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We describe both systems together in terms of three lines of defense. The first line comprises the physical, chemical, and mechanical barriers that keep pathogens on the outside of the body (Figure 38.2). Innate immunity, the second line of defense, begins after tissue is damaged, or after a PAMP is detected inside the body. Its general response mechanisms rid the body of many different kinds of invaders before populations of them become established in the internal environment.

Activation of innate immunity triggers the third line of defense, adaptive immunity. White blood cells form huge populations that target a specific antigen and destroy anything bearing it. Some of the cells persist after infection ends. If the same antigen returns, these memory cells mount a secondary response. Adaptive immunity can specifically target billions of antigens. Table 38.1 compares innate and adaptive immunity.

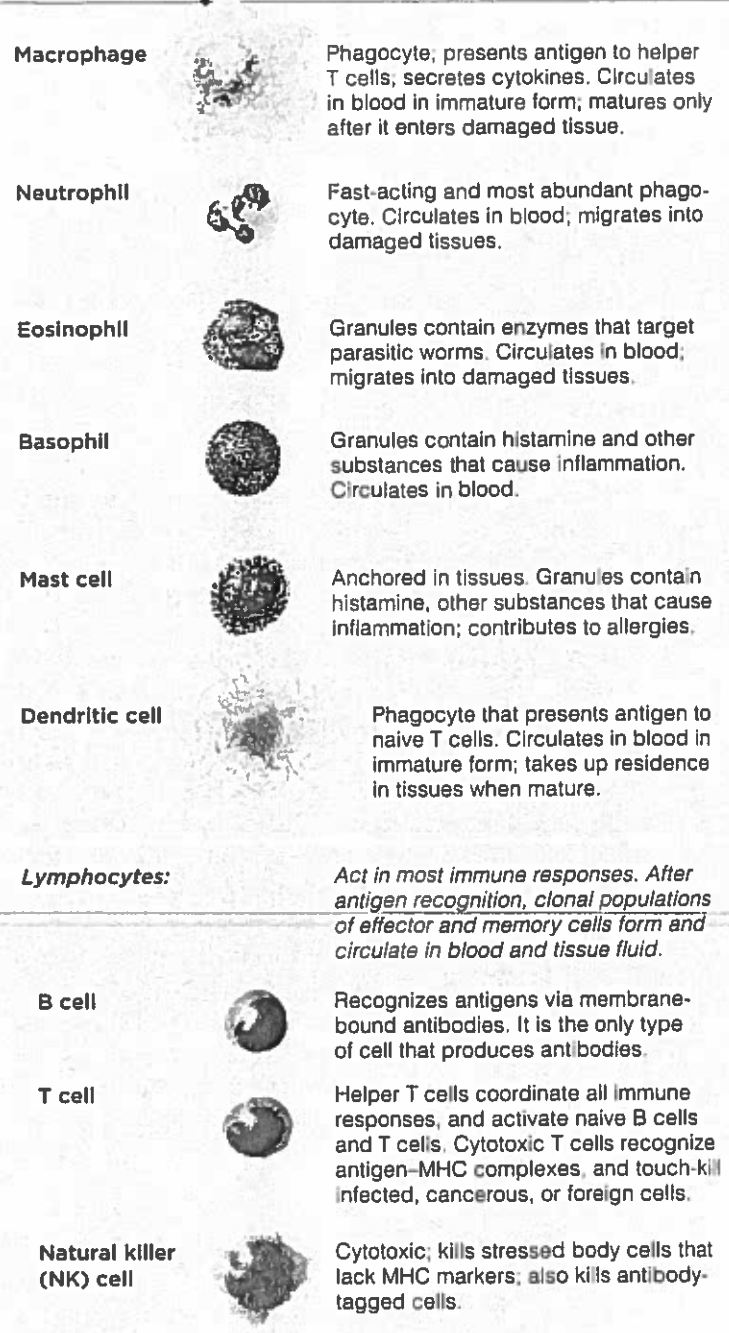
The Defenders

White blood cells (Figure 38.3) carry out all immune responses. Many kinds circulate through the body in blood and lymph; others populate the lymph nodes, spleen, and other tissues. Some white blood cells are phagocytic; all are secretory. Their secretions include cell-to-cell signaling molecules called **cytokines**. These peptides and proteins coordinate all aspects of immunity. Vertebrate cytokines include interleukins, interferons, and tumor necrosis factors (Table 38.2).

Different types of white blood cells are specialized for specific tasks, such as phagocytosis. **Neutrophils** are the most abundant of the circulating phagocytes. **Macrophages** that patrol tissue fluids are mature monocytes, which patrol the blood. **Dendritic cells** alert the adaptive immune system to the presence of antigen.

Some white blood cells contain secretory vesicles: granules that hold cytokines, enzymes, or pathogen-busting toxins. **Eosinophils** target parasites too big for phagocytosis. **Basophils** circulating in blood and **mast cells** anchored in tissues secrete substances contained by their granules in response to injury or antigen. Often associated with nerves, mast cells also respond to neuropeptides (Section 33.6), so they link the nervous and immune systems.

Lymphocytes are a special category of white blood cells that are central to adaptive immunity. **B** and **T lymphocytes** (B and T cells) have the capacity to collectively recognize billions of specific antigens. There are several kinds of T cells, including some that target infected or cancerous body cells. **Natural killer cells** (NK cells) can destroy infected or cancerous body cells that are undetectable by cytotoxic T cells.



Macrophage	Phagocyte; presents antigen to helper T cells; secretes cytokines. Circulates in blood in immature form; matures only after it enters damaged tissue.
Neutrophil	Fast-acting and most abundant phagocyte. Circulates in blood; migrates into damaged tissues.
Eosinophil	Granules contain enzymes that target parasitic worms. Circulates in blood; migrates into damaged tissues.
Basophil	Granules contain histamine and other substances that cause inflammation. Circulates in blood.
Mast cell	Anchored in tissues. Granules contain histamine, other substances that cause inflammation; contributes to allergies.
Dendritic cell	Phagocyte that presents antigen to naive T cells. Circulates in blood in immature form; takes up residence in tissues when mature.
Lymphocytes:	*Act in most immune responses. After antigen recognition, clonal populations of effector and memory cells form and circulate in blood and tissue fluid.*
B cell	Recognizes antigens via membrane-bound antibodies. It is the only type of cell that produces antibodies.
T cell	Helper T cells coordinate all immune responses, and activate naive B cells and T cells. Cytotoxic T cells recognize antigen–MHC complexes, and touch-kill infected, cancerous, or foreign cells.
Natural killer (NK) cell	Cytotoxic; kills stressed body cells that lack MHC markers; also kills antibody-tagged cells.

Figure 38.3 White blood cells (leukocytes). Staining shows details such as cytoplasmic granules that contain enzymes, toxins, and signaling molecules.

Take-Home Message

What is immunity?

- The innate immune system is a set of general defenses against a fixed number of antigens. It acts immediately to prevent infection.
- Vertebrate adaptive immunity is a system of defenses that can specifically target billions of different antigens.
- White blood cells are central to both systems; signaling molecules such as cytokines integrate their activities.

38.2 Surface Barriers

- A pathogen can cause infection only if it enters the internal environment by penetrating skin or other protective barriers at the body's surfaces.
- Links to Bacterial cell walls 4.4, Internal environment 27.1, Hair follicles and skin 32.7

Your skin is in constant contact with the external environment, so it picks up many microorganisms. It normally teems with about 200 different kinds of yeast, protozoa, and bacteria (Figure 38.4*a*). If you showered today, there are probably thousands of them on every square inch of your external surfaces. If you did not, there may be billions. They tend to flourish in warmer, moister parts, such as between the toes. Huge populations inhabit cavities and tubes that open out on the body's surface, including the eyes, nose, mouth, and anal and genital openings.

Microorganisms that typically live on human surfaces, including the interior tubes and cavities of the digestive and respiratory tracts, are called **normal flora**. Our surfaces provide them with a stable environment and nutrients. In return, their populations deter more aggressive species from colonizing (and penetrating) body surfaces; help us digest food; and make nutrients that we depend on, including a cobalt-containing vitamin (B_{12}) made only by bacteria.

Normal flora are helpful only on the outside of body tissues. Consider a type of rod-shaped bacteria that is a major constituent of normal flora, *Propionibacterium acnes* (Figure 38.4*b*). It feeds on sebum, a greasy mixture of fats, waxes and glycerides that lubricates hair and skin. Sebaceous glands secrete sebum into hair follicles (Section 32.7). During puberty, higher levels of steroid hormones trigger sebaceous glands to make more sebum than before. Excess sebum combines with dead, shed skin cells and so blocks the openings of hair follicles. *P. acnes* can survive on the surface of the skin, but far prefer anaerobic habitats such as the interior of blocked hair follicles. There, they multiply to tremendous numbers. Secretions of the flourishing *P. acnes* populations leak into internal tissues, attracting neutrophils that initiate inflammation in the tissue around the follicles. The resulting pustules are called acne.

Table 38.3 Vertebrate Surface Barriers

Physical	Intact skin and epithelia that line tubes and cavities such as the gut and eye sockets; established populations of normal flora
Mechanical	Mucus; broomlike action of cilia; flushing action of tears, saliva, urination, diarrhea
Chemical	Secretions (sebum, other waxy coatings); low pH of urine, gastric juices, urinary and vaginal tracts; lysozyme

Normal flora can cause serious illness if they invade tissues. The bacterial agent of tetanus, *Clostridium tetani*, passes through our intestines so often that we consider it a normal inhabitant. The bacteria responsible for diphtheria, *Corynebacterium diphtheriae*, was normal skin flora before widespread use of the vaccine eradicated the disease. *Staphylococcus aureus*, a resident of human skin, nasal membranes, and intestines, is also a leading cause of human bacterial disease (Figure 38.4*c*). Normal flora cause or worsen pneumonia; ulcers; colitis; whooping cough; meningitis; abscesses of the lung and brain; and colon, stomach, and intestinal cancers.

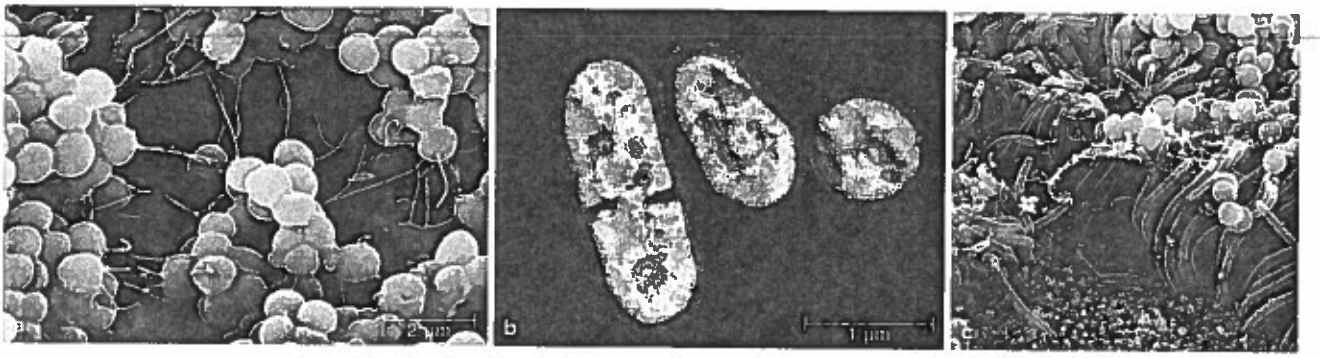


Figure 38.4 Some microbial inhabitants of human surfaces. (**a**) *Staphylococcus epidermidis*, the most common colonizer of human skin. (**b**) *Propionibacterium acnes*, the bacterial cause of acne. (**c**) *Staphylococcus aureus* cells (*yellow*) adhering to mucus-coated cilia of human nasal epithelial cells. *S. aureus* is a common inhabitant of human skin and linings of the mouth, nose, throat, and intestines. It is also the leading cause of bacterial disease in humans. Antibiotic-resistant strains of *S. aureus* are now widespread. A particularly dangerous kind (MRSA) that is resistant to all penicillins is now endemic in most hospitals around the world. MRSA is called a "superbug."

