-I proteins.

57.3 T cells organize attacks against invading microbes.

T cells: The Cell-Mediated Immune Response

The cell-mediated immune response, carried out by T cells, protects the body from virus infection and cancer, killing abnormal or virus-infected body cells.

Once a helper T cell that initiates this response is presented with foreign antigen together with MHC proteins by a macrophage or other antigen-presenting cell, a complex series of steps is initiated. An integral part of this process is the secretion of autocrine regulatory molecules known generally as **cytokines,** or more specifically as **lymphokines** if they are secreted by lymphocytes.

When a cytokine is first discovered, it is named according to its biological activity (such as *B cell–stimulating factor*). However, because each cytokine has many different actions, such names can be misleading. Scientists have thus agreed to use the name **interleukin,** followed by a number, to indicate a cytokine whose amino acid sequence has been determined. *Interleukin-1*, for example, is secreted by macrophages and can activate the T cell system. B cell–stimulating factor, now called interleukin-4, is secreted by T cells and is required for the proliferation and clone development of B cells. *Interleukin-2* is released by helper T cells and, among its effects, is required for the activation of cytotoxic T lymphocytes. We will consider the actions of the cytokines as we describe the development of the T cell immune response.

Cell Interactions in the T Cell Response

When macrophages process the foreign antigens, they secrete **interleukin-1,** which stimulates cell division and proliferation of T cells (figure 57.10). Once the helper T cells have been activated by the antigens presented to them by

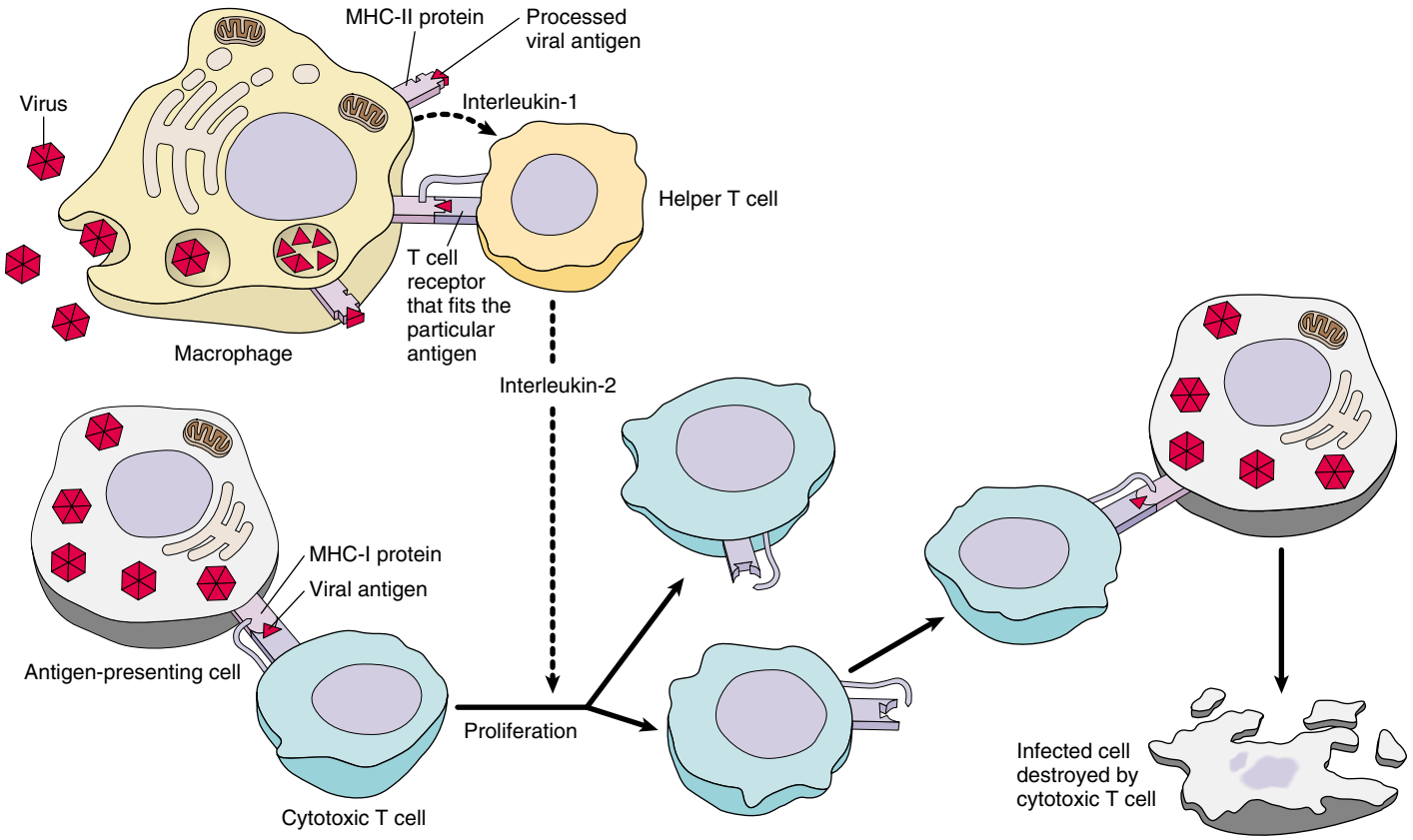
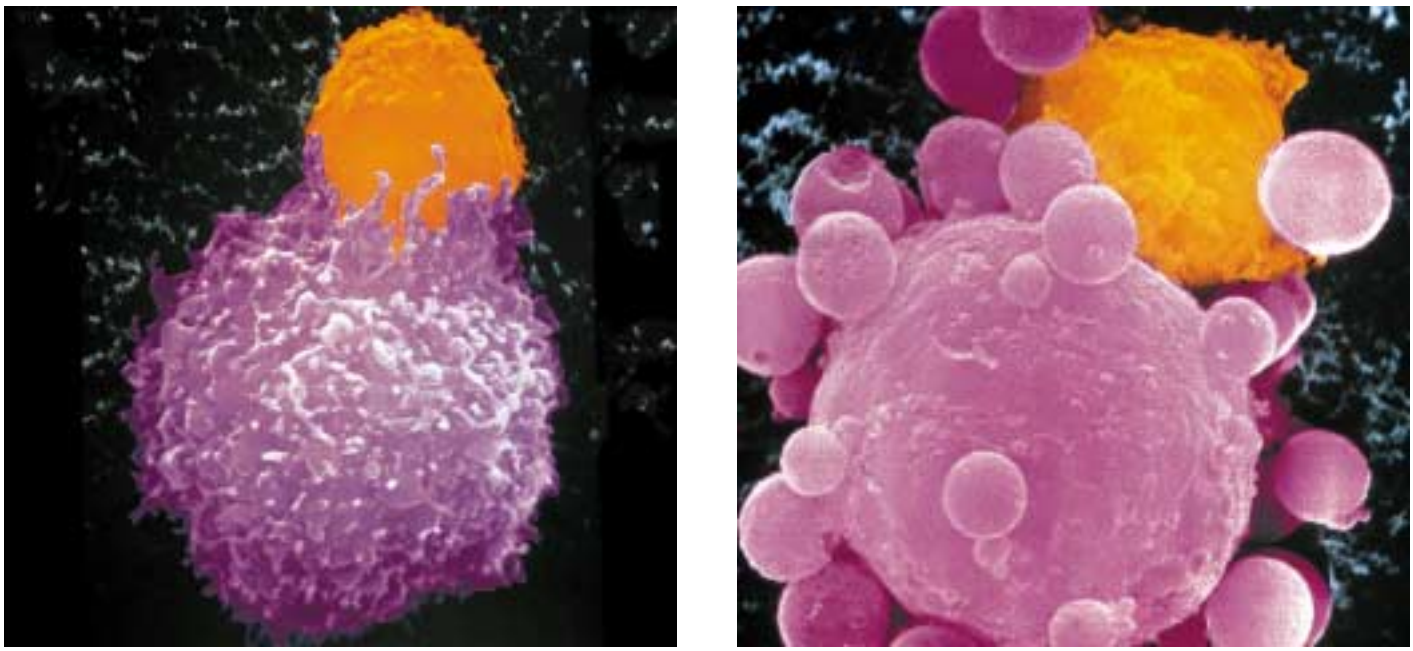


FIGURE 57.10
The T cell immune defense. After a macrophage has processed an antigen, it releases interleukin-1, signaling helper T cells to bind to the antigen-MHC protein complex. This triggers the helper T cell to release interleukin-2, which stimulates the multiplication of cytotoxic T cells. In addition, proliferation of cytotoxic T cells is stimulated when a T cell with a receptor that fits the antigen displayed by an antigen-presenting cell binds to the antigen-MHC protein complex. Body cells that have been infected by the antigen are destroyed by the cytotoxic T cells. As the infection subsides, suppressor T cells "turn off" the immune response.



(a) (b)

FIGURE 57.11
Cytotoxic T cells destroy cancer cells. (*a*) The cytotoxic T cell *(orange)* comes into contact with a cancer cell *(pink)*. (*b*) The T cell recognizes that the cancer cell is "nonself" and causes the destruction of the cancer.

the macrophages, they secrete the cytokines known as macrophage colony-stimulating factor and gamma interferon, which promote the activity of macrophages. In addition, the helper T cells secrete **interleukin-2,** which stimulates the proliferation of cytotoxic T cells that are specific for the antigen. (Interleukin-2 also stimulates B cells, as we will see in the next section.) Cytotoxic T cells can destroy infected cells only if those cells display the foreign antigen together with their MHC-I proteins (see figure 57.10).

T Cells in Transplant Rejection and Surveillance against Cancer

Cytotoxic T cells will also attack any foreign version of MHC-I as if it signaled a virus-infected cell. Therefore, even though vertebrates did not evolve the immune system as a defense against tissue transplants, their immune systems will attack transplanted tissue and cause graft rejection. Recall that the MHC proteins are polymorphic, but because of their genetic basis, the closer that two individuals are related, the less variance in their MHC proteins and the more likely they will tolerate each other's tissues—this is why relatives are often sought for kidney transplants. The drug cyclosporin inhibits graft rejection by inactivating cytotoxic T cells.

As tumors develop, they reveal surface antigens that can stimulate the immune destruction of the tumor cells. Tumor antigens activate the immune system, initiating an attack primarily by cytotoxic T cells (figure 57.11) and natural killer cells. The concept of **immunological surveillance** against cancer was introduced in the early 1970s to describe the proposed role of the immune system in fighting cancer.

The production of human interferons by genetically engineered bacteria has made large amounts of these substances available for the experimental treatment of cancer. Thus far, interferons have proven to be a useful addition to the treatment of particular forms of cancer, including some types of lymphomas, renal carcinoma, melanoma, Kaposi's sarcoma, and breast cancer.

Interleukin-2 (IL-2), which activates both cytotoxic T cells and B cells, is now also available for therapeutic use through genetic-engineering techniques. Particular lymphocytes from cancer patients have been removed, treated with IL-2, and given back to the patients together with IL-2 and gamma interferon. Scientists are also attempting to identify specific antigens and their genes that may become uniquely expressed in cancer cells, in an effort to help the immune system to better target cancer cells for destruction.

Helper T cells are only activated when a foreign antigen is presented together with MHC antigens by a macrophage or other antigen-presenting cells. The helper T cells are also stimulated by interleukin-1 secreted by the macrophages, and, when activated, secrete a number of lymphokines. Interleukin-2, secreted by helper T cells, activates both cytotoxic T cells and B cells. Cytotoxic T cells destroy infected cells, transplanted cells, and cancer cells by cell-mediated attack.

B Cells: The Humoral Response

B cells also respond to helper T cells activated by interleukin-1. Like cytotoxic T cells, B cells have receptor proteins on their surface, one type of receptor for each type of B cell. B cells recognize invading microbes much as cytotoxic T cells recognize infected cells, but unlike cytotoxic T cells, they do not go on the attack themselves. Rather, they mark the pathogen for destruction by mechanisms that have no "ID check" system of their own. Early in the immune response, the markers placed by B cells alert complement proteins to attack the cells carrying them. Later in the immune response, the markers placed by B cells activate macrophages and natural killer cells.

The way B cells do their marking is simple and foolproof. Unlike the receptors on T cells, which bind only to antigen-MHC protein complexes on antigen-presenting cells, B cell receptors can bind to free, unprocessed antigens. When a B cell encounters an antigen, antigen particles will enter the B cell by endocytosis and get processed. Helper T cells that are able to recognize the specific antigen will bind to the antigen-MHC protein complex on the B cell and release interleukin-2, which stimulates the B cell to divide. In addition, free, unprocessed antigens stick to antibodies on the B cell surface. This antigen exposure triggers even more B cell proliferation. B cells divide to produce long-lived memory B cells and plasma cells that serve as short-lived antibody factories (figure 57.12). The antibodies are released into the blood plasma, lymph, and other extracellular fluids. Figure 57.13 summarizes the roles of helper T cells, which are essential in both the cell-mediated and humoral immune responses.

Antibodies are proteins in a class called **immunoglobulins** (abbreviated Ig), which is divided into subclasses based on the structures and functions of the

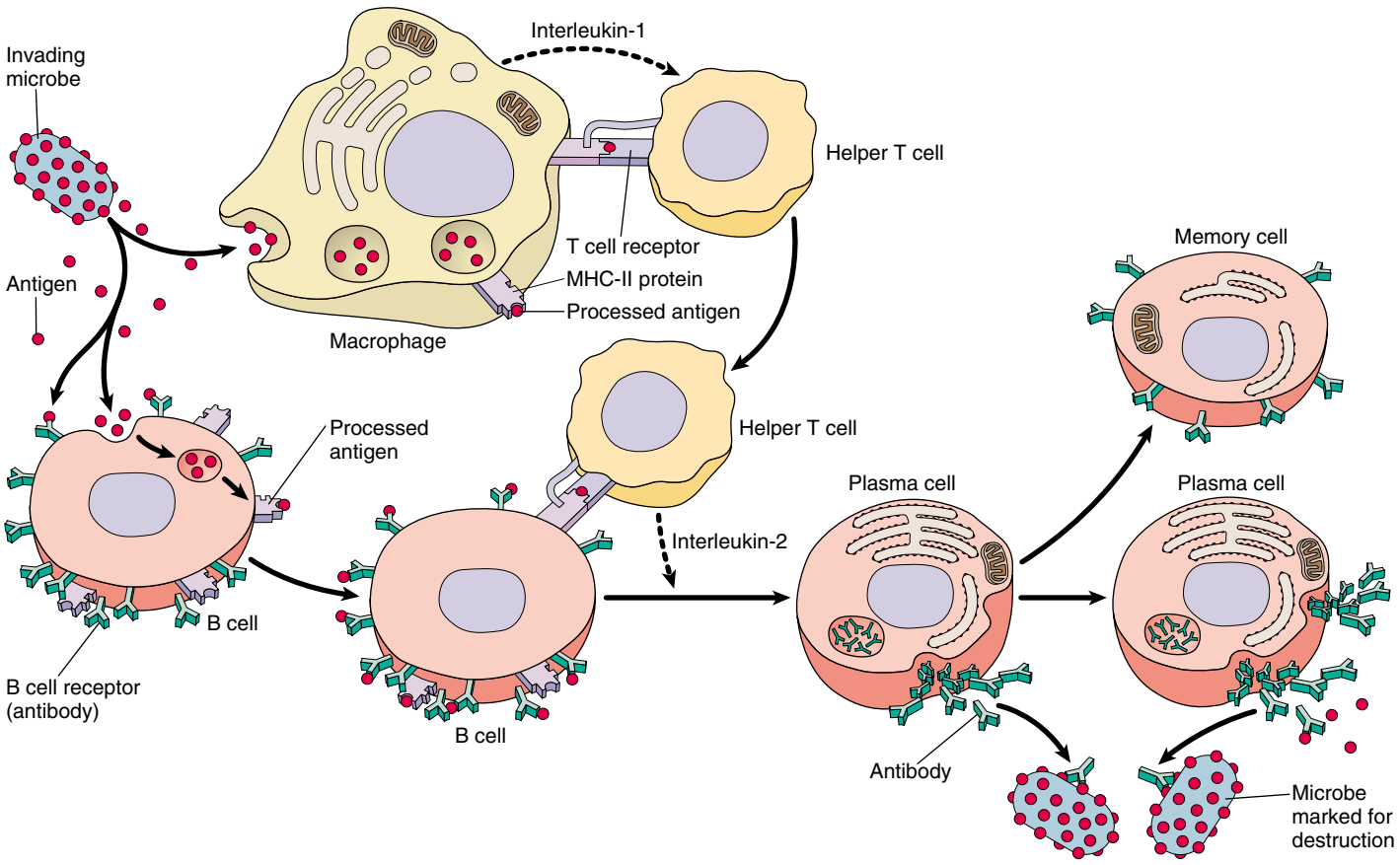


FIGURE 57.12
The B cell immune defense. Invading particles are bound by B cells, which interact with helper T cells and are activated to divide. The multiplying B cells produce either memory B cells or plasma cells that secrete antibodies which bind to invading microbes and tag them for destruction by macrophages.

antibodies. The different immunoglobulin subclasses are as follows:

1. **IgM.** This is the first type of antibody to be secreted during the primary response and they serve as receptors on the lymphocyte surface. These antibodies also promote agglutination reactions (causing antigen-containing particles to stick together, or agglutinate).
2. **IgG.** This is the major form of antibody in the blood plasma and is secreted in a secondary response.
3. **IgD.** These antibodies serve as receptors for antigens on the B cell surface. Their other functions are unknown.
4. **IgA.** This is the major form of antibody in external secretions, such as saliva and mother's milk.
5. **IgE.** This form of antibodies promotes the release of histamine and other agents that aid in attacking a pathogen. Unfortunately, they sometimes trigger a full-blown response when a harmless antigen enters the body producing allergic symptoms, such as those of hay fever.

Each B cell has on its surface about 100,000 IgM or IgD receptors. Unlike the receptors on T cells, which bind only to antigens presented by certain cells, B receptors can bind to *free* antigens. This provokes a primary response in which antibodies of the IgM class are secreted, and also stimulates cell division and clonal expansion. Upon subsequent exposure, the plasma cells secrete large amounts of antibodies that are generally of the IgG class. Although plasma cells live only a few days, they produce a vast number of antibodies. In fact, antibodies constitute about 20% by weight of the total protein in blood plasma. Production of IgG antibodies peaks after about three weeks (figure 57.14).

When IgM (and to a lesser extent IgG) antibodies bind to antigens on a cell, they cause the aggregation of complement proteins. As we mentioned earlier, these proteins form a pore that pierces the plasma membrane of the infected cell (see figure 57.5), allowing water to enter and causing the cell to burst. In contrast, when IgG antibodies bind to antigens on a cell, they serve as markers that stimulate phagocytosis by macrophages. Because certain complement proteins attract phagocytic cells, activation of complement is generally accompanied by increased phagocytosis. Notice that antibodies don't kill invading pathogens directly; rather, they cause destruction of the pathogens by activating the complement system and by targeting the pathogen for attack by phagocytic cells.

In the humoral immune response, B cells recognize antigens and divide to produce plasma cells, producing large numbers of circulating antibodies directed against those antigens. IgM antibodies are produced first, and they activate the complement system. Thereafter, IgG antibodies are produced and promote phagocytosis.

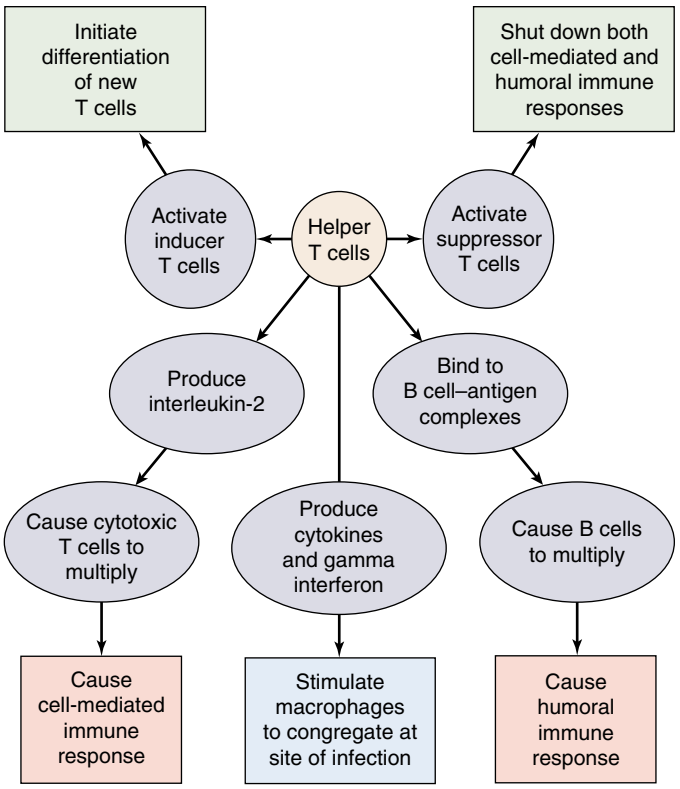


FIGURE 57.13
The many roles of helper T cells. Helper T cells, through their secretion of lymphokines and interaction with other cells of the immune system, participate in every aspect of the immune response.