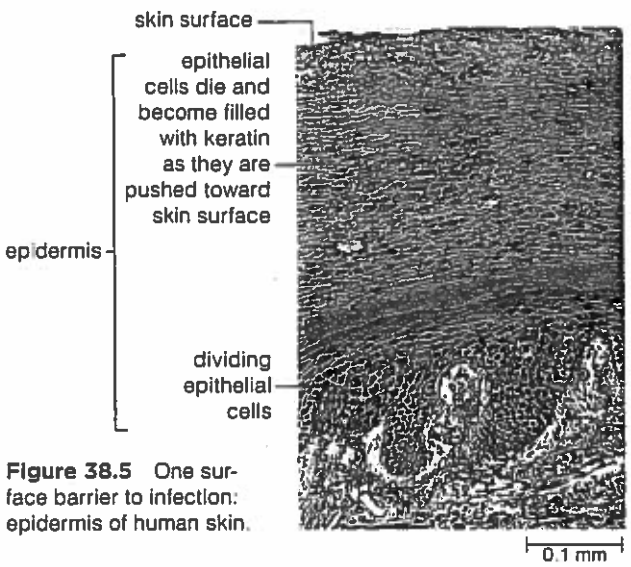


Figure 38.5 One surface barrier to infection: epidermis of human skin.

In contrast to body surfaces, the blood and tissue fluids of healthy people are typically microorganism-free. Physical, chemical, and mechanical barriers keep microorganisms on the outside of body tissues (Table 38.3). For example, healthy, intact skin is an effective physical barrier. Vertebrate skin has a tough outer layer (Figure 38.5). Microorganisms flourish on this waterproof, oily surface, but rarely penetrate it.

Sticky mucus that coats the surfaces of many epithelial linings can trap microorganisms. Broomlike cilia on cells of the linings sweep the trapped microorganisms toward the outside of the body (Figure 38.4*c*). Mucus also contains **lysozyme**, an enzyme that chops up the polysaccharides in bacterial cell walls and so unravels their structure. Lysozyme ensures that bacteria stuck in the mucus do not survive long enough to breach the walls of the sinuses and lower respiratory tract.

Normal flora in the mouth resist lysozyme in saliva. Most microorganisms that enter the stomach are killed by gastric fluid, a potent brew of protein-digesting enzymes and acid. Most of those that survive to reach the small intestine are killed by bile salts. The hardy ones that make it to the large intestine must compete with about 500 resident species. Any that displace normal flora there are typically flushed out by diarrhea.

Lactic acid produced by *Lactobacillus* helps keep the vaginal pH outside the range of tolerance of most fungi and other bacteria. Urination's flushing action usually stops pathogens from colonizing the urinary tract.

Take-Home Message

What prevents ever-present microorganisms from entering the body's internal environment?

- Surface barriers keep microorganisms that contact or inhabit vertebrate surfaces from invading the internal environment.

38.3 Remember to Floss

- Nine of every ten cardiovascular disease patients have serious periodontal disease. There is a connection.
- Links to Biofilms 4.5, Cell junctions 32.1, Cardiovascular disease 37.9

Your mouth is a particularly inviting habitat for microorganisms, offering plenty of nutrients, warmth, moisture, and surfaces for colonization. Accordingly, it harbors huge populations of various species of *Streptococcus*, *Lactobacillus*, *Staphylococcus*, and other bacteria.

A few of the 400 or so species of microorganisms that normally live in the mouth cause dental **plaque**, a thick biofilm of various bacteria and occasional archaea, their extracellular products, and saliva glycoproteins. Plaque sticks tenaciously to teeth (Figure 38.6). Some bacteria that live in it are fermenters. They break down bits of carbohydrate that stick to teeth and then secrete organic acids, which etch away tooth enamel and make cavities.

In young, healthy people, tight junctions (Section 32.1) between the gum epithelium and teeth form a barrier that keeps oral microorganisms out of the internal environment. As we age, the connective tissue beneath gum epithelium thins, and the barrier becomes vulnerable. Deep pockets form between the teeth and gums, and a very nasty gang of anaerobic bacteria and archaea accumulates in these pockets. Their noxious secretions, including destructive enzymes and acids, cause inflammation of surrounding gum tissues—a condition called periodontitis.

Porphyromonas gingivalis is one of those anaerobic species. Along with every other species of oral bacteria associated with periodontitis, *P. gingivalis* also occurs in atherosclerotic plaque (Section 37.9). Periodontal wounds are an open door to the circulatory system and its arteries.

Atherosclerosis is now known to be a disease of inflammation. Macrophages and T cells are attracted to lipid deposits in the vessel walls. Their secretions initiate inflammation that further attracts lipids, and the lesion grows as the immune cells die and become part of the deposits. What role the oral microorganisms play in this scenario is not yet clear, but one thing is certain—they contribute to the inflammation that fuels coronary artery disease.

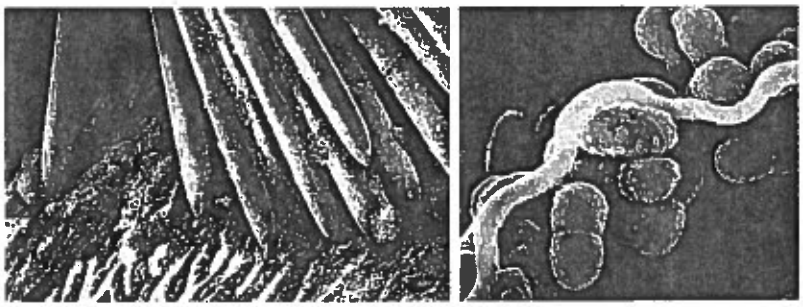


Figure 38.6 Plaque. *Left*, micrograph of toothbrush bristles scrubbing plaque on a tooth surface. *Right*, the main cause of plaque, *Streptococcus mutans*.

38.4 Innate Immune Responses

- Innate immune mechanisms nonspecifically protect animals from pathogens that invade internal tissues.
- Links to Osmosis 5.6, Fever 6.3, Lysis 21.2, Effectors 27.3, Prostaglandins 35.1, Blood 37.2, Capillary function 37.8

What happens if a pathogen slips by surface defenses and enters the body's internal environment? All animals are normally born with a set of fast-acting, off-the-shelf immune defenses that can keep an invading pathogen from establishing a population in the body's internal environment. These innate immune defenses include phagocyte and complement action, inflammation, and fever—all general mechanisms that normally do not change much over an individual's lifetime.

Phagocytes and Complement Macrophages are large phagocytes that engulf and digest essentially everything except undamaged body cells. They patrol the interstitial fluid, so they are often the first white blood cells to encounter an invading pathogen. When receptors on a macrophage bind to antigen, the cell begins to secrete cytokines. These signaling molecules attract more macrophages, neutrophils, and dendritic cells to the site of invasion.

Antigen also triggers complement activation (Figure 38.7*a*,*b*). In vertebrates, about 30 different types of complement protein circulate in inactive form throughout the blood and interstitial fluid. Some become activated when they encounter antigen, or an antibody bound to antigen (we will return to antibodies in Section 38.6). The activated complement proteins are enzymes that cut other inactive complement proteins, which thereby become activated and cut other inactive complement proteins, and so on. These cascading reactions quickly produce tremendous concentrations of activated complement localized at the site of invasion.

Activated complement attracts phagocytic cells. Like snuffling bloodhounds, these cells can follow complement gradients back to an affected tissue. Some complement proteins attach directly to pathogens. Phagocytes have complement receptors, so a pathogen coated with complement is recognized and engulfed faster than an uncoated pathogen. Other activated complement proteins self-assemble into complexes that puncture bacterial cell walls or plasma membranes (Figure 38.7*c*–*e*).

Activated complement proteins also work in adaptive immunity, by guiding the maturation of immune cells and mediating some interactions among them.

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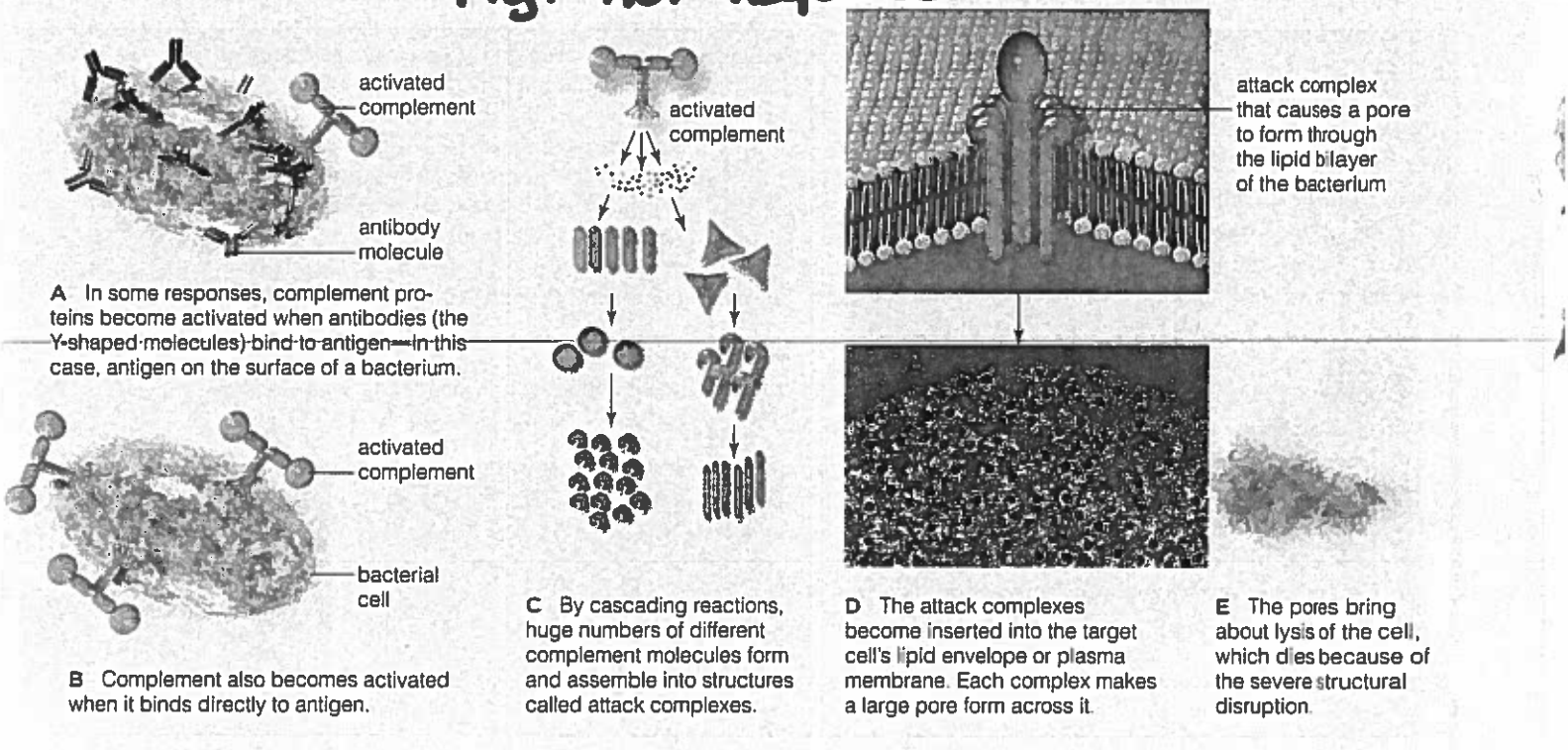

Figure 38.7 Animated One effect of complement protein activation. Activation causes lysis-inducing pore complexes to form. The micrograph shows holes in a pathogen's surface that were made by membrane attack complexes.

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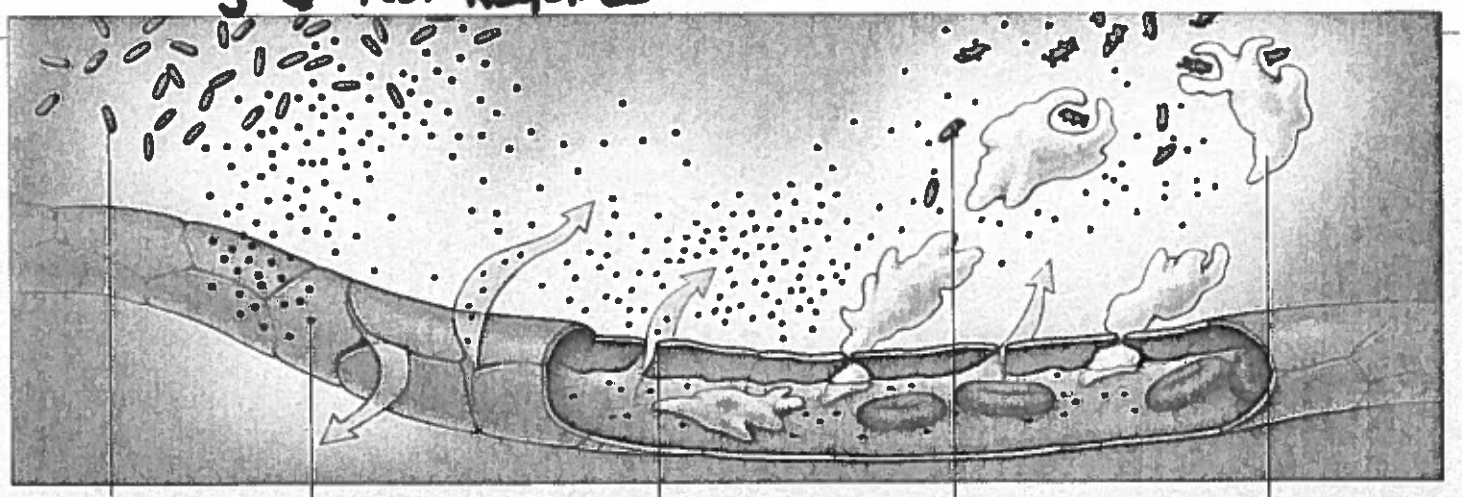


A Bacteria invade a tissue and release toxins or metabolic products that damage tissue.