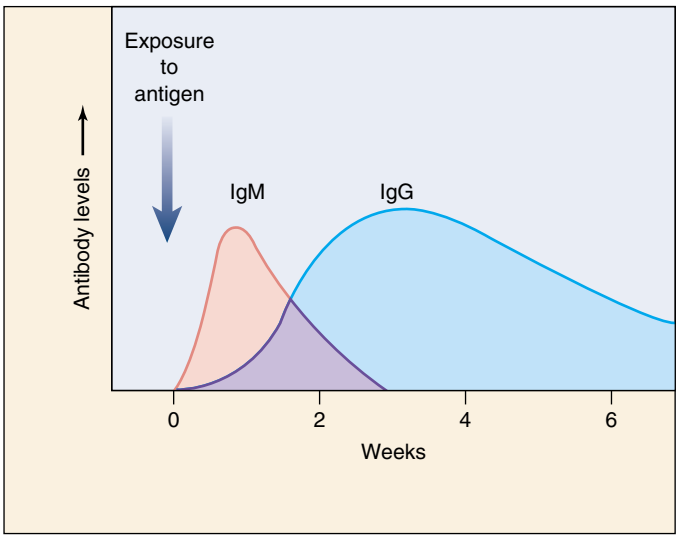


FIGURE 57.14
IgM and IgG antibodies. The first antibodies produced in the humoral immune response are IgM antibodies, which are very effective at activating the complement system. This initial wave of antibody production peaks after about one week and is followed by a far more extended production of IgG antibodies.

Antibodies

Structure of Antibodies

Each antibody molecule consists of two identical short polypeptides, called **light chains,** and two identical long polypeptides, called **heavy chains** (figure 57.15). The four chains in an antibody molecule are held together by disulfide (—S—S—) bonds, forming a Y-shaped molecule (figure 57.16).

Comparing the amino acid sequences of different antibody molecules shows that the specificity of antibodies for antigens resides in the two arms of the Y, which have a variable amino acid sequence. The amino acid sequence of the polypeptides in the stem of the Y is constant within a given class of immunoglobulins. Most of the sequence variation between antibodies of different specificity is found in the variable region of each arm. Here, a cleft forms that acts as the binding site for the antigen. Both arms always have exactly the same cleft and so bind to the same antigen.

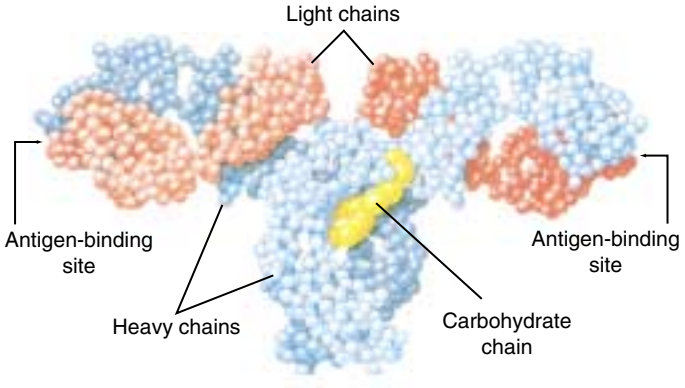


FIGURE 57.15
The structure of an antibody molecule. In this molecular model of an antibody molecule, each amino acid is represented by a small sphere. The heavy chains are colored blue; the light chains are red. The four chains wind about one another to form a Y shape, with two identical antigen-binding sites at the arms of the Y and a stem region that directs the antibody to a particular portion of the immune response.

Antibodies with the same variable segments have identical clefts and therefore recognize the same antigen, but they may differ in the stem portions of the antibody molecule. The stem is formed by the so-called "constant" regions of the heavy chains. In mammals there are five different classes of heavy chain that form five classes of immunoglobulins: IgM, IgG, IgA, IgD, and IgE. We have already discussed the roles of IgM and IgG antibodies in the humoral immune response.

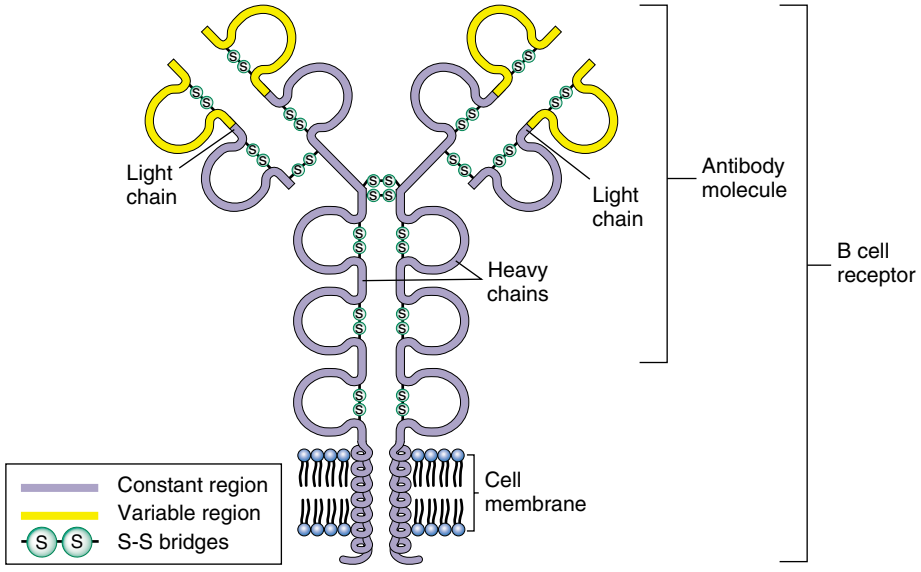


FIGURE 57.16
Structure of an antibody as a B cell receptor. The receptor molecules are characterized by domains of about 100 amino acids (represented as loops) joined by —S—S— covalent bonds. Each receptor has a constant region *(purple)* and a variable region *(yellow)*. The receptor binds to antigens at the ends of its two variable regions.

IgE antibodies bind to **mast cells.** The heavy-chain stems of the IgE antibody molecules insert into receptors on the mast cell plasma membrane, in effect creating B receptors on the mast cell surface. When these cells encounter the specific antigen recognized by the arms of the antibody, they initiate the inflammatory response by releasing histamine. The resulting vasodilation and increased capillary permeability enable lymphocytes, macrophages, and complement proteins to more easily reach the site where the mast cell encountered the antigen. The IgE antibodies are involved in allergic reactions and will be discussed in more detail in a later section.

IgA antibodies are present in secretions such as milk, mucus, and saliva. In milk, these antibodies are thought to provide immune protection to nursing infants, whose own immune systems are not yet fully developed.

Antibody Diversity

The vertebrate immune system is capable of recognizing as foreign millions nonself molecule presented to it. Although vertebrate chromosomes contain only a few hundred receptor-encoding genes, it is estimated that human B cells can make between 10^6 and 10^9 different antibody molecules. How do vertebrates generate millions of different antigen receptors when their chromosomes con-

tain only a few hundred copies of the genes encoding those receptors?

The answer to this question is that in the B cell the millions of immune receptor genes do not have to be inherited at conception because they do not exist as single sequences of nucleotides. Rather, they are assembled by stitching together three or four DNA segments that code for different parts of the receptor molecule. When an antibody is assembled, the different sequences of DNA are brought together to form a composite gene (figure 57.17). This process is called **somatic rearrangement.** For example, combining DNA in different ways can produce 16,000 different heavy chains and about 1200 different light chains (in mouse antibodies).

Two other processes generate even more sequences. First, the DNA segments are often joined together with one or two nucleotides off-register, shifting the reading frame during gene transcription and so generating a totally different sequence of amino acids in the protein. Second, random mistakes occur during successive DNA replications as the lymphocytes divide during clonal expansion. Both mutational processes produce changes in amino acid sequences, a phenomenon known as **somatic mutation** because it takes place in a somatic cell, a B cell rather than in a gamete.

Because a B cell may end up with any heavy-chain gene and any light-chain gene during its maturation, the total number of different antibodies possible is staggering: 16,000 heavy-chain combinations × 1200 light-chain combinations = 19 million different possible antibodies. If one also takes into account the changes induced by somatic mutation, the total can exceed 200 million! It should be understood that, although this discussion has centered on B cells and their receptors, the receptors on T cells are as diverse as those on B cells because they also are subject to similar somatic rearrangements and mutations.

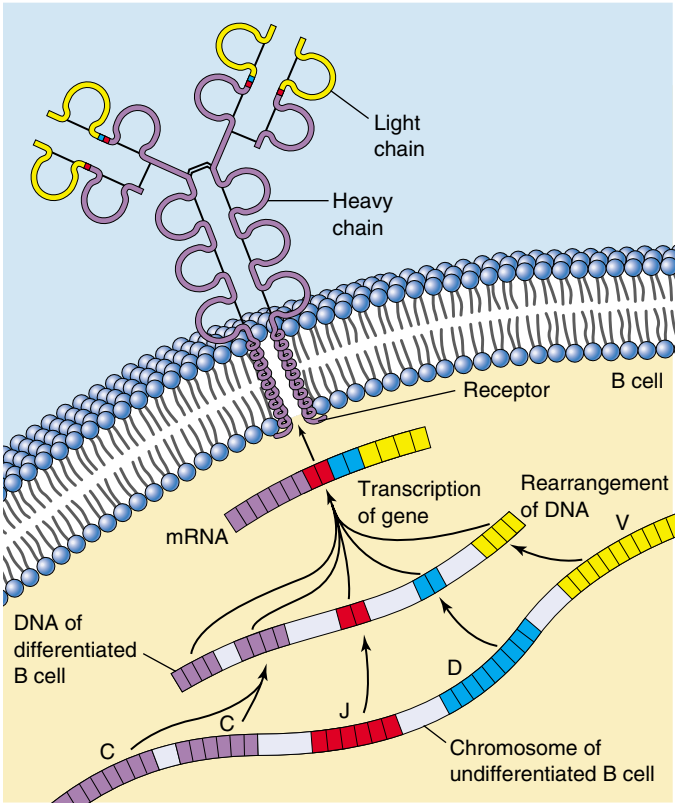


FIGURE 57.17
The lymphocyte receptor molecule is produced by a composite gene. Different regions of the DNA code for different regions of the receptor structure (*C*, constant regions; *J*, joining regions; *D*, diversity regions; and *V*, variable regions) and are brought together to make a composite gene that codes for the receptor. Through different somatic rearrangements of these DNA segments, an enormous number of different receptor molecules can be produced.

Immunological Tolerance

A mature animal's immune system normally does not respond to that animal's own tissue. This acceptance of self cells is known as **immunological tolerance.** The immune system of an embryo, on the other hand, is able to respond to both foreign and self molecules, but it loses the ability to respond to self molecules as its development proceeds. Indeed, if foreign tissue is introduced into an embryo before its immune system has developed, the mature animal that results will not recognize that tissue as foreign and will accept grafts of similar tissue without rejection.

There are two general mechanisms for immunological tolerance: clonal deletion and clonal suppression. During the normal maturation of hemopoietic stem cells in an embryo, fetus, or newborn, most lymphocyte clones that have receptors for self antigens are either eliminated (clonal deletion) or suppressed (clonal suppression). The cells "learn" to identify self antigens because the antigens are encountered very frequently. If a receptor is activated frequently, it is assumed that the cell is recognizing a self antigen and the lymphocytes are eliminated or suppressed. Thus, the only clones that survive this phase of development are those that are directed against foreign rather than self molecules.

Immunological tolerance sometimes breaks down, causing either B cells or T cells (or both) to recognize their own tissue antigens. This loss of immune tolerance results in autoimmune disease. Myasthenia gravis, for example, is an autoimmune disease in which individuals produce antibodies directed against acetylcholine receptors on their own skeletal muscle cells, causing paralysis. Autoimmunity will be discussed in more detail later in this chapter.

An antibody molecule is composed of constant and variable regions. The variable regions recognize a specific antigen because they possess clefts into which the antigen can fit. Lymphocyte receptors are encoded by genes that are assembled by somatic rearrangement and mutation of the DNA.

Active Immunity through Clonal Selection

As we discussed earlier, B and T cells have receptors on their cell surfaces that recognize and bind to specific antigens. When a particular antigen enters the body, it must, by chance, encounter the specific lymphocyte with the appropriate receptor in order to provoke an immune response. The first time a pathogen invades the body, there are only a few B or T cells that may have the receptors that can recognize the invader's antigens. Binding of the antigen to its receptor on the lymphocyte surface, however, stimulates cell division and produces a *clone* (a population of genetically identical cells). This process is known as **clonal selection.** In this first encounter, there are only a few cells that can mount an immune response and the response is relatively weak. This is called a **primary immune response** (figure 57.18).

If the primary immune response involves B cells, some become plasma cells that secrete antibodies, and some become memory cells. Because a clone of memory cells specific for that antigen develops after the primary response, the immune response to a second infection by the same pathogen is swifter and stronger. The next time the body is invaded by the same pathogen, the immune system is ready. As a result of the first infection, there is now a large clone of lymphocytes that can recognize that pathogen (figure 57.19). This more effective response, elicited by subsequent exposures to an antigen, is called a **secondary immune response.**

Memory cells can survive for several decades, which is why people rarely contract chicken pox a second time after they have had it once. Memory cells are also the reason that vaccinations are effective. The vaccine triggers the primary response so that if the actual pathogen is encountered later, the large and rapid secondary response occurs and stops the infection before it can start. The viruses causing childhood diseases have surface antigens that change little from year to year, so the same antibody is effective for decades.

Figure 57.20 summarizes how the cellular and humoral lines of defense work together to produce the body's specific immune response.

Active immunity is produced by clonal selection and expansion. This occurs because interaction of an antigen with its receptor on the lymphocyte surface stimulates cell division, so that more lymphocytes are available to combat subsequent exposures to the same antigen.

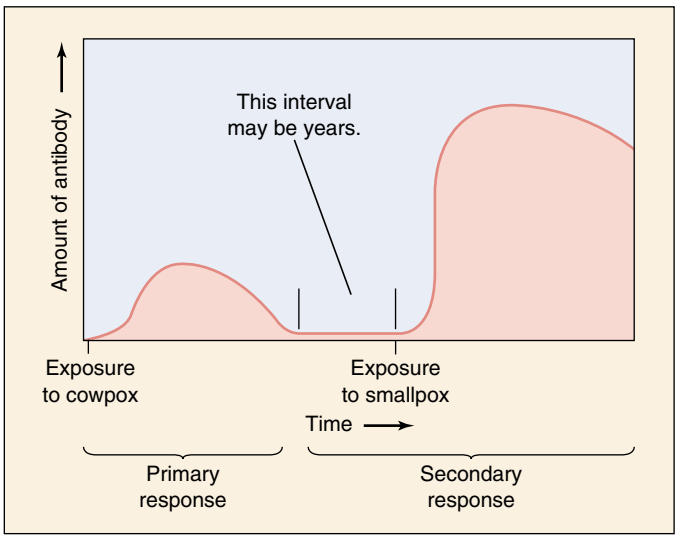


FIGURE 57.18
The development of active immunity. Immunity to smallpox in Jenner's patients occurred because their inoculation with cowpox stimulated the development of lymphocyte clones with receptors that could bind not only to cowpox but also to smallpox antigens. As a result of clonal selection, a second exposure, this time to smallpox, stimulates the immune system to produce large amounts of the antibody more rapidly than before.

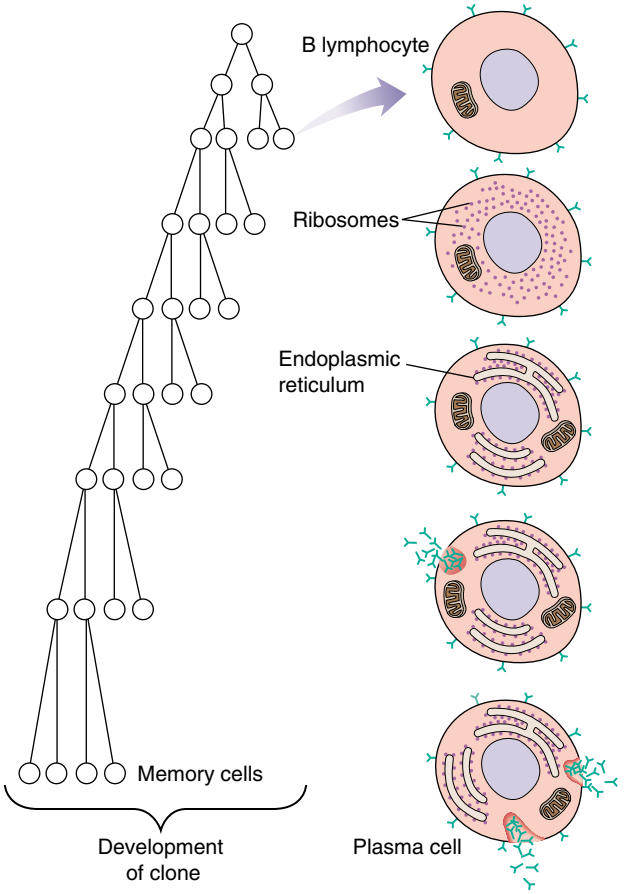


FIGURE 57.19
The clonal selection theory of active immunity. In response to interaction with an antigen that binds specifically to its surface receptors, a B cell divides many times to produce a clone of B cells. Some of these become plasma cells that secrete antibodies for the primary response, while others become memory cells that await subsequent exposures to the antigen for the mounting of a secondary immune response.

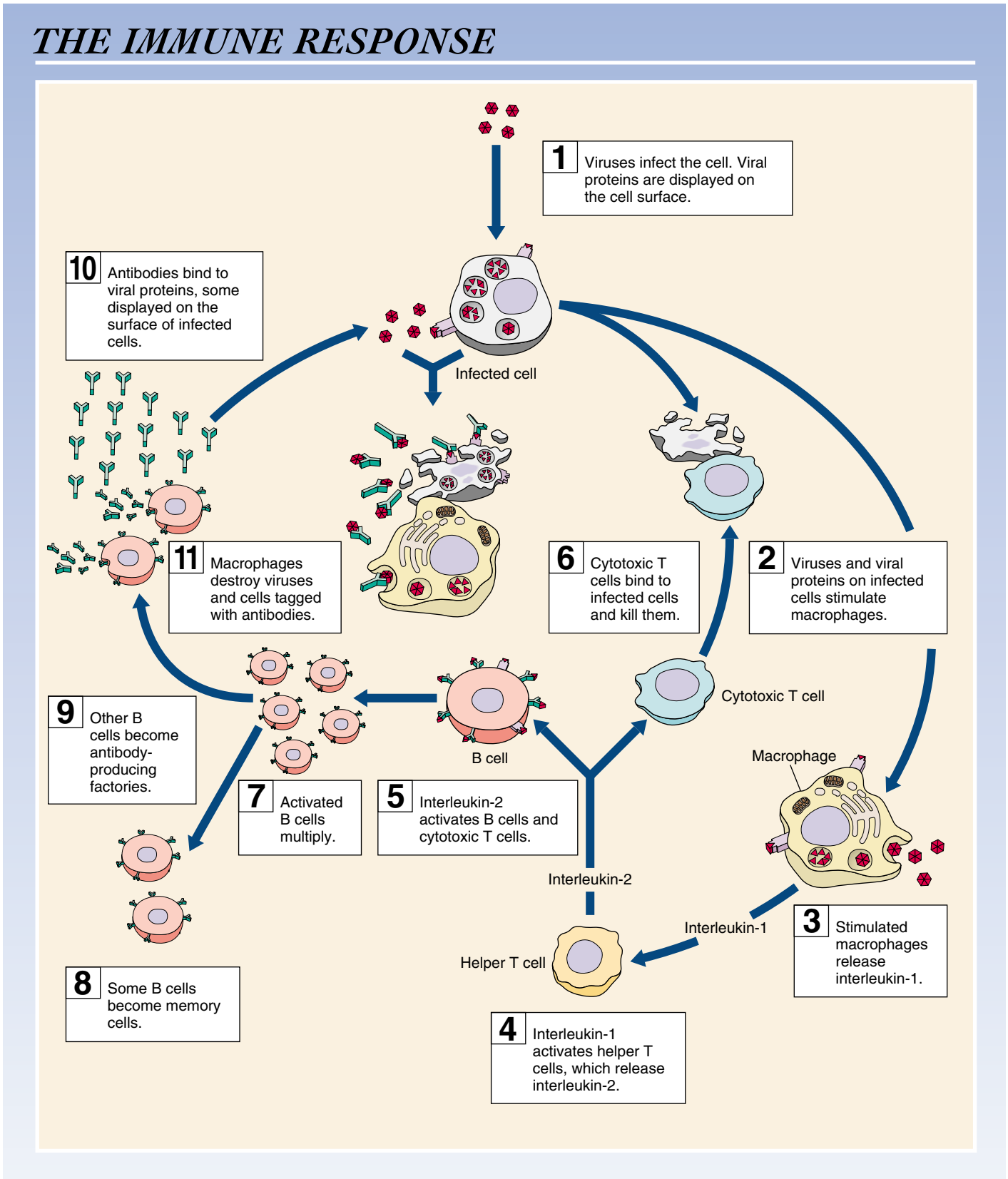


FIGURE 57.20
Overview of the specific immune response.