B Mast cells in tissue release histamine, which widens arterioles (causing redness and warmth) and increases capillary permeability.

C Fluid and plasma proteins leak out of capillaries; localized edema (tissue swelling) and pain result.

D Complement proteins attack bacteria. Clotting factors also wall off inflamed area.

E Neutrophils and macrophages engulf invaders and debris. Macrophage secretions kill bacteria, attract more lymphocytes, and initiate fever.

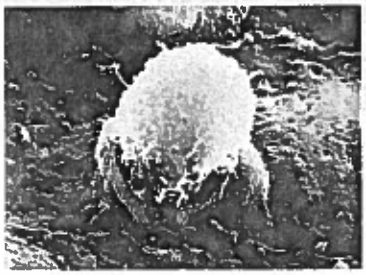


Figure 38.8 Animated Inflammation in response to bacterial infection. *Above*, in this example, white blood cells and plasma proteins enter a damaged tissue. *Right*, the micrograph shows a phagocyte squeezing through a blood vessel wall.

Inflammation Activated complement and cytokines trigger **inflammation**, a local response to tissue damage. The outward symptoms include redness, warmth, swelling, and pain. Inflammation begins when pattern receptors on basophils, mast cells, or neutrophils bind to antigen, or when mast cells directly bind to activated complement. In response to the binding, the cells release prostaglandins, histamines, and other substances into the affected tissue (Section 35.1).

These substances have two effects. First, they cause nearby arterioles to widen. As a result, blood flow to the area increases, reddening and warming the tissue. The increased flow speeds the arrival of more phagocytes, which are attracted to the cytokines. Second, the signaling molecules cause spaces between cells in capillary walls to widen, so they make capillaries in an affected tissue "leakier." Phagocytes and plasma proteins squeeze between the cells, out of the blood vessel and into interstitial fluid (Figure 38.8). The transfer changes the osmotic balance across the capillary wall, so more water diffuses from the blood into tissue. The tissue swells with fluid, putting pressure on free nerve endings and thus giving rise to sensations of pain.

Fever **Fever** is a temporary rise in body temperature above the normal 37°C (98.6°F) that often occurs in response to infection. Some cytokines stimulate brain cells to make and release prostaglandins, which act on the hypothalamus to raise the body's internal temperature set point. As long as the temperature of the body is below the new set point, the hypothalamus signals effectors (Section 27.3) to give rise to a sensation of cold, to constrict blood vessels in the skin, and to trigger shivering, or "chills." All of these responses help raise the internal temperature of the body.

Fever enhances immune defenses by increasing the rate of enzyme activity, thus speeding up metabolism, tissue repair, and formation and activity of phagocytes. Some pathogens multiply more slowly at the higher temperature, so white blood cells can get a head start in the proliferation race against them. A fever is a sign that the body is fighting something, so it should never be ignored. However, a fever of 40.6°C (105°F) or less does not necessarily require treatment in an otherwise healthy adult. Body temperature usually will not rise above that value, but if it does, immediate hospitalization is recommended because a fever of 42°C (107.6°F) can result in brain damage or death.

Take-Home Message

What is innate immunity?

- Innate immunity is the body's built-in set of general immune defenses.
- Complement, phagocytes, inflammation, and fever quickly eliminate most invaders from the body before their populations become established.

38.5 Overview of Adaptive Immunity

- Vertebrate adaptive immunity is defined by self/nonself recognition, specificity, diversity, and memory.
- Links to Lysosomes 4.9, Recognition proteins 5.2, Phagocytosis 5.5, Lymphatic system 37.10

If innate immune mechanisms do not quickly rid the body of an invading pathogen, populations of pathogenic cells may become established in body tissues. By that time, long-lasting adaptive immune mechanisms have begun to target the invaders specifically.

Tailoring Responses to Specific Threats

Life is so diverse that the number of different antigens is essentially unlimited. No system can recognize all of them, but vertebrate adaptive immunity comes close. Unlike innate immunity, the adaptive immune system changes: It "adapts" to different antigens an individual encounters during its lifetime. Lymphocytes and phagocytes interact to effect the four defining characteristics of adaptive immunity: self/nonself recognition, specificity, diversity, and memory.

MHC marker

Self versus nonself recognition starts with the molecular patterns that give each kind of cell or virus a unique identity. The plasma membrane of your cells bears **MHC markers** (*left*), which are self-recognition proteins named after the genes that encode them. Your T cells also bear antigen receptors called **T cell receptors**, or **TCRs**. Part of a TCR recognizes MHC markers as self; part also recognizes an antigen as nonself.

Specificity means that defenses are tailored to target specific antigens.

Diversity refers to the antigen receptors on a body's collection of B and T cells. There are potentially billions of different antigen receptors, so an individual has the potential to counter billions of different threats.

Memory refers to the capacity of the adaptive immune system to "remember" an antigen. It take a few days for B and T cells to respond in force the first time they encounter an antigen. If the same antigen shows up again, they make a faster, stronger response. That is why we do not get as sick the second time around.

First Step—The Antigen-Alert

Recognition of a specific antigen is the first step of the adaptive immune response. A new B or T cell is naive, which means that no antigen has bound to its receptors yet. Once it binds to an antigen, it begins to divide by mitosis, and tremendous populations form.

T cell receptors do not recognize antigen unless it is presented by an antigen-presenting cell. Macrophages, B cells, and dendritic cells do the presenting. First, they engulf something antigenic (Figure 38.9*a*). Vesicles that contain the antigenic particle form in the cells' cytoplasm and fuse with lysosomes. Lysosomal enzymes digest the particle into bits (Sections 4.9 and 5.5).

The lysosomes also contain MHC markers that bind to some of the antigen bits. The resulting antigen–MHC complexes become displayed at the cell's surface when the vesicles fuse with (and become part of) the plasma membrane (Figure 38.9*b*). The display of MHC markers paired with antigen fragments is a call to arms.

Any T cell that bears a receptor for this antigen will bind the antigen–MHC complex. The T cell then starts secreting cytokines, which signal all other B or T cells with the same antigen receptor to divide again and again. Huge populations of B and T cells form after a few days; all of the cells recognize the same antigen. Most are **effector cells**, differentiated lymphocytes that

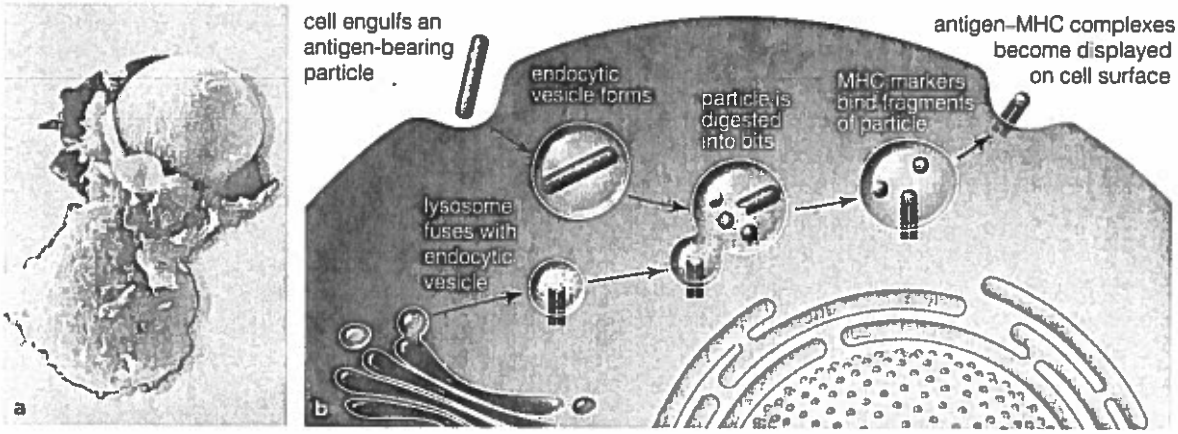


Figure 38.9 Antigen processing. (**a**) A macrophage ingests a foreign cell.

(**b**) From encounter to display, what happens when a B cell, macrophage, or dendritic cell engulfs an antigenic particle—in this case, a bacterium. These cells engulf, process, and then display antigen bound to MHC markers. The displayed antigen is presented to T cells.

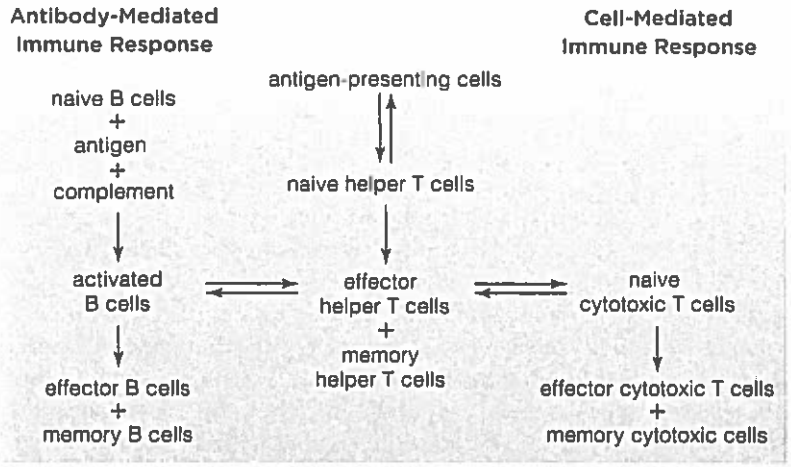


Figure 38.10 Overview of key interactions between antibody-mediated and cell-mediated responses—the two arms of adaptive immunity. A "naive" cell is one that has not made contact with its specific antigen.

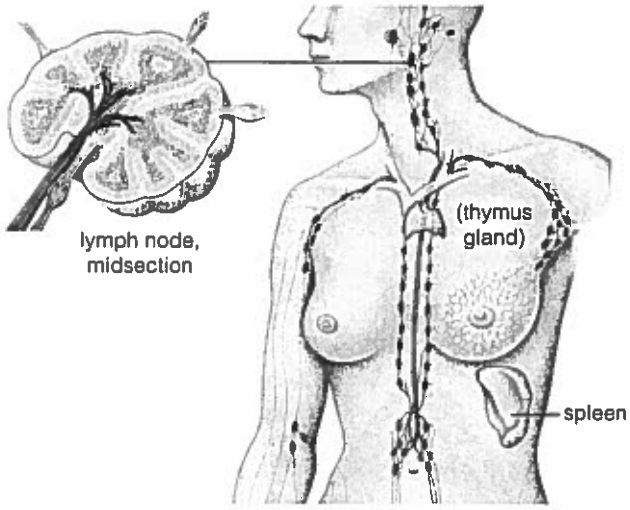


Figure 38.11 Battlegrounds of adaptive immunity. Lymph nodes along lymph vascular highways hold macrophages, dendritic cells, B cells, and T cells. The spleen filters antigenic particles from blood.

act at once. Some are **memory cells**, long-lived B and T cells reserved for future encounters with the antigen.

Two Arms of Adaptive Immunity

Like a boxer's one-two punch, adaptive immunity has two separate arms: the antibody-mediated and the cell-mediated immune responses (Figure 38.10). These two responses work together to eliminate diverse threats.

Not all threats present themselves in the same way. For example, bacteria, fungi, or toxins can circulate in blood or interstitial fluid. These cells are intercepted quickly by B cells and other phagocytes that interact in the **antibody-mediated immune response**. In this response, B cells produce antibodies, which are proteins that can bind to specific antigen-bearing particles. We return to antibodies in the next section.