Antibodies in Medical Diagnosis

Blood Typing

The blood type denotes the class of antigens found on the red blood cell surface. Red blood cell antigens are clinically important because their types must be matched between donors and recipients for blood transfusions. There are several groups of red blood cell antigens, but the major group is known as the **ABO system.** In terms of the antigens present on the red blood cell surface, a person may be *type A* (with only A antigens), *type B* (with only B antigens), *type AB* (with both A and B antigens), or *type O* (with neither A nor B antigens).

The immune system is tolerant to its own red blood cell antigens. A person who is type A, for example, does not produce anti-A antibodies. Surprisingly, however, people with type A blood do make antibodies against the B antigen, and conversely, people with blood type B make antibodies against the A antigen. This is believed to result from the fact that antibodies made in response to some common bacteria cross-react with the A or B antigens. A person who is type A, therefore, acquires antibodies that can react with B antigens by exposure to these bacteria but does not develop antibodies that can react with A antigens. People who are type AB develop tolerance to both antigens and thus do not produce either anti-A or anti-B antibodies. Those who are type O, in contrast, do not develop tolerance to either antigen and, therefore, have both anti-A and anti-B antibodies in their plasma.

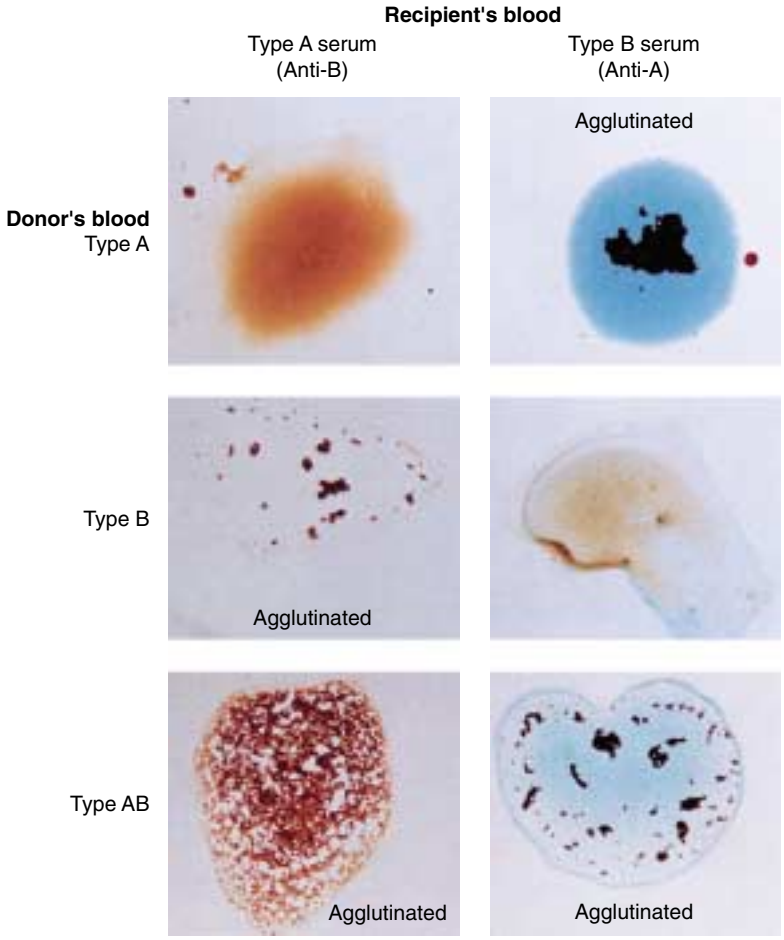


FIGURE 57.21
Blood typing. Agglutination of the red blood cells is seen when blood types are mixed with sera containing antibodies against the ABO antigens. Note that no agglutination would be seen if type O blood (not shown) were used.

If type A blood is mixed on a glass slide with serum from a person with type B blood, the anti-A antibodies in the serum will cause the type A red blood cells to clump together, or **agglutinate** (figure 57.21). These tests allow the blood types to be matched prior to transfusions, so that agglutination will not occur in the blood vessels, where it could lead to inflammation and organ damage.

Rh Factor. Another group of antigens found in most red blood cells is the *Rh factor* (Rh stands for rhesus monkey, in which these antigens were first discovered). People who have these antigens are said to be **Rh-positive,** whereas those who do not are **Rh-negative.** There are fewer Rh-negative people because this condition is recessive to Rh-positive. The Rh factor is of particular significance when Rh-negative mothers give birth to Rh-positive babies.

Because the fetal and maternal blood are normally kept separate across the placenta (see chapter 60), the Rh-negative mother is not usually exposed to the Rh antigen of the fetus during the pregnancy. At the time of birth, however, a variable degree of exposure may occur, and the mother's immune system may become sensitized and produce antibodies against the Rh antigen. If the woman does produce antibodies against the Rh factor, these antibodies can cross the placenta in subsequent pregnancies and cause hemolysis of the Rh-positive red blood cells of the fetus. The baby is therefore born anemic, with a condition called *erythroblastosis fetalis*, or *hemolytic disease of the newborn*.

Erythroblastosis fetalis can be prevented by injecting the Rh-negative mother with an antibody preparation against the Rh factor within 72 hours after the birth of each Rh-positive baby. This is a type of passive immunization in which the injected antibodies inactivate the Rh antigens and thus prevent the mother from becoming actively immunized to them.

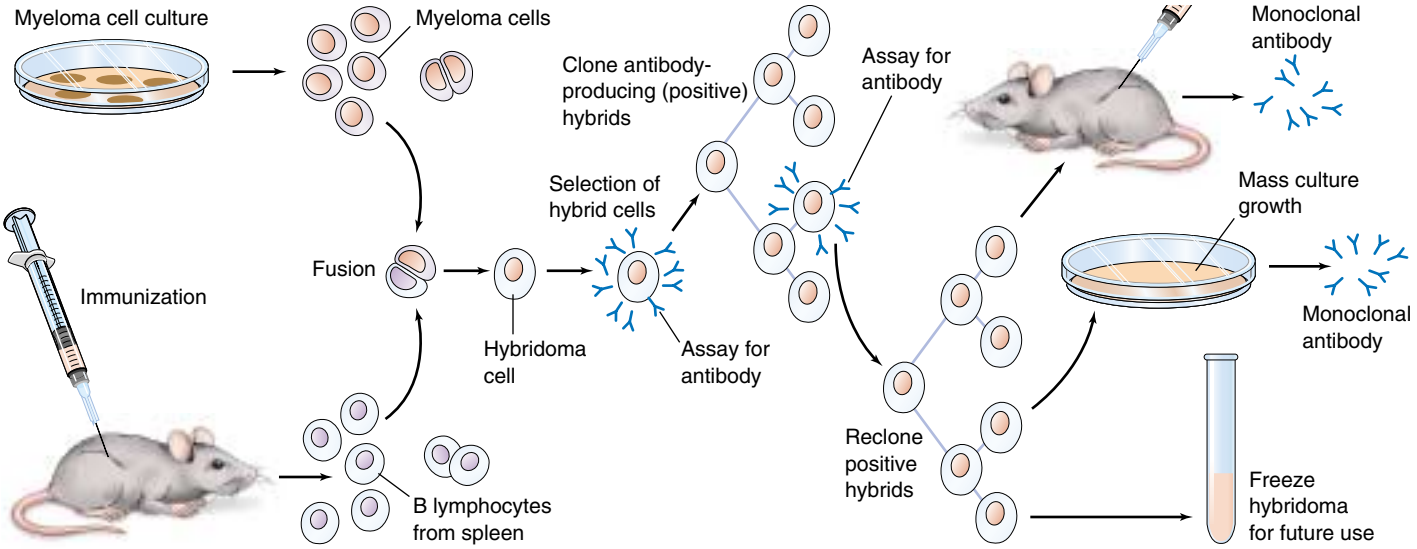


FIGURE 57.22
The production of monoclonal antibodies. These antibodies are produced by cells that arise from successive divisions of a single B cell, and hence all of the antibodies target a single antigenic determinant site. Such antibodies are used for a variety of medical applications, including pregnancy testing.

Monoclonal Antibodies

Antibodies are commercially prepared for use in medical diagnosis and research. In the past, antibodies were obtained by chemically purifying a specific antigen and then injecting this antigen into animals. However, because an antigen typically has many different antigenic determinant sites, the antibodies obtained by this method were *polyclonal*; they stimulated the development of different B-cell clones with different specificities. This decreased their sensitivity to a particular antigenic site and resulted in some degree of cross-reaction with closely related antigen molecules.

Monoclonal antibodies, by contrast, exhibit specificity for one antigenic determinant only. In the preparation of monoclonal antibodies, an animal (frequently, a mouse) is injected with an antigen and subsequently killed. B lymphocytes are then obtained from the animal's spleen and placed in thousands of different in vitro incubation vessels. These cells soon die, however, unless they are hybridized with cancerous multiple myeloma cells. The fusion of a B lymphocyte with a cancerous cell produces a hybrid that undergoes cell division and produces a clone called a *hybridoma*. Each hybridoma secretes large amounts of identical, monoclonal antibodies. From among the thousands of hybridomas produced in this way, the one that produces the desired antibody is cultured for large-scale production, and the rest are discarded (figure 57.22).

The availability of large quantities of pure monoclonal antibodies has resulted in the development of much more sensitive clinical laboratory tests. Modern pregnancy tests, for example, use particles (latex rubber or red blood cells) that are covered with monoclonal antibodies produced against a pregnancy hormone (abbreviated hCG—see chapter 59) as the antigen. When these particles are mixed with a sample that contains this hormone antigen from a pregnant woman, the antigen-antibody reaction causes a visible agglutination of the particles (figure 57.23).

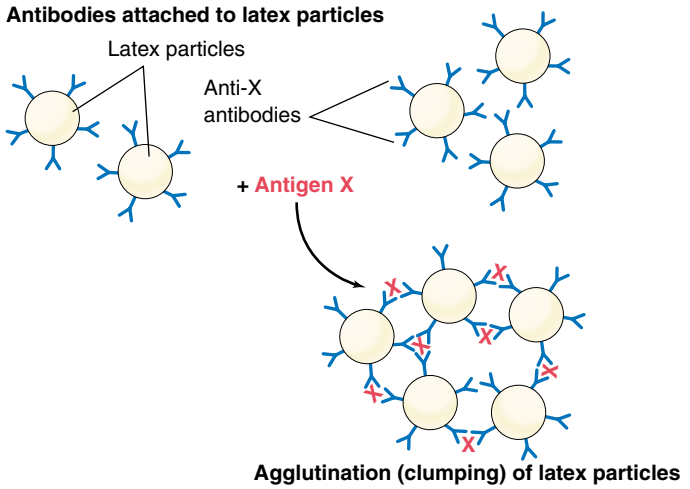


FIGURE 57.23
Using monoclonal antibodies to detect an antigen. In many clinical tests (such as pregnancy testing), the monoclonal antibodies are bound to particles of latex, which agglutinate in the presence of the antigen.