Some kinds of threats are not targeted by B cells. For example, B cells cannot detect body cells altered by cancer. As another example, some viruses, bacteria, fungi, and protists can hide and reproduce inside body cells; B cells can detect them only briefly, when they slip out of one cell to infect others. Such intracellular pathogens are targeted primarily by the **cell-mediated immune response**, which does not involve antibodies. In this response, cytotoxic T cells and NK cells detect and destroy altered or infected body cells.

Intercepting and Clearing Out Antigen

After engulfing an antigen-bearing particle, a dendritic cell or macrophage migrates to a lymph node (Section 37.10), where it will present antigen to many T cells that filter through the node (Figure 38.11). Every day, about 25 billion T cells pass through each node. T cells that recognize and bind to antigen presented by a phagocyte initiate an adaptive response.

Antigen-bearing particles in interstitial fluid flow through lymph vessels to a lymph node, where they meet up with arrays of resident B cells, dendritic cells, and macrophages. These phagocytes engulf, process, and present antigen to T cells that are passing through the node. Any antigenic particle that escapes a lymph node to enter blood is taken up by the spleen.

During an infection, the lymph nodes swell because T cells accumulate inside of them. When you are ill, you may notice your swollen lymph nodes as tender lumps under the jaw or elsewhere.

The tide of battle turns when the effector cells and their secretions destroy most antigen-bearing agents. With less antigen present, fewer immune fighters are recruited. Complement proteins assist in the cleanup by binding antibody–antigen complexes, forming large clumps that can be quickly cleared from the blood by the liver and spleen. Immune responses subside after the antigenic particles are cleared from the body.

Take-Home Message

What is the adaptive immune system?

- Phagocytes and lymphocytes interact to bring about vertebrate adaptive immunity, which has four defining characteristics: self/nonself recognition, specificity, diversity, and memory.
- The two arms of adaptive immunity work together. Antibody-mediated responses target antigen in blood or interstitial fluid; cell-mediated responses target altered body cells.

38.6 Antibodies and Other Antigen Receptors

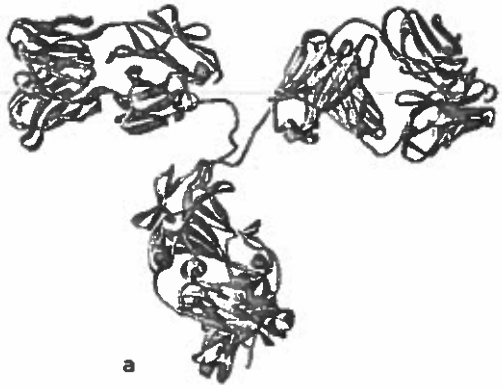
- Antigen receptors give lymphocytes the potential to recognize billions of different antigens.
- Links to Protein structure 3.5, Membrane proteins 5.2, Alternative splicing 14.3, Exocrine glands 32.2

Antibody Structure and Function

If we liken B cells to assassins, then each one has a genetic assignment to liquidate one particular target—an antigen-bearing extracellular pathogen or toxin. Antibodies are their molecular bullets. **Antibodies** are proteins, Y-shaped antigen receptors made only by B cells. Each can bind to the antigen that prompted its synthesis. Many antibodies circulate in blood and enter interstitial fluid during inflammation, but they do not kill pathogens directly. Instead, they activate complement, facilitate phagocytosis, prevent pathogens from attaching to body cells, and neutralize toxins.

An antibody molecule consists of four polypeptides: two identical "light" chains and two identical "heavy" chains (Figure 38.12). Each chain has a variable and a constant region. When the chains fold up together as an intact antibody, the variable regions form two antigen binding sites that have a specific distribution of bumps, grooves, and charge. These binding sites are the antigen receptor part of an antibody: they can bind only to antigen with a complementary distribution of bumps, grooves, and charge.

In addition to the antigen-binding sites, each antibody also has a constant region that determines its structural identity, or class. There are five antibody classes: IgG, IgA, IgE, IgM, and IgD (Ig stands for immunoglobulin, which is another name for antibody). The different classes serve different functions (Table 38.4). Most of the antibodies circulating in the bloodstream and tissue fluids are IgG, which binds pathogens, neutralizes toxins, and activates complement. IgG is the only antibody that can cross the placenta to protect a fetus before its own immune system is active. IgA is the main antibody in mucus and other exocrine



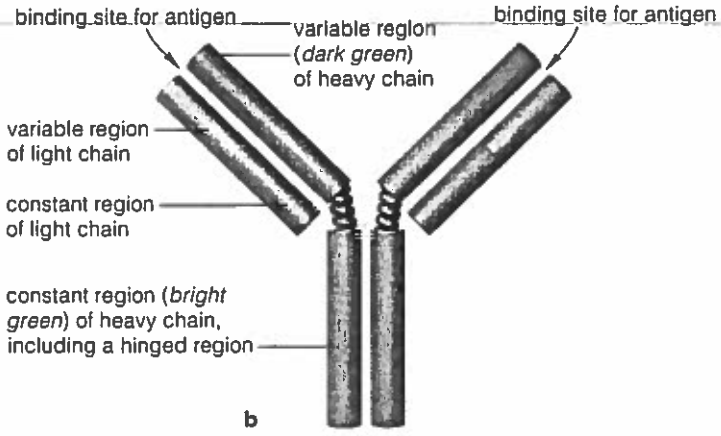
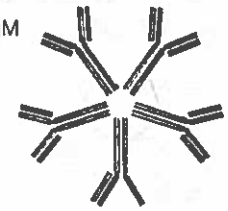


Figure 38.12 Antibody structure. (**a**) An antibody molecule has four polypeptide chains joined in a Y-shaped configuration. In this ribbon model, the two heavy chains are shown in *green*, and the two light chains are *teal*. (**b**) Each chain has a variable and a constant region.

Not Required ↓

Table 38.4 Structural Classes of Antibodies

Secreted antibodies		
IgG		Main antibody in blood; activates complement, neutralizes toxins; protects fetus and is secreted in early milk.
IgA		Abundant in exocrine gland secretions (e.g., tears, saliva, milk, mucus), where it occurs in dimeric form (*shown*). Interferes with binding of bacteria and viruses to body cells.
Membrane-bound antibodies		
IgE		Anchored to surface of basophils, mast cells, eosinophils, and some dendritic cells. IgE binding to antigen induces anchoring cell to release histamines and cytokines. Factor in allergies and asthma.
IgD		B cell receptor.
IgM		B cell receptor, as a monomer. Also is secreted as pentamer (group of five, *shown*).

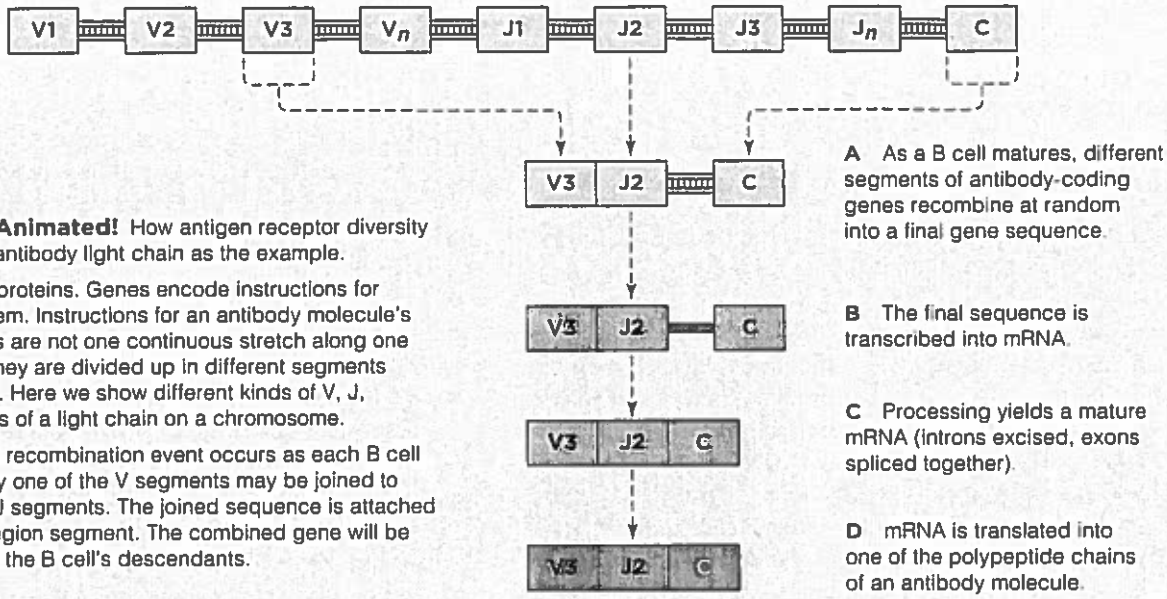


Figure 38.13 Animated! How antigen receptor diversity arises, with an antibody light chain as the example.

Antibodies are proteins. Genes encode instructions for synthesizing them. Instructions for an antibody molecule's variable regions are not one continuous stretch along one chromosome; they are divided up in different segments along its length. Here we show different kinds of V, J, and C segments of a light chain on a chromosome.

In this region, a recombination event occurs as each B cell is maturing. Any one of the V segments may be joined to any one of the J segments. The joined sequence is attached to a constant region segment. The combined gene will be present in all of the B cell's descendants.

gland secretions (Section 32.2). Bound to antigen, it interacts with mast cells, basophils, macrophages, and NK cells to initiate inflammation. IgA is secreted as a dimer (two antibodies bound together), which makes it stable enough to patrol harsh environments such as the interior of the digestive tract. There, IgA encounters pathogens before they contact body cells. IgE is incorporated into the plasma membrane of mast cells, basophils, and some types of dendritic cells. Binding of antigen to IgE triggers the anchoring cell to release histamines and cytokines. A new B cell bristles with **B cell receptors**, which are membrane-bound IgM or IgD antibodies. Secreted IgM pentamers (polymers of five) efficiently bind antigen and activate complement.

The Making of Antigen Receptors

Most humans can make about 2.5 billion unique antigen receptors. This diversity arises because the genes that encode the receptors do not occur in a continuous stretch on one chromosome; instead, they occur in several segments on different chromosomes, and there are several different versions of each segment. The segments are spliced together during B and T cell differentiation, but which version of each segment gets spliced into the antigen receptor gene of a particular cell is random (Section 14.3 and Figure 38.13). As a B or T cell differentiates, it ends up with one out of about 2.5 billion different combinations of gene segments.

Before a new B cell leaves bone marrow, it already is synthesizing its unique antigen receptors. The constant region of each receptor is embedded in the lipid bilayer of the cell's plasma membrane, and the two arms project above the membrane. In time the B cell bristles with more than 100,000 antigen receptors. It is now a "naive" B cell, meaning it has not yet met its antigen.

T cells also form in bone marrow, but they mature only after they take a tour in the thymus gland (Section 37.10). There, they encounter hormones that stimulate them to make MHC receptors and T cell receptors.

Because of the random splicing of antigen receptor gene segments, the TCRs of some new T cells bind body proteins instead of antigen, and most do not recognize MHC markers. So how does an individual end up with a working set of T cells that does not attack its own body? Thymus cells have a built-in quality control that weeds out "bad" TCRs. They snip small peptides from a variety of body proteins and attach them to MHC markers. T cells that bind to a peptide–MHC complex have TCRs that recognize a self protein; those that do not bind any complex do not recognize MHC markers. Both types of cells die. Thus, any T cell that leaves the thymus to begin its journey through the circulatory system bristles with functional TCRs.

Take-Home Message

What are antigen receptors?

- The adaptive immune system has the potential to recognize about 2.5 billion different antigens via receptors on B cells and T cells.
- Antibodies are secreted or membrane-bound antigen receptors. They are made only by B cells.

38.7 The Antibody-Mediated Immune Response

- In an antibody-mediated immune response, B cells are stimulated to produce antibodies targeting a specific antigen.
- Link to Receptor-mediated endocytosis 5.5

An Antibody-Mediated Response

Suppose that you accidentally nick your finger. Being opportunists, some *Staphylococcus aureus* cells on your skin invade your internal environment. Complement in interstitial fluid quickly attaches to carbohydrates in the bacterial cell walls, and cascading complement activation reactions begin. Within an hour, complement-coated bacteria tumbling along in lymph vessels reach a lymph node in your elbow. There they filter past an army of naive B cells.

As it happens, one of the naive B cells in that lymph node makes antigen receptors that recognize a polysaccharide in *S. aureus* cell walls. This and every other B cell has receptors that recognize a complement coating on bacteria. Binding to antigen and complement together stimulates the B cell to engulf one of the bacteria by receptor-mediated endocytosis (Section 5.5). The B cell is now activated (Figure 38.14*a*).

Meanwhile, more *S. aureus* cells have been secreting metabolic products into interstitial fluid around your cut. The secretions attract phagocytes. A dendritic cell engulfs several bacteria, then migrates to the lymph node in your elbow. By the time it gets there, it has digested the bacteria and is displaying their fragments bound to MHC markers on its surface (Figure 38.14*b*).

Each hour, about 500 different naive T cells travel through the lymph node, inspecting resident dendritic cells. In this case, one of those T cells has TCRs that bind the *S. aureus* antigen–MHC complexes displayed by the dendritic cell.

For the next 24 hours, the T cell and the dendritic cell interact. When they disengage, the T cell returns to the circulatory system and begins to divide (Figure 38.14*c*). A huge population of genetically identical T cells forms; each cell has receptors that can bind the *S. aureus* antigen. These clones differentiate into helper T cells and memory T cells.

By the theory of clonal selection, the T cell was "selected" because its receptors bind to the *S. aureus* antigen. T cells with receptors that do not bind the antigen do not divide to form huge clonal populations.

A The B cell receptors on a naive B cell bind to a specific antigen on the surface of a bacterium. The bacterium's complement coating triggers the B cell to engulf it. Fragments of the bacterium bind MHC markers, and the complexes become displayed at the surface of the now-activated B cell.

B A dendritic cell engulfs the same kind of bacterium that the B cell encountered. Digested fragments of the bacterium bind to MHC markers, and the complexes become displayed at the dendritic cell's surface. The dendritic cell is now an antigen-presenting cell.

C The antigen–MHC complexes on the antigen-presenting cell are recognized by antigen receptors on a naive T cell. Binding causes the T cell to divide and differentiate into effector and memory helper T cells.

D Antigen receptors of one of the effector helper T cells bind antigen–MHC complexes on the B cell. Binding makes the T cell secrete cytokines.

E The cytokines induce the B cell to divide, giving rise to many identical B cells. The cells differentiate into effector B cells and memory B cells.

F The effector B cells begin making and secreting huge numbers of IgA, IgG, or IgE, all of which recognize the same antigen as the original B cell receptor. The new antibodies circulate throughout the body and bind to any remaining bacteria.

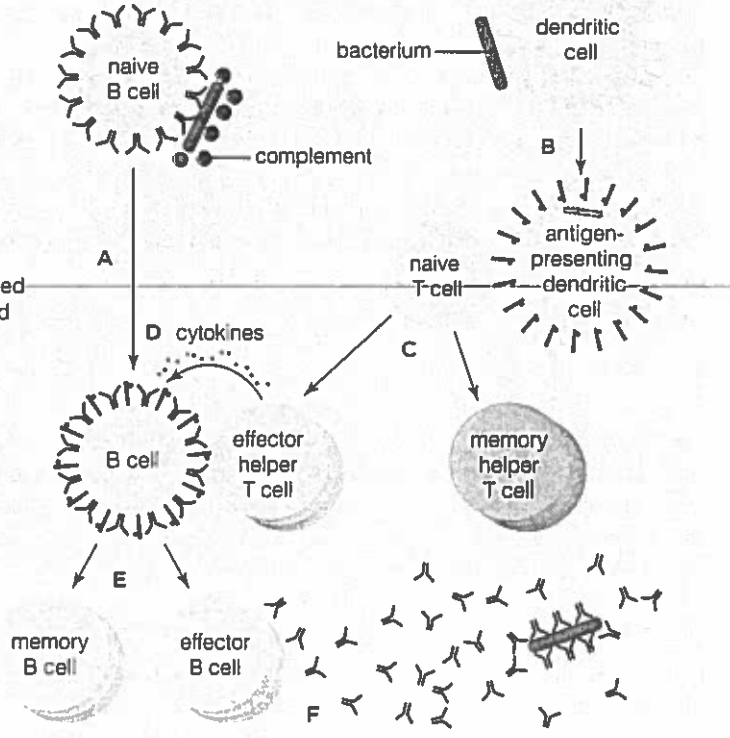
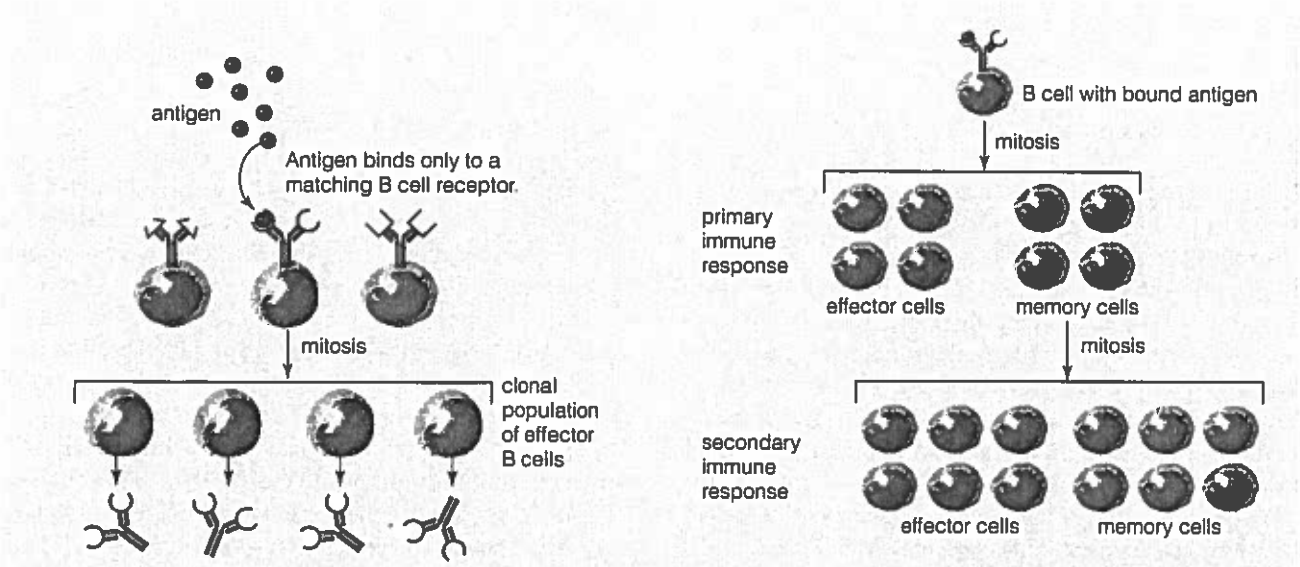


Figure 38.14 Animated Example of an antibody-mediated immune response.



A Clonal selection of one B cell. Only B cells with receptors that bind to antigen divide and differentiate.

B A first exposure to antigen generates a primary immune response in which effector cells fight the infection. Memory cells also form in a primary response but are set aside, sometimes for decades. If the antigen returns, the memory cells initiate a secondary response.

Figure 38.15 Animated B cell maturation.

Let's go back to that B cell in the lymph node. By now, it has digested the bacterium, and it is displaying bits of *S. aureus* bound to MHC molecules on its plasma membrane. One of the new helper T cells recognizes the antigen–MHC complexes displayed by the B cell. Like long-lost friends, the B cell and the helper T cell stay together for a while and communicate.

One of the messages that is communicated consists of cytokines secreted by the helper T cell. The cytokines stimulate the B cell to begin mitosis after the two cells disengage (Figure 38.14*d*). The B cell divides again and again to form a huge population of genetically identical cells, all with receptors that can bind to the *S. aureus* antigen (Figure 38.15*a*). These clones differentiate into effector and memory B cells (Figure 38.14*e*).

The effector cells start working immediately. They switch antibody classes, which means they begin to produce and secrete IgG, IgA, or IgE instead of making membrane-bound B cell receptors. The new antibody molecules recognize the same *S. aureus* antigen as the original B cell receptor. Antibodies now circulate throughout the body and attach themselves to any remaining bacterial cells. An antibody coating prevents bacteria from attaching to body cells, and flags them for phagocytosis and disposal (Figure 38.14*f*).

Memory B and T cells also form, but these do not act right away. They persist long after the initial infection

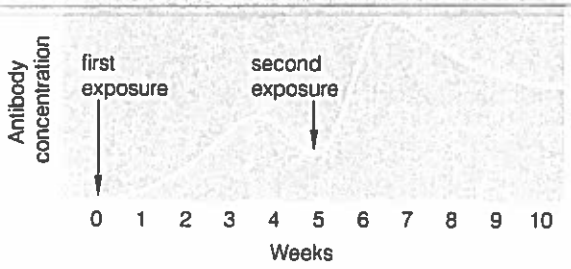


Figure 38.16 Antibody levels in a primary and secondary immune response. A secondary immune response is faster and stronger than the primary response that preceded it.

ends. If the same antigen enters the body at a later time, these memory cells will initiate a secondary response (Figures 38.15*b* and 38.16). In the secondary response, larger populations of effector cell clones form much more quickly than they did in the primary response, so more antibodies can be produced in a shorter time.

Take-Home Message

What happens during an antibody-mediated immune response?

- Antigen-presenting cells, T cells, and B cells interact in an antibody-mediated immune response targeting a specific antigen.
- Populations of B cells form; these make and secrete antibodies that recognize and bind the antigen.

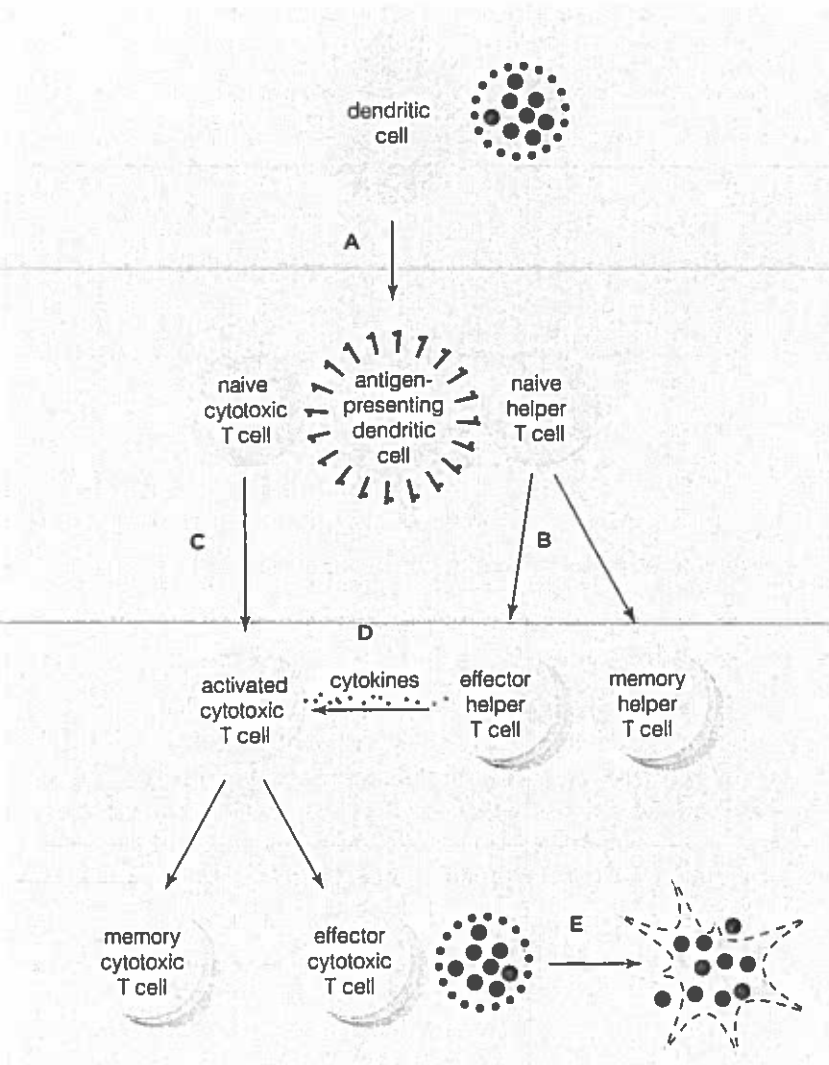
38.8 The Cell-Mediated Response

- In a cell-mediated immune response, cytotoxic T cells and NK cells are stimulated to kill infected or altered body cells.
- Link to Apoptosis 27.6

If B cells are like assassins, cytotoxic T cells are specialists in cell-to-cell combat. Antibody-mediated immune responses efficiently target pathogens that circulate in blood and interstitial fluid, but they are not as effective against pathogens hidden inside cells. As part of a cell-mediated immune response, cytotoxic T cells kill ailing body cells that may be missed by an antibody-mediated response. Such cells typically display antigen: Cancer cells display altered body proteins, and body cells infected with intracellular pathogens display polypeptides of the infecting agent. Both types of cell are detected and killed by cytotoxic T cells.