Agglutination occurs because different antibodies exist for the ABO and Rh factor antigens on the surface of red blood cells. Monoclonal antibodies are commercially produced antibodies that react against one specific antigen.

57.5 All animals exhibit nonspecific immune response but specific ones evolved in vertebrates.

Evolution of the Immune System

All organisms possess mechanisms to protect themselves from the onslaught of smaller organisms and viruses. Bacteria defend against viral invasion by means of *restriction endonucleases*, enzymes that degrade any foreign DNA lacking the specific pattern of DNA methylation characteristic of that bacterium. Multicellular organisms face a more difficult problem in defense because their bodies often take up whole viruses, bacteria, or fungi instead of naked DNA.

Invertebrates

Invertebrate animals solve this problem by marking the surfaces of their cells with proteins that serve as "self" labels. Special amoeboid cells in the invertebrate attack and engulf any invading cells that lack such labels. By looking for the absence of specific markers, invertebrates employ a *negative* test to recognize foreign cells and viruses. This method provides invertebrates with a very effective surveillance system, although it has one great weakness: any microorganism or virus with a surface protein resembling the invertebrate self marker will not be recognized as foreign. An invertebrate has no defense against such a "copycat" invader.

In 1882, Russian zoologist Elie Metchnikoff became the first to recognize that invertebrate animals possess immune defenses. On a beach in Sicily, he collected the tiny transparent larva of a common starfish. Carefully he pierced it with a rose thorn. When he looked at the larva the next morning, he saw a host of tiny cells covering the surface of the thorn as if trying to engulf it (figure 57.24). The cells were attempting to defend the larva by ingesting the invader by phagocytosis (described in chapter 6). For this discovery of what came to be known as the **cellular immune response,** Metchnikoff was awarded the 1908 Nobel Prize in Physiology or Medicine, along with Paul Ehrlich for his work on the other major part of the immune defense, the antibody or **humoral immune response.** The invertebrate immune response shares several elements with the vertebrate one.

Phagocytes. All animals possess phagocytic cells that attack invading microbes. These phagocytic cells travel through the animal's circulatory system or circulate within the fluid-filled body cavity. In simple animals like sponges that lack either a circulatory system or a body cavity, the phagocytic cells circulate among the spaces between cells.

Distinguishing Self from Nonself. The ability to recognize the difference between cells of one's own body and those of another individual appears to have evolved early in the history of life. Sponges, thought to be the oldest animals, attack grafts from other sponges, as do insects and starfish. None of these invertebrates, however, exhibit any evidence of immunological memory; apparently, the antibody-based humoral immune defense did not evolve until the vertebrates.

FIGURE 57.24
Discovering the cellular immune response in invertebrates. In a Nobel-Prize-winning experiment, the Russian zoologist Metchnikoff pierced the larva of a starfish with a rose thorn and the next day found tiny phagocytic cells covering the thorn.

Complement. While invertebrates lack complement, many arthropods (including crabs and a variety of insects) possess an analogous nonspecific defense called the prophenyloxidase (proPO) system. Like the vertebrate complement defense, the proPO defense is activated as a cascade of enzyme reactions, the last of which converts the inactive protein prophenyloxidase into the active enzyme phenyloxidase. Phenyloxidase both kills microbes and aids in encapsulating foreign objects.

Lymphocytes. Invertebrates also lack lymphocytes, but annelid earthworms and other invertebrates do possess lymphocyte-like cells that may be evolutionary precursors of lymphocytes.

Antibodies. All invertebrates possess proteins called lectins that may be the evolutionary forerunners of antibodies. Lectins bind to sugar molecules on cells, making the cells stick to one another. Lectins isolated from sea urchins, mollusks, annelids, and insects appear to tag invading microorganisms, enhancing phagocytosis. The genes encoding vertebrate antibodies are part of a very ancient gene family, the immunoglobulin superfamily. Proteins in

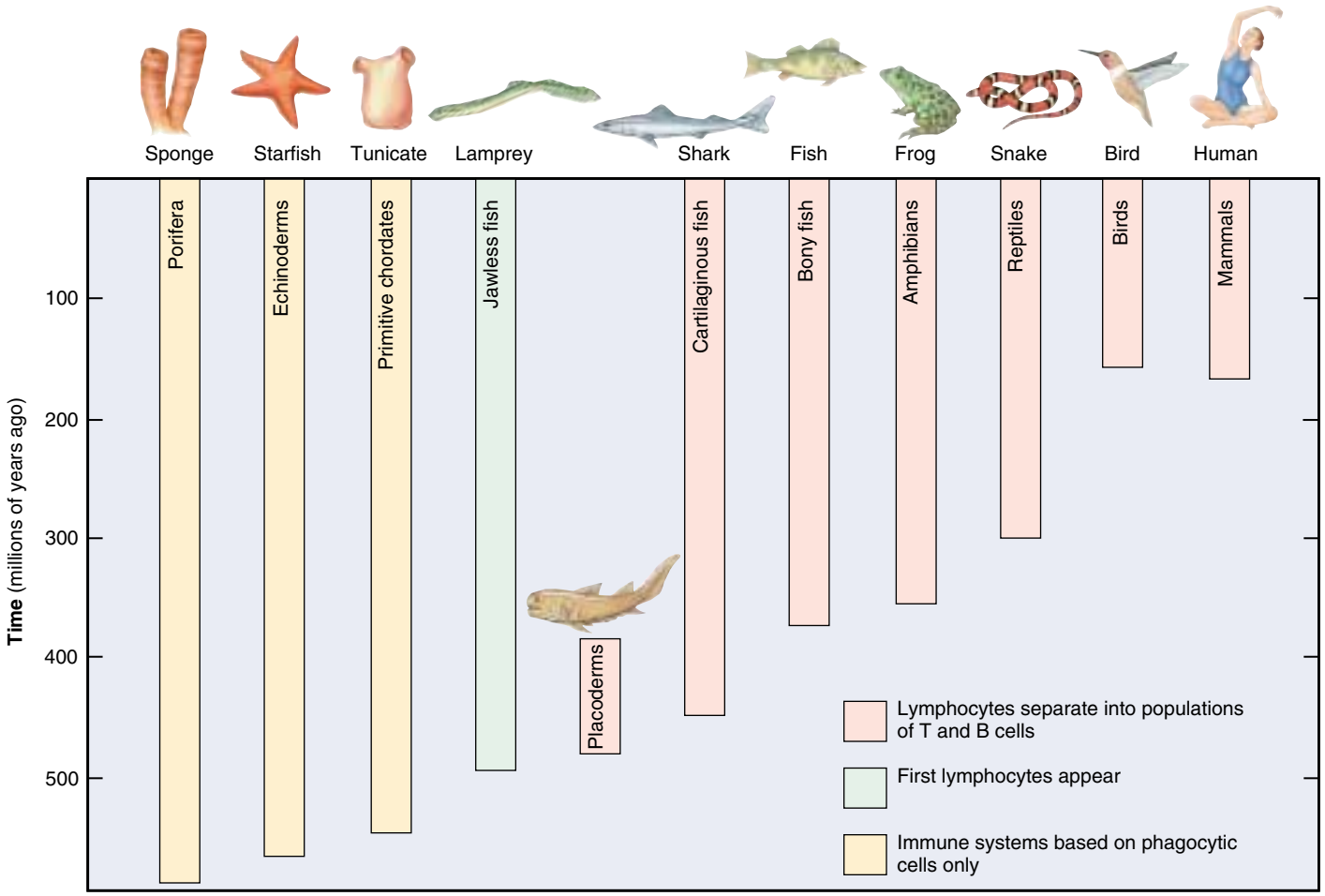


FIGURE 57.25
How immune systems evolved. Lampreys were the first vertebrates to possess an immune system based on lymphocytes, although distinct B and T cells did not appear until the jawed fishes evolved. By the time sharks and other cartilaginous fish appeared, the vertebrate immune response was fully formed.

this group all have a characteristic recognition structure called the Ig fold. The fold probably evolved as a self-recognition molecule in early metazoans. Insect immunoglobulins have been described in moths, grasshoppers, and flies that bind to microbial surfaces and promote their destruction by phagocytes. The antibody immune response appears to have evolved from these earlier, less complex systems.

Vertebrates

The earliest vertebrates of which we have any clear information, the jawless lampreys that first evolved some 500 million years ago, possess an immune system based on lymphocytes. At this early stage of vertebrate evolution, however, lampreys lack distinct populations of B and T cells such as found in all higher vertebrates (figure 57.25).

With the evolution of fish with jaws, the modern vertebrate immune system first arose. The oldest surviving group of jawed fishes are the sharks, which evolved some 450 million years ago. By then, the vertebrate immune defense had fully evolved. Sharks have an immune response much like that seen in mammals, with a cellular response carried out by T-cell lymphocytes and an antibody-mediated humoral response carried out by B cells. The similarities of the cellular and humoral immune defenses are far more striking than the differences. Both sharks and mammals possess a thymus that produces T cells and a spleen that is a rich source of B cells. Four hundred fifty million years of evolution did little to change the antibody molecule—the amino acid sequences of shark and human antibody molecules are very similar. The most notable difference between sharks and mammals is that their antibody-encoding genes are arrayed somewhat differently.

The sophisticated two-part immune defense of mammals evolved about the time jawed fishes appeared. Before then, animals utilized a simpler immune defense based on mobile phagocytic cells.

57.6 The immune system can be defeated.

T Cell Destruction: AIDS

One mechanism for defeating the vertebrate immune system is to attack the immune mechanism itself. Helper T cells and inducer T cells are $CD4^+$ T cells. Therefore, any pathogen that inactivates $CD4^+$ T cells leaves the immune system unable to mount a response to *any* foreign antigen. Acquired immune deficiency syndrome (AIDS) is a deadly disease for just this reason. The AIDS retrovirus, called human immunodeficiency virus (HIV), mounts a direct attack on $CD4^+$ T cells because it recognizes the CD4 coreceptors associated with these cells.

HIV's attack on $CD4^+$ T cells cripples the immune system in at least three ways. First, HIV-infected cells die only after releasing replicated viruses that infect other $CD4^+$ T cells, until the entire population of $CD4^+$ T cells is destroyed (figure 57.26). In a normal individual, $CD4^+$ T cells make up 60 to 80% of circulating T cells; in AIDS patients, $CD4^+$ T cells often become too rare to detect (figure 57.27). Second, HIV causes infected $CD4^+$ T cells to secrete a soluble suppressing factor that blocks other T cells from responding to the HIV antigen. Finally, HIV may block transcription of MHC genes, hindering the recognition and destruction of infected $CD4^+$ T cells and thus protecting those cells from any remaining vestiges of the immune system.