A typical cell-mediated response begins in interstitial fluid during inflammation when a dendritic cell recognizes, engulfs, and digests a sick body cell or the remains of one (Figure 38.17*a*). The dendritic cell begins to display antigen that was part of the sick cell, and migrates to the spleen or a lymph node. There, the dendritic cell presents its antigen–MHC complexes to huge populations of naive helper T cells and naive cytotoxic T cells. Some of the naive cells have TCRs that recognize the complexes on the dendritic cell. Those helper T cells and cytotoxic T cells that bind the antigen–MHC complexes on the dendritic cell become activated.

The activated helper T cells divide and differentiate into populations of effector and memory helper T cells (Figure 38.17*b*). The effector cells immediately begin to secrete cytokines. Activated cytotoxic T cells



A A dendritic cell engulfs a virus-infected cell. Digested fragments of the virus bind to MHC markers, and the complexes are displayed at the dendritic cell's surface. The dendritic cell, now an antigen-presenting cell, migrates to a lymph node.

B Receptors on a naive helper T cell bind to antigen–MHC complexes on the dendritic cell. The interaction activates the helper T cell, which then begins to divide. A large population of descendant cells forms. Each cell bears T cell receptors that recognize the same antigen. The cells differentiate into effector and memory cells.

C Receptors on a naive cytotoxic T cell bind to the antigen–MHC complexes on the surface of the dendritic cell. The interaction activates the cytotoxic T cell.

D The activated cytotoxic T cell recognizes cytokines secreted by the effector helper T cells as signals to divide. A large population of descendant cells forms. Each cell bears T cell receptors that recognize the same antigen. The cells differentiate into effector and memory cells.

E The new cytotoxic T cells circulate through the body. They recognize and touch-kill any body cell that displays the viral antigen–MHC complexes on its surface.

Figure 38.17 Animated Example of a primary cell-mediated immune response.
Figure It Out: What do the large red spots represent? *Answer: Viruses*

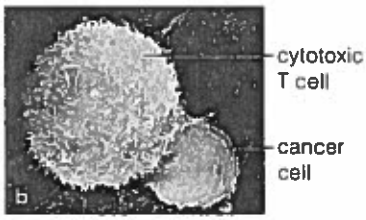


Figure 38.18 T cell receptor function. (**a**) A TCR (*green*) on a T cell binds to an MHC marker (*tan*) on an antigen-presenting cell. An antigen (*red*) is bound to the MHC marker. (**b**) A cytotoxic T cell caught in the act of touch-killing a cancer cell.

recognize the cytokines as signals to divide and differentiate, and tremendous populations of effector and memory cytotoxic T cells form (Figure 38.17*c,d*). All of them recognize and bind the same antigen—the one displayed by that first ailing cell. As in an antibody-mediated response, the memory cells that form in a primary cell-mediated response will mount a secondary response if the antigen returns at a later time.

The effector cytotoxic T cells start working immediately. They circulate throughout blood and interstitial fluid, and bind to any other body cell displaying the original antigen together with MHC markers (Figure 38.18*a*). After it is bound to an ailing cell, a cytotoxic T cell releases perforin and proteases. These toxins poke holes in the sick cell and induce it to die by apoptosis (Figures 38.17*e* and 38.18*b*).

Cytotoxic T cells also recognize the MHC markers of foreign body cells (cytotoxic T cells are responsible for rejection of transplanted organs). They must recognize MHC molecules on the surface of a body cell in order to kill it. However, some infections or cancer can alter a cell so that it is missing part or all of its MHC markers. NK ("natural killer") cells are crucial for fighting such cells. Unlike cytotoxic T cells, NK cells can kill body cells that lack MHC markers. Cytokines secreted by helper T cells (Figure 38.17*d*) also stimulate NK cell division. The resulting populations of effector NK cells attack body cells tagged for destruction by antibodies. They also recognize certain proteins displayed by body cells under stress. Stressed body cells with normal MHC markers are not killed; only those with altered or missing MHC markers are destroyed.

Take-Home Message

What happens during a cell-mediated immune response?

■ Antigen-presenting cells, T cells, and NK cells interact in a cell-mediated immune response targeting body cells that have been altered by cancer or infected.

38.9 Allergies

Not Required ↓

■ An immune response to a typically harmless substance is an allergy. Allergies can be annoying or life-threatening.

In millions of people, exposure to harmless substances stimulates an immune response. Any substance that is ordinarily harmless yet provokes such responses is an **allergen**. Sensitivity to an allergen is called an **allergy**. Drugs, foods, pollen, dust mites, fungal spores, poison ivy, and venom from bees, wasps, and other insects are among the most common allergens.

Some people are genetically predisposed to having allergies. Infections, emotional stress, and changes in air temperature can trigger reactions. A first exposure to an allergen stimulates the immune system to make IgE, which becomes anchored to mast cells and basophils. With later exposures, antigen binds to the IgE. Binding triggers the anchoring cell to secrete histamine and cytokines that initiate inflammation. If this reaction occurs at the lining of the respiratory tract, a copious amount of mucus is secreted and the airways constrict; sneezing, stuffed-up sinuses, and a drippy nose result (Figure 38.19*a*). Contact with an allergen that penetrates the skin's outer layers causes the skin to redden, swell, and become itchy.

Antihistamines relieve allergy symptoms by dampening the effects of histamines. These drugs act on histamine receptors, and also inhibit the release of cytokines and histamines from basophils and mast cells.

Some people are hypersensitive to drugs, insect stings, foods, or vaccines. A second exposure to the allergen can result in anaphylactic shock, a severe, whole-body allergic reaction. Huge amounts of cytokines and histamines released in all parts of the body provoke an immediate, systemic reaction. Fluid leaking from blood into tissues causes the blood pressure to drop too much (shock), and tissues to swell. Swelling tissue constricts airways and may block them. Anaphylactic shock is rare but life-threatening and requires immediate treatment (Figure 38.19*c*). It may occur at any time, upon exposure to even a tiny amount of allergen. Risks include a prior allergic reaction of any kind.

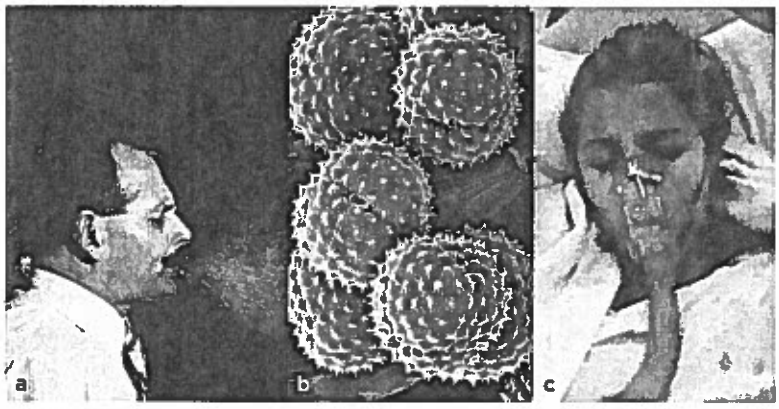


Figure 38.19 Allergies. (**a**) A mild allergy may cause upper respiratory symptoms. (**b**) Ragweed pollen, a common allergen. (**c**) Anaphylactic shock is a severe allergic reaction that requires immediate treatment.

38.10 Vaccines

■ Vaccines are designed to elicit immunity to a disease.

Immunization refers to processes designed to induce immunity. In active immunization, a preparation that contains antigen—a **vaccine**—is administered orally or injected. The first immunization elicits a primary immune response, just as an infection would. A second immunization, or booster, elicits a secondary immune response for enhanced immunity.

In passive immunization, a person receives antibodies purified from the blood of another individual. The treatment offers immediate benefit for someone who has been exposed to a potentially lethal agent, such as tetanus or rabies, Ebola virus, or a venom or toxin. Because the antibodies were not made by the recipient's lymphocytes, memory cells do not form, so benefits last only as long as the injected antibodies do.

The first vaccine was the result of desperate attempts to survive smallpox epidemics that swept repeatedly through cities all over the world. Smallpox is a severe disease that kills up to one-third of the people it infects (Figure 38.20). Before 1880, no one knew what caused infectious diseases or how to protect anyone from getting them, but there were clues. In the case of smallpox, survivors seldom contracted the disease a second time. They were immune, or protected from infection.

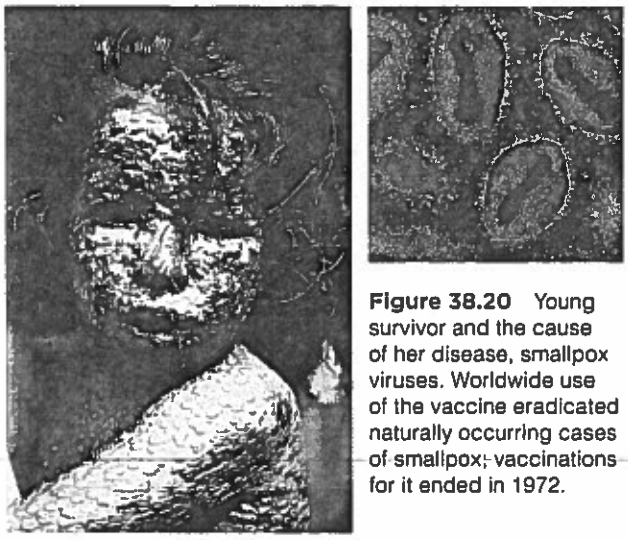


Figure 38.20 Young survivor and the cause of her disease, smallpox viruses. Worldwide use of the vaccine eradicated naturally occurring cases of smallpox; vaccinations for it ended in 1972.

The idea of acquiring immunity to smallpox was so appealing that people had been risking their lives on it for two thousand years. For example, many people poked into their skin bits of scabs or threads soaked in pus. Some survived the crude practices and became immune to smallpox, but many others did not.

By the late 1700s, it was widely known that dairymaids did not get smallpox if they had already recovered from cowpox (a mild disease that affects cattle as well as humans). In 1796, Edward Jenner, an English physician, injected liquid from a cowpox sore into the arm of a healthy boy. Six weeks later, Jenner injected the boy with liquid from a smallpox sore. Luckily, the boy did not get smallpox. Jenner's experiment showed directly that the agent of cowpox elicits immunity to smallpox. Jenner named his procedure "vaccination," after the Latin word for cowpox (*vaccinia*). The use of Jenner's vaccine spread quickly through Europe, then to the rest of the world. The last known case of naturally occurring smallpox was in 1977, in Somalia. The vaccine had eradicated the disease.

We now know that the cowpox virus is an effective vaccine for smallpox because the antibodies it elicits also recognize smallpox virus antigens. Our knowledge of how the immune system works has allowed us to develop many other vaccines that save millions of lives every year. These vaccines are an important part of worldwide public health programs (Table 38.5).

Table 38.5 Recommended Immunization Schedule

Vaccine	Age of Vaccination
Hepatitis B	Birth to 2 months
Hepatitis B boosters	1–4 months and 6–18 months
Rotavirus	2, 4, and 6 months
DTP: diphtheria, tetanus, and pertussis (whooping cough)	2, 4, and 6 months
DTP boosters	15–18 months, 4–6 years, and 11–12 years
HiB (*Haemophilus influenzae*)	2, 4, and 6 months
HiB booster	12–15 months
Pneumococcal	2, 4, and 6 months
Pneumococcal booster	12–15 months
Inactivated poliovirus	2 and 4 months
Inactivated poliovirus boosters	6–18 months and 4–6 years
Influenza	Yearly, 6 months–18 years
MMR (measles, mumps, rubella)	12–15 months
MMR booster	4–6 years
Varicella (chicken pox)	12–15 months
Varicella booster	4–6 years
Hepatitis A series	1–2 years
HPV series	11–12 years
Meningococcal	11–12 years

Source: Centers for Disease Control and Prevention (CDC), 2008

Take-Home Message

How does immunization work?

■ Immunization is the administration of an antigen-bearing vaccine designed to elicit immunity to a specific disease.

38.11 Immunity Gone Wrong

- The immune system of some people does not function properly. The outcome is often severe or lethal.
- Links to Multiple sclerosis 33.13, Arthritis 36.5

Despite the redundancies of immune system functions and built-in quality controls, immunity does not always work as well as it should. Its sheer complexity is part of the problem, because there are so many points at which it could go wrong. Autoimmune disorders occur when an immune response is misdirected against the person's own body cells. In immunodeficiency, the immune response is insufficient to protect a person from disease.

Autoimmune Disorders

Sometimes lymphocytes and antibody molecules fail to discriminate between self and nonself. When that happens, they mount an **autoimmune response**, or an immune response that targets one's own tissues.

For example, autoimmunity occurs in rheumatoid arthritis, a disease in which self antibodies form and bind to the soft tissue in joints. The resulting inflammation leads to eventual disintegration of bone and cartilage in the joints (Section 36.5).

Antibodies to self proteins may bind to hormone receptors, as in Graves' disease. Self antibodies that bind stimulatory receptors on the thyroid gland cause it to produce excess thyroid hormone, which quickens the body's overall metabolic rate. Antibodies are not part of the feedback loops that normally regulate thyroid hormone production. So, antibody binding continues unchecked, the thyroid continues to release too much hormone, and the metabolic rate spins out of control. Symptoms of Graves' disease include uncontrollable weight loss; rapid, irregular heartbeat; sleeplessness; pronounced mood swings; and bulging eyes.

A neurological disorder, multiple sclerosis, occurs when self-reactive T cells attack the myelin sheaths of axons in the central nervous system (Section 33.13). Symptoms range from weakness and loss of balance to paralysis and blindness. Specific MHC gene alleles increase susceptibility, but a bacterial or viral infection may trigger the disorder.

Immune responses tend to be stronger in women than in men, and autoimmunity is far more frequent in women. We know that estrogen receptors are part of gene expression controls throughout the body. T cells have receptors for estrogens, so these hormones may enhance T cell activation in autoimmune diseases. Women's bodies have more estrogen, so interactions between their B cells and T cells may be amplified.

Figure 38.21 A case of severe combined immunodeficiency (SCID). Cindy Cutshwall was born with a deficient immune system. She carries a mutated gene for adenosine deaminase (ADA). Without this enzyme, her cells cannot break down adenosine completely, so a reaction product that is toxic to white blood cells accumulated in her body. High fevers, severe ear and lung infections, diarrhea, and an inability to gain weight were outcomes.

In 1991, when Cindy was nine years old, she and her parents consented to one of the first human gene therapies. Genetic engineers spliced the normal ADA gene into the genetic material of a harmless virus. The modified virus delivered copies of the normal gene into her bone marrow cells. Some cells incorporated the gene in their DNA and started making the missing enzyme.

Now in her twenties, Cindy is doing well. She still requires weekly injections to supplement her ADA production. Other than that, she is able to live a normal life. She is a strong advocate of gene therapy.

Immunodeficiency

Impaired immune function is dangerous and sometimes lethal. Immune deficiencies render individuals vulnerable to infections by opportunistic agents that are typically harmless to those in good health. Primary immune deficiencies, which are present at birth, are the outcome of mutations. Severe combined immunodeficiencies (SCIDs) are examples. A genetic disorder called adenosine deaminase (ADA) deficiency is a type of SCID (Figure 38.21). Secondary immune deficiency is the loss of immune function after exposure to an outside agent, such as a virus. AIDS (acquired immunodeficiency syndrome, described in the next section) is the most common secondary immune deficiency.

Take-Home Message

What happens when the immune system does not function as it should?

- Misdirected or compromised immunity, which sometimes occurs as a result of mutation or environmental factors, can have severe or lethal outcomes.

38.12 AIDS Revisited—Immunity Lost

- AIDS is an outcome of interactions between the HIV virus and the human immune system.
- Links to cDNA 16.1, Viruses 21.1, HIV replication 21.2

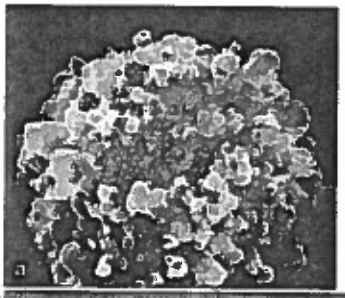
Acquired immune deficiency syndrome, or **AIDS**, is a constellation of disorders that occur as a consequence of infection with HIV, the human immunodeficiency virus (Figure 38.22*a*). This virus cripples the immune system, so it makes the body very susceptible to infections and rare forms of cancer. Worldwide, approximately 39.5 million individuals currently have AIDS (Table 38.6 and Figure 38.22*b*).

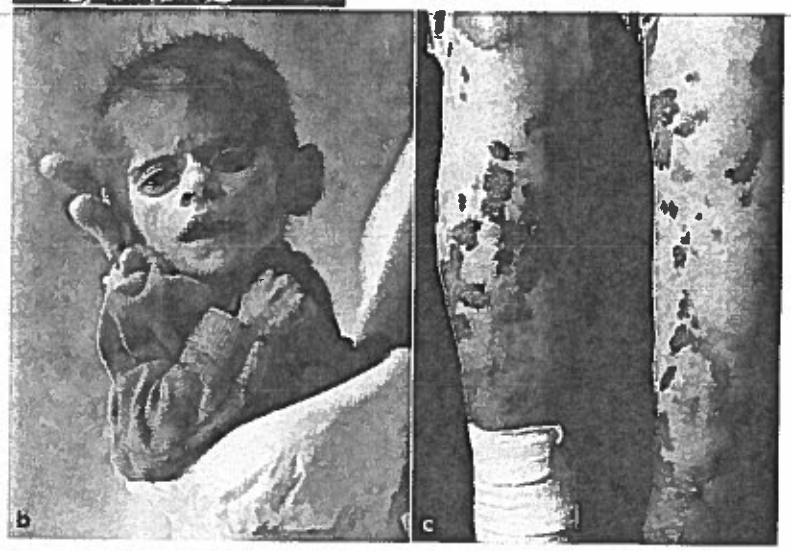
There is no way to rid the body of the HIV virus, no cure for those already infected. At first, an infected person appears to be in good health, perhaps fighting "a bout of flu." But symptoms eventually emerge that foreshadow AIDS: fever, many enlarged lymph nodes, chronic fatigue and weight loss, and drenching night sweats. Then, infections caused by normally harmless microorganisms strike. Yeast infections of the mouth, esophagus, and vagina often occur, as well as a form of pneumonia caused by the fungus *Pneumocystis carinii*. Colored lesions erupt. These lesions are evidence of Kaposi's sarcoma, a type of cancer that is common among AIDS patients (Figure 38.22*c*).

Table 38.6 Global HIV and AIDS Cases

Region	AIDS Cases	New HIV Cases
Sub-Saharan Africa	22,500,000	1,700,000
South/Southeast Asia	4,000,000	340,000
Central Asia/East Europe	1,600,000	150,000
Latin America	1,600,000	100,000
North America	1,300,000	46,000
East Asia	800,000	92,000
Western/Central Europe	760,000	31,000
Middle East/North Africa	380,000	35,000
Caribbean Islands	230,000	17,000
Australia/New Zealand	75,000	14,000
Worldwide total	33,200,000	2,500,000

Source: Joint United Nations Programme HIV/AIDS, 2007 data





HIV Revisited HIV is a retrovirus that has a lipid envelope. Remember, this type of envelope is a small piece of plasma membrane a virus particle acquires as it buds from a cell (Section 21.2). Proteins jut out from the envelope, span it, and line its inner surface. Just beneath the envelope, more viral proteins enclose two RNA strands and copies of reverse transcriptase. When a virus particle infects a cell, the reverse transcriptase copies the viral RNA into DNA, which becomes integrated into the host cell's DNA.

A Titanic Struggle HIV mainly infects macrophages, dendritic cells, and helper T cells. When virus particles enter the body, dendritic cells engulf them. The dendritic cells then migrate to lymph nodes, where they present processed HIV antigen to naive T cells. An army of HIV-neutralizing IgG antibodies and HIV-specific cytotoxic T cells forms.

We have just described a typical adaptive immune response. It rids the body of most—but not all—of the virus. In this first response, HIV infects a few helper T cells in a few lymph nodes. For years or even decades, the IgG antibodies keep the level of HIV in the blood low, and the cytotoxic T cells kill HIV-infected cells.

Patients are contagious during this stage, although they might show no symptoms of AIDS. HIV viruses persist in a few of their helper T cells, in a few lymph nodes. Eventually, the level of virus-neutralizing IgG in the blood plummets, and T cell production slows. Why IgG decreases is still a major topic of research, but its effect is certain: The adaptive immune system

Figure 38.22 AIDS. (**a**) A human T cell (*blue*), infected with HIV (*red*). (**b**) This Romanian baby contracted AIDS from his mother's breast milk. He did not live long enough to develop lesions of Kaposi's sarcoma (**c**), a cancer that is a common symptom of HIV infection in older AIDS patients.

becomes less and less effective at fighting the virus. The number of virus particles rises; up to 1 billion HIV viruses are built each day. Up to 2 billion helper T cells become infected. Half of the viruses are destroyed and half of the helper T cells are replaced every two days. Lymph nodes begin to swell with infected T cells.

Eventually, the battle tilts as the body makes fewer replacement helper T cells and the body's capacity for adaptive immunity is destroyed. Other types of viruses make more particles in a day, but the immune system eventually wins. HIV demolishes the immune system. Secondary infections and tumors kill the patient.

Transmission HIV is transmitted most frequently by having unprotected sex with an infected partner. The virus occurs in semen and vaginal secretions, and can enter a partner through epithelial linings of the penis, vagina, rectum, and the mouth. The risk of transmission increases by the type of sexual act; for example, anal sex carries 50 times the risk of oral sex.

Infected mothers can transmit HIV to a child during pregnancy, labor, delivery, or breast-feeding. HIV also travels in tiny amounts of infected blood in the syringes shared by intravenous drug abusers, or by patients in hospitals of poor countries. HIV is not transmitted by casual contact.

Testing Most AIDS tests check blood, saliva, or urine for antibodies that bind to HIV antigens. These antibodies are detectable in 99 percent of infected people within three months of exposure to the virus. One test can detect viral RNA at about eleven days after exposure. Currently, the only reliable tests are performed in clinical laboratories; home test kits may result in false negatives, which may cause an infected person to unknowingly transmit the virus.

Drugs and Vaccines Drugs cannot cure AIDS, but they can slow its progress. Of the twenty or so FDA-approved AIDS drugs, most target processes unique to retroviral replication. For example, RNA nucleotide analogs such as AZT are called reverse transcriptase inhibitors. They interrupt HIV replication when they substitute for normal nucleotides in the viral RNA-to-DNA synthesis process (Sections 16.1 and 21.2). Other drugs such as protease inhibitors affect different parts of the viral replication cycle.

A three-drug "cocktail" of one protease inhibitor plus two reverse transcriptase inhibitors is currently the most successful AIDS therapy, and has changed the course of the disease from a short-term death sentence to a long-term, often manageable illness.

Figure 38.23 At the Global AIDS Program's International Laboratory Branch of the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, researcher Amanda McNulty examines a DNA electrophoresis gel. She is investigating HIV drug resistance in people from Africa, Vietnam, and Haiti.

Researchers are using several strategies to develop an HIV vaccine. At this writing, organizations around the world are testing 42 different HIV vaccines. Most of them consist of isolated HIV proteins or peptides, and many deliver the antigens in viral vectors. Live, weakened HIV virus is an effective vaccine in chimpanzees, but the risk of HIV infection from the vaccines themselves far outweighs their potential benefits in humans. Other types of HIV vaccines are notoriously ineffective. IgG antibody exerts selective pressure on the virus, which has a very high mutation rate because it replicates so fast. The human immune system just cannot produce antibodies fast enough to keep up with the mutations (Figure 38.23).

At present, our best option for halting the spread of HIV is prevention, by teaching people how to avoid being infected. The best protection against AIDS is to avoid unsafe behaviors. In most circumstances, HIV infection is the consequence of a choice: either to have unprotected sex, or to use a shared needle for intravenous drugs. Educational programs around the world are having an effect on the spread of the virus: In many (but not all) countries, the incidence of new cases of HIV each year is beginning to slow. Overall, however, our global battle against AIDS is not being won.

Take-Home Message

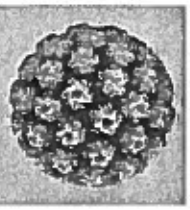
What is AIDS?

- AIDS occurs as a result of infection by HIV, a virus that infects lymphocytes and so cripples the human immune system.

IMPACTS, ISSUES REVISITED | Frankie's Last Wish

The Gardasil HPV vaccine consists of viral capsid proteins that self-assemble into virus-like particles (VLPs). These proteins are produced by a recombinant yeast, *Saccharomyces cerevisiae*. The yeast carries genes for one capsid protein from each of four strains of HPV, so the VLPs carry no viral DNA. Thus, the VLPs are not infectious, but the antigenic proteins they consist of elicit an immune response at least as strong as infection with HPV virus.

How would you vote?
Should clinical trials of potential vaccines be held to the same ethical standards no matter where they take place? See CengageNOW for details, then vote online.