The combined effect of these responses to HIV infection is to wipe out the human immune defense. With no defense against infection, any of a variety of otherwise commonplace infections proves fatal. With no ability to recognize and destroy cancer cells when they arise, death by cancer becomes far more likely. Indeed, AIDS was first recognized as a disease because of a cluster of cases of an unusually rare form of cancer. More AIDS victims die of cancer than from any other cause.

Although HIV became a human disease vector only recently, possibly through transmission to humans from chimpanzees in Central Africa, it is already clear that AIDS is one of the most serious diseases in human history (figure 57.28). The fatality rate of AIDS is 100%; no patient exhibiting the symptoms of AIDS has ever been known to survive more than a few years without treatment. Aggressive treatments can prolong life but how much longer has not been determined. However, the disease is *not* highly contagious, as it is transmitted from one individual to another through the transfer of internal body fluids, typically in semen and in blood during transfusions. Not all individuals exposed to HIV (as judged by anti-HIV antibodies in their blood) have yet acquired the disease.

Until recently, the only effective treatment for slowing the progression of the disease involved treatment with drugs such as AZT that inhibit the activity of reverse transcriptase, the enzyme needed by the virus to produce DNA from RNA. Recently, however, a new type of drug has be-

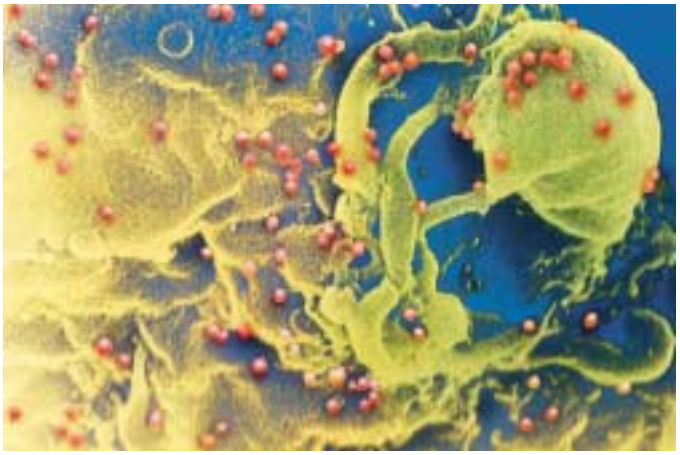


FIGURE 57.26
HIV, the virus that causes AIDS. Viruses released from infected $CD4^+$ T cells soon spread to neighboring $CD4^+$ T cells, infecting them in turn. The individual viruses, colored blue in this scanning electron micrograph, are extremely small; over 200 million would fit on the period at the end of this sentence.

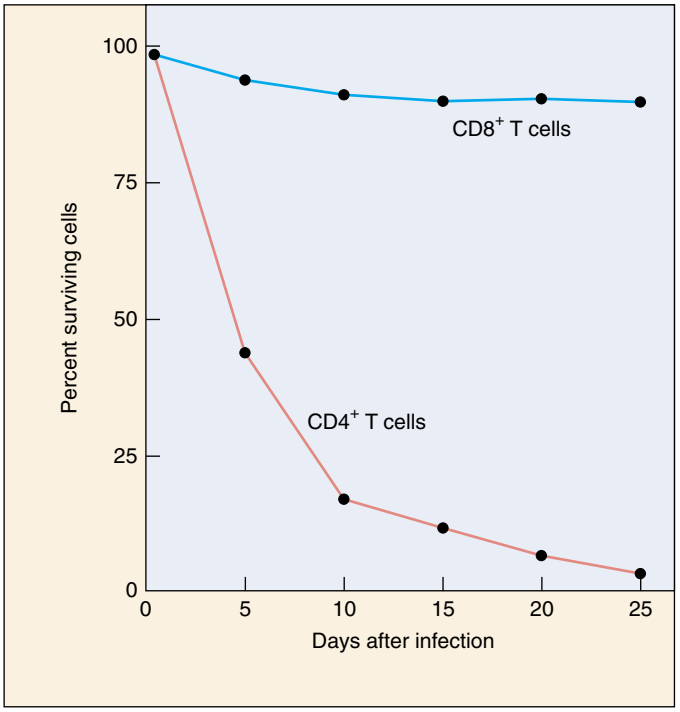


FIGURE 57.27
Survival of T cells in culture after exposure to HIV. The virus has little effect on the number of $CD8^+$ T cells, but it causes the number of $CD4^+$ T cells (this group includes helper T cells) to decline dramatically.

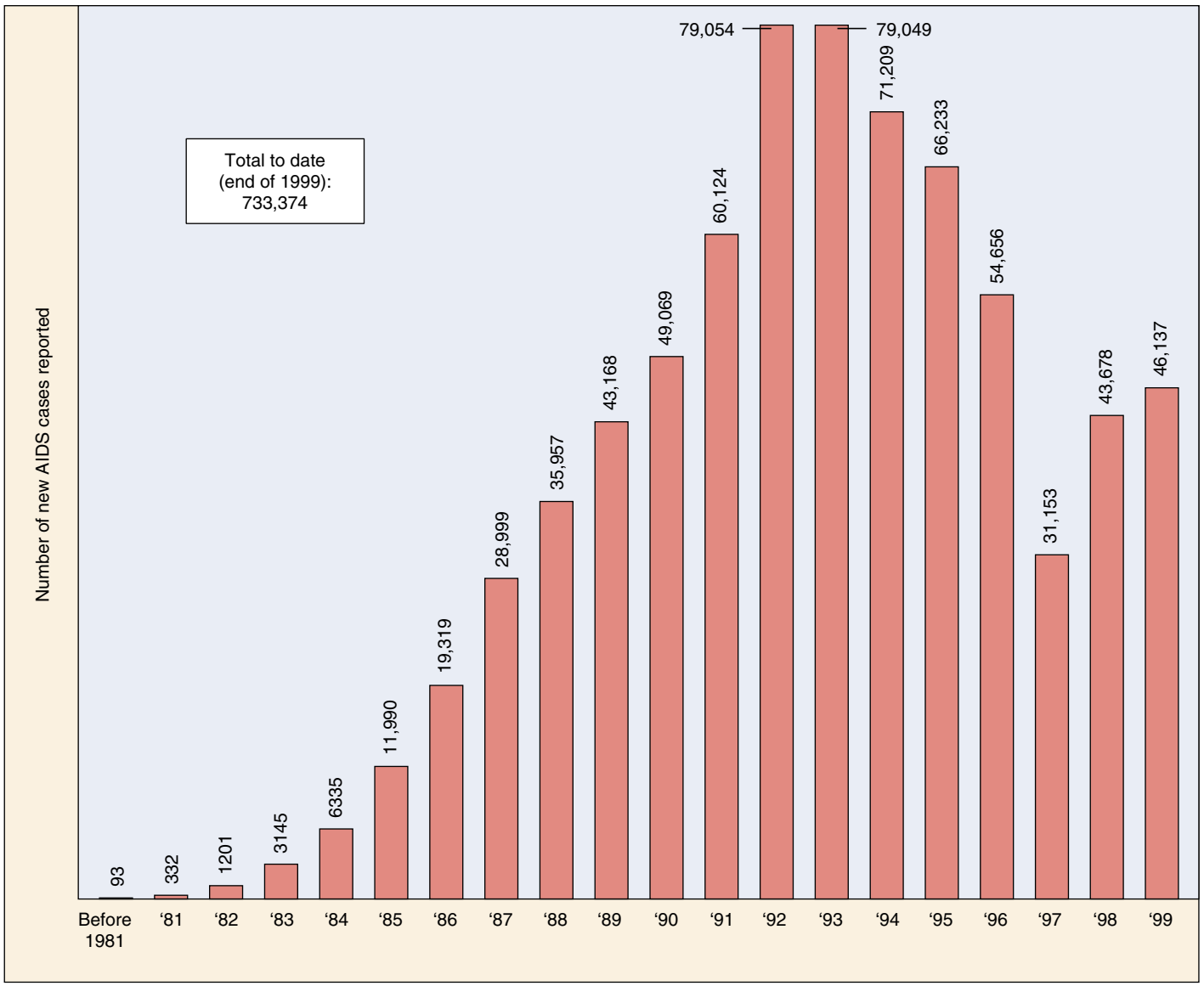


FIGURE 57.28
The AIDS epidemic in the United States: new cases. The U.S. Centers for Disease Control and Prevention (CDC) reports that 43,678 new AIDS cases were reported in 1998 and 46,137 new cases in 1999, with a total of 733,374 cases and 390,692 deaths in the United States. Over 1.5 million other individuals are thought to be infected with the HIV virus in the United States, and 14 million worldwide. The 100,000th AIDS case was reported in August 1989, eight years into the epidemic; the next 100,000 cases took just 26 months; the third 100,000 cases took barely 19 months (May 1993), and the fourth 100,000 took only 13 months (June 1994). The extraordinarily high numbers seen in 1992 reflect an expansion of the definition of what constitutes an AIDS case.
Source: Data from U.S. Centers for Disease Control and Prevention, Atlanta, GA.

come available that acts to inhibit protease, an enzyme needed for viral assembly. Treatments that include a combination of reverse transcriptase inhibitors and protease inhibitors (p. 672) appear to lower levels of HIV, though they are very costly. Efforts to develop a vaccine against AIDS continue, both by splicing portions of the HIV surface protein gene into vaccinia virus and by attempting to develop a harmless strain of HIV. These approaches, while promising, have not yet proved successful and are limited by the fact that different strains of HIV seem to possess different surface antigens. Like the influenza virus, HIV engages in some form of antigen shifting, making it difficult to develop an effective vaccine.

AIDS destroys the ability of the immune system to mount a defense against any infection. HIV, the virus that causes AIDS, induces a state of immune deficiency by attacking and destroying $CD4^+$ T cells.

Antigen Shifting

A second way that a pathogen may defeat the immune system is to mutate frequently so that it varies the nature of its surface antigens. The virus which causes influenza uses this mechanism, and so we have to be immunized against a different strain of this virus periodically. This way of escaping immune attack is known as antigen shifting, and is practiced very effectively by trypanosomes, the protists responsible for sleeping sickness (see chapter 35). Trypanosomes possess several thousand different versions of the genes encoding their surface protein, but the cluster containing these genes has no promoter and so is not transcribed as a unit. The necessary promoter is located within a transposable element that jumps at random from one position to another within the cluster, transcribing a different surface protein gene with every move. Because such moves occur in at least one cell of an infective trypanosome population every few weeks, the vertebrate immune system is unable to mount an effective defense against trypanosome infection. By the time a significant number of antibodies have been generated against one form of trypanosome surface protein, another form is already present in the trypanosome population that survives immunological attack, and the infection cycle is renewed. People with sleeping sickness rarely rid themselves of the infection.

Although this mechanism of mutation to alter surface proteins seems very "directed" or intentional on the part of the pathogen, it is actually the process of evolution by natural selection at work. We usually think of evolution as requiring thousands of years to occur, and not in the time frame of weeks. However, evolution can occur whenever mutations are passed on to offspring that provide an organism with a competitive advantage. In the case of viruses, bacteria, and other pathogenic agents, their generation times are on the order of hours. Thus, in the time frame of a week, the population has gone through millions of cell divisions. Looking at it from this perspective, it is easy to see how random mutations in the genes for the surface antigens could occur and change the surface of the pathogen in as little as a week's time.

How Malaria Hides from the Immune System

Every year, about a half-million people become infected with the protozoan parasite *Plasmodium falciparum*, which multiplies in their bodies to cause the disease malaria. The plasmodium parasites enter the red blood cells and consume the hemoglobin of their hosts. Normally this sort of damage to a red blood cell would cause the damaged cell to be transported to the spleen for disassembly, destroying the plasmodium as well. The plasmodium avoids this fate, however, by secreting knoblike proteins that extend through the surface of the red blood cell and anchor the cell to the inner surface of the blood vessel.

Over the course of several days, the immune system of the infected person slowly brings the infection under control. During this time, however, a small proportion of the plasmodium parasites change their knob proteins to a form different from those that sensitized the immune system. Cells infected with these individuals survive the immune response, only to start a new wave of infection.

Scientists have recently discovered how the malarial parasite carries out this antigen-shifting defense. About 6% of the total DNA of the plasmodium is devoted to encoding a block of some 150 *var* genes, which are shifted on and off in multiple combinations. Each time a plasmodium divides, it alters the pattern of *var* gene expression about 2%, an incredibly rapid rate of antigen shifting. The exact means by which this is done is not yet completely understood.

DNA Vaccines May Get around Antigen Shifting

Vaccination against diseases such as smallpox, measles, and polio involves introducing into your body a dead or disabled pathogen, or a harmless microbe with pathogen proteins displayed on its surface. The vaccination triggers an immune response against the pathogen, and the bloodstream of the vaccinated person contains B cells which will remember and quickly destroy the pathogen in future infections. However, for some diseases, vaccination is nearly impossible because of antigen shifting; the pathogens change over time, and the B cells no longer recognize them. Influenza, as we have discussed, presents different surface proteins yearly. The trypanosomes responsible for sleeping sickness change their surface proteins every few weeks.

A new type of vaccine, based on DNA, may prove to be effective against almost any disease. The vaccine makes use of the killer T cells instead of the B cells of the immune system. DNA vaccines consist of a plasmid, a harmless circle of bacterial DNA, that contains a gene from the pathogen that encodes an internal protein, one which is critical to the function of the pathogen and does not change. When this plasmid is injected into cells, the gene they carry is transcribed into protein but is not incorporated into the DNA of the cell's nucleus. Fragments of the pathogen protein are then stuck on the cell's membrane, marking it for destruction by T cells. In actual infections later, the immune system will be able to respond immediately. Studies are now underway to isolate the critical, unchanging proteins of pathogens and to investigate fully the use of the vaccines in humans.

Antigen shifting refers to the way a pathogen may defeat the immune system by changing its surface antigens and thereby escaping immune recognition. Pathogens that employ this mechanism include flu viruses, trypanosomes, and the protozoans that cause malaria.

Autoimmunity and Allergy

The previous section described ways that pathogens can elude the immune system to cause diseases. There is another way the immune system can fail; it can itself be the agent of disease. Such is the case with autoimmune diseases and allergies—the immune system is the cause of the problem, not the cure.

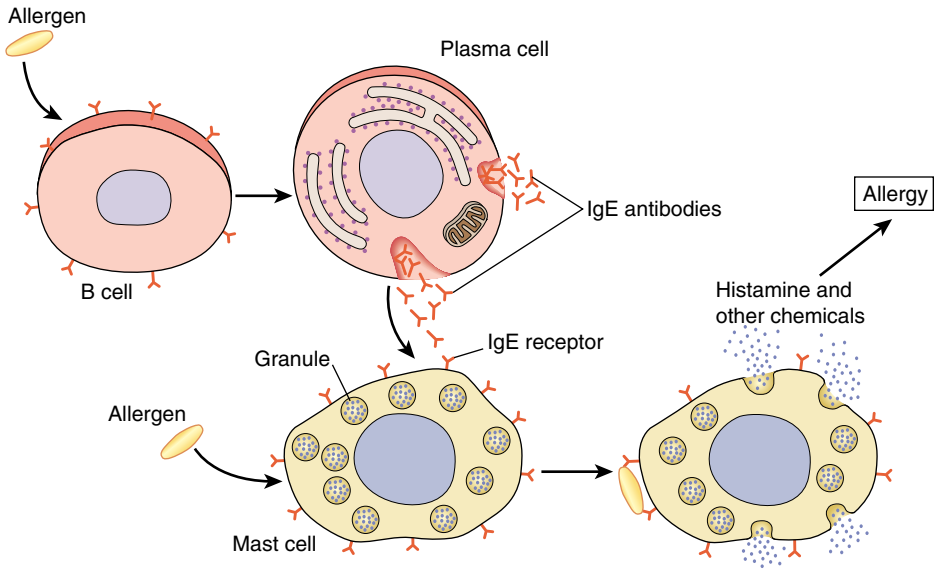


FIGURE 57.29
An allergic reaction. This is an immediate hypersensitivity response, in which B cells secrete antibodies of the IgE class. These antibodies attach to the plasma membranes of mast cells, which secrete histamine in response to antigen-antibody binding.

Autoimmune Diseases

Autoimmune diseases are produced by failure of the immune system to recognize and tolerate self antigens. This failure results in the activation of autoreactive T cells and the production of autoantibodies by B cells, causing inflammation and organ damage. There are over 40 known or suspected autoimmune diseases that affect 5 to 7% of the population. For reasons that are not understood, two-thirds of the people with autoimmune diseases are women.

Autoimmune diseases can result from a variety of mechanisms. The self antigen may normally be hidden from the immune system, for example, so that the immune system treats it as foreign if exposure later occurs. This occurs when a protein normally trapped in the thyroid follicles triggers autoimmune destruction of the thyroid (Hashimoto's thyroiditis). It also occurs in systemic lupus erythematosus, in which antibodies are made to nucleoproteins. Because the immune attack triggers inflammation, and inflammation causes organ damage, the immune system must be suppressed to alleviate the symptoms of autoimmune diseases. Immune suppression is generally accomplished with corticosteroids (including hydrocortisone) and by nonsteroidal antiinflammatory drugs, including aspirin.

Allergy

The term *allergy*, often used interchangeably with *hypersensitivity*, refers to particular types of abnormal immune responses to antigens, which are called *allergens* in these cases. There are two major forms of allergy: (1) **immediate hypersensitivity,** which is due to an abnormal B-cell response to an allergen that produces symptoms within seconds or minutes, and (2) **delayed hypersensitivity,** which is an abnormal T cell response that produces symptoms within about 48 hours after exposure to an allergen.

Immediate hypersensitivity results from the production of antibodies of the IgE subclass instead of the normal IgG antibodies. Unlike IgG antibodies, IgE antibodies do not circulate in the blood. Instead, they attach to tissue mast cells and basophils, which have membrane receptors for these antibodies. When the person is again exposed to the same allergen, the allergen binds to the antibodies attached to the mast cells and basophils. This stimulates these cells to secrete various chemicals, including histamine, which produce the symptom of the allergy (figure 57.29).

Allergens that provoke immediate hypersensitivity include various foods, bee stings, and pollen grains. The most common allergy of this type is seasonal hay fever, which may be provoked by ragweed *(Ambrosia)* pollen grains. These allergic reactions are generally mild, but in some allergies (as to penicillin or peanuts in susceptible people) the widespread and excessive release of histamine may cause **anaphylactic shock,** an uncontrolled fall in blood pressure.

In delayed hypersensitivity, symptoms take a longer time (hours to days) to develop than in immediate hypersensitivity. This may be due to the fact that immediate hypersensitivity is mediated by antibodies, whereas delayed hypersensitivity is a T cell response. One of the best-known examples of delayed hypersensitivity is **contact dermatitis,** caused by poison ivy, poison oak, and poison sumac. Because the symptoms are caused by the secretion of lymphokines rather than by the secretion of histamine, treatment with antihistamines provides little benefit. At present, corticosteroids are the only drugs that can effectively treat delayed hypersensitivity.

Autoimmune diseases are produced when the immune system fails to tolerate self antigens.

Chapter 57

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Summary

Questions

Media Resources

57.1 Many of the body's most effective defenses are nonspecific.

- Nonspecific defenses include physical barriers such as the skin, phagocytic cells, killer cells, and complement proteins.
- The inflammatory response aids the mobilization of defensive cells at infected sites.

1. How do macrophages destroy foreign cells?

2. How does the complement system participate in defense against infection?

- Art Activity: Human skin anatomy

57.2 Specific immune defenses require the recognition of antigens.

- Lymphocytes called B cells secrete antibodies and produce the humoral response; lymphocytes called T cells are responsible for cell-mediated immunity.

3. On what types of cells are the two classes of MHC proteins found?

- Specific immunity
- Lymphocytes
- Cell mediated immunity

57.3 T cells organize attacks against invading microbes.

- T cells only respond to antigens presented to them by macrophages or other antigen-presenting cells together with MHC proteins.
- Cytotoxic T cells kill cells that have foreign antigens presented together with MHC-I proteins.

4. In what two ways do macrophages activate helper T cells? How do helper T cells stimulate the proliferation of cytotoxic T cells?

- T-cell function

57.4 B cells label specific cells for destruction.

- The antibody molecules consist of two heavy and two light polypeptide regions arranged like a "Y"; the ends of the two arms bind to antigens.
- An individual can produce a tremendous variety of different antibodies because the genes which produce those antibodies recombine extensively.
- Active immunity occurs when an individual gains immunity by prior exposure to a pathogen; passive immunity is produced by the transfer of antibodies from one individual to another.

5. How do IgM and IgG antibodies differ in triggering destruction of infected cells?

6. How does the clonal selection model help to explain active immunity?

7. How are lymphocytes able to produce millions of different types of immune receptors?

- Clonal selection

- Activity: Plasma cell production

57.5 All animals exhibit nonspecific immune response but specific ones evolved in vertebrates.

- The immune system evolved in animals from a strictly nonspecific immune response in invertebrates to the two-part immune defense found in mammals.

8. Compare insect and mammalian immune defenses.

- Phagocytic cells

57.6 The immune system can be defeated.

- Flu viruses, trypanosomes, and the protozoan that causes malaria are able to evade the immune system by mutating the genes that produce their surface antigens. In autoimmune diseases, the immune system targets the body's own antigens.

9. What might cause an immune attack of self antigens?

10. How does HIV defeat human immune defenses?

- Abnormalities