Summary

Section 38.1 Three lines of immune defense protect vertebrates from infection. An **antigen**-bearing pathogen that breaches surface barriers triggers **innate immunity**, a set of general defenses that usually prevents populations of pathogens from becoming established in the internal environment. **Adaptive immunity**, which can specifically target billions of different antigens, follows. **Complement** and signaling molecules such as **cytokines** coordinate the activities of white blood cells (**dendritic cells, macrophages, neutrophils, basophils, mast cells, eosinophils, B** and **T lymphocytes**, and **NK cells**) in **immunity**.

Sections 38.2, 38.3 Vertebrates can fend off pathogens such as those that cause dental **plaque** at body surfaces with physical, mechanical, and chemical barriers (including **lysozyme**). Most **normal flora** do not cause disease unless they penetrate inner tissues.

Section 38.4 An innate immune response includes fast, general responses that can eliminate invaders before an infection can become established. Complement attracts phagocytes, and punctures some invaders. **Inflammation** begins when mast cells in tissue release histamine, which increases blood flow and also makes capillaries leaky to phagocytes and plasma proteins. **Fever** fights infection by increasing the metabolic rate.

- *Use the animation on CengageNOW to investigate inflammation and the action of complement.*

Section 38.5 Adaptive immunity is characterized by self/nonself recognition, target specificity, diversity (the capacity to intercept billions of different pathogens), and memory. B and T cells carry out adaptive responses.

The **antibody-mediated immune response** and the **cell-mediated immune response** work together to rid the body of a specific pathogen. Macrophages, dendritic cells, and B cells engulf and digest viruses or bacteria into bits. The phagocytes then present the antigenic bits on their surfaces bound to **MHC markers** (self markers). T cells that recognize the complexes via **T cell receptors (TCRs)** initiate the formation of many **effector cells** that target other antigen-bearing particles. **Memory cells** that are reserved for later encounters with the same antigen also form.

Sections 38.6, 38.7 B cells, assisted by T cells and signaling molecules, carry out antibody-mediated immune responses. B cells make **antibodies** that bind to specific antigens. Antigen receptors—**T cell receptors** and **B cell receptors** (a type of antibody)—recognize specific antigens. These receptors are the basis of the immune system's capacity to recognize billions of different antigens.

- *Use the animations on CengageNOW to see an antibody-mediated immune response, how antigen receptor diversity is generated, and clonal selection of B cells.*

Section 38.8 Antigen-presenting cells, T cells, and NK cells interact in cell-mediated responses. They target and kill body cells altered by infection or cancer.

- *Use the animation on CengageNOW to observe a cell-mediated immune response.*

Sections 38.9–38.11 **Allergens** are normally harmless substances that induce an immune response; sensitivity to an allergen is called an **allergy**. **Immunization** with **vaccines** designed to elicit immunity to specific diseases saves millions of lives each year. In an **autoimmune response**, a body's own cells are inappropriately recognized as foreign and attacked. Immune deficiency is a reduced capacity to mount an immune response.

Section 38.12 **AIDS** is caused by HIV, a virus that destroys the immune system mainly by infecting helper T cells. At present, AIDS cannot be cured.

Self-Quiz

Answers in Appendix III

1. _____ is/are the first line of defense against threats.
   a. Skin, mucous membranes
   b. Tears, saliva, gastric fluid
   c. Urine flow
   d. Resident bacteria
   e. a through c
   f. all of the above
2. Complement proteins _____.
   a. form pore complexes
   b. promote inflammation
   c. neutralize toxins
   d. a and b
3. _____ trigger immune responses.
   a. Cytokines
   b. Lysozymes
   c. Immunoglobulins
   d. Antigens
   e. Histamines
   f. all of the above
4. Name one defining characteristic of innate immunity.
5. Name one defining characteristic of adaptive immunity.
6. Antibodies are _____.
   a. antigen receptors
   b. made only by B cells
   c. proteins
   d. all of the above
7. _____ binding antigen triggers allergic responses.
   a. IgA b. IgE c. IgG d. IgM e. IgD

39 Respiration

IMPACTS, ISSUES Up in Smoke

Each day, 3,000 or so teenagers join the ranks of habitual smokers in the United States. Most are not even fifteen years old. When they first light up, they cough and choke on the irritants in the smoke. Most become dizzy and nauseated, and develop headaches. Sound like fun? Hardly. Why, then, do they ignore signals about threats to the body and work so hard to be a smoker? Mainly to fit in. To many adolescents, a misguided perception of social benefits overwhelms the seemingly remote threats to health (Figure 39.1).

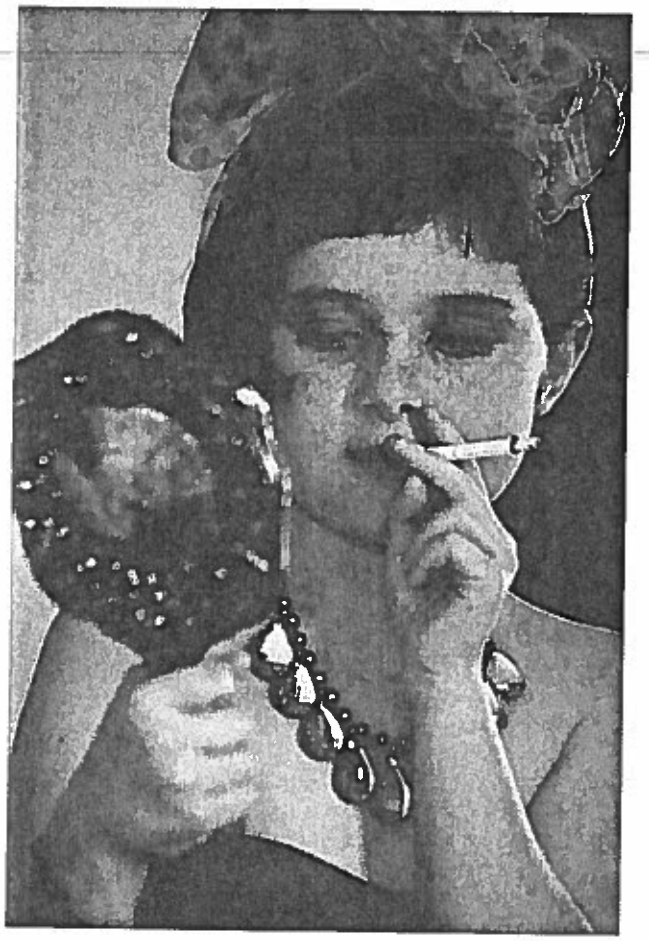
Despite teenage perceptions, changes that can make the threat a reality start right away. Ciliated cells keep many pathogens and pollutants that enter airways from reaching the lungs. These cells can be immobilized for hours by the smoke from a single cigarette. Smoke also kills white blood cells that patrol and defend respiratory tissues. Pathogens multiply in the undefended airways. The result is more colds, more asthma attacks, and more bronchitis.

The highly addictive stimulant nicotine constricts blood vessels, which increases blood pressure. The heart has to work harder to pump blood through the narrowed tubes. Nicotine also triggers a rise in "bad" cholesterol (LDL) and a decline in the "good" kind (HDL) in blood. It makes blood stickier, encouraging clots that can block blood vessels.

Tobacco smoke has more than forty known carcinogens and 80 percent of lung cancers occur in smokers. Women who smoke are more susceptible to cancers than men. On average, women develop cancers earlier, and with lower exposure to tobacco. Fewer than 15 percent of women diagnosed with lung cancer survive five years. Smoking also increases breast cancer risk; females who start to smoke as teenagers are about 70 percent more likely to get breast cancer than those women who never smoked. Therefore, the trend of increased smoking among women in less-developed countries especially troubling.

Families, coworkers, and friends get unfiltered doses of the carcinogens in tobacco smoke. Each year in the United States, lung cancers arising from secondhand smoke kill about 3,000. Children exposed to secondhand smoke also are more likely to develop chronic middle ear infections, asthma, and other respiratory problems later in life.

This chapter samples a few respiratory systems. All exchange gases with the outside environment. They also contribute to homeostasis—maintaining the body's internal operating conditions within ranges that cells can tolerate. If you or someone you know smokes, you might use the chapter as a guide to smoking's impact on health. For a more graphic preview, find out what goes on every day with smokers in hospital emergency rooms or intensive care units. There's no glamor there. It is not cool, and it is not pretty.



See the video! Figure 39.1 Learning to smoke is easy, compared with trying to quit. In one survey, two-thirds of female smokers who were sixteen to twenty-four wanted to give up smoking entirely. Of those who tried to quit, only about 3 percent remained nonsmokers for an entire year.

Data Analysis Exercise

In 2003, Michelle Khan and her coworkers published their findings on a 10-year study in which they followed cervical cancer incidence and HPV status in 20,514 women. All women who participated in the study were free of cervical cancer when the test began. Pap tests were taken at regular intervals, and the researchers used a DNA probe hybridization test to detect the presence of specific types of HPV in the women's cervical cells.

The results are shown in Figure 38.24 as a graph of the incidence rate of cervical cancer by HPV type. Women who are HPV positive are often infected by more than one type, so the data were sorted into groups based on the women's HPV status ranked by type: either positive for HPV16; or negative for HPV16 and positive for HPV18; or negative for HPV16 and 18 and positive for any other cancer-causing HPV; or negative for all cancer-causing HPV.

1. At 110 months into the study, what percentage of women who were not infected with any type of cancer-causing HPV had cervical cancer? What percentage of women who were infected with HPV16 also had cervical cancer?

2. In which group would women infected with both HPV16 and HPV18 fall?

3. Is it possible to estimate from this graph the overall risk of cervical cancer that is associated with infection of cancer-causing HPV of any type?

4. Do these data support the conclusion that being infected with HPV16 or HPV18 raises the risk of cervical cancer?

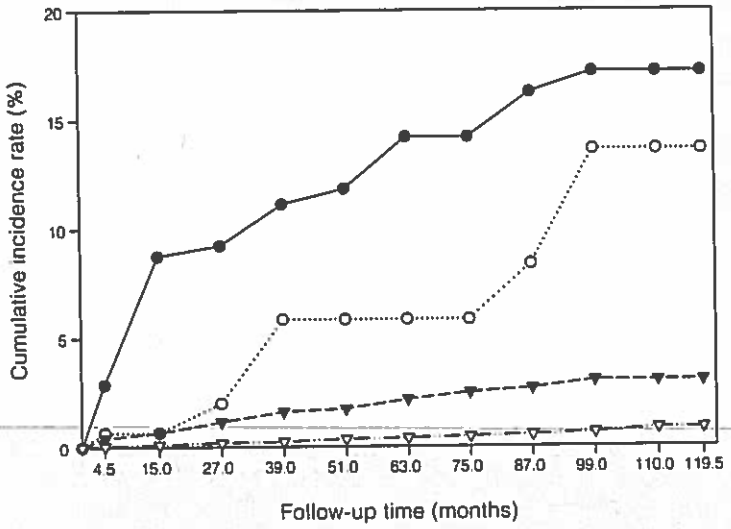


Figure 38.24 Cumulative incidence rate of cervical cancer correlated with HPV status in 20,514 women aged 16 years and older.

The data were grouped as follows: HPV16 positive (closed circles), or else HPV18 positive (open circles), or else all other cancer-causing HPV types combined (closed triangles). Open triangles: no cancer-causing HPV type was detected.

8. Antibody-mediated responses work against _____.
   a. intracellular pathogens
   b. extracellular pathogens
   c. cancerous cells
   d. both a and b
   e. both b and c
   f. a, b, and c

9. Cell-mediated responses work against _____.
   a. intracellular pathogens
   b. extracellular pathogens
   c. cancerous cells
   d. both a and b
   e. both a and c
   f. a, b, and c

10. _____ are targets of cytotoxic T cells.
   a. Extracellular virus particles in blood
   b. Virus-infected body cells or tumor cells
   c. Parasitic flukes in the liver
   d. Bacterial cells in pus
   e. Pollen grains in nasal mucus

11. Allergies occur when the body responds to _____.
   a. pathogens
   b. normally harmless substances
   c. toxins
   d. all of the above

12. Match the immunity concepts.

___anaphylactic shock	a. neutrophil
___antibody secretion	b. effector B cell
___phagocyte	c. general defense
___immune memory	d. immune response against own body
___autoimmunity	e. secondary response
___antigen receptor	f. B cell receptor
___inflammation	g. hypersensitivity to an allergen

Visit CengageNOW for additional questions.

Critical Thinking

1. As described in Section 38.10, Edward Jenner was lucky. He performed a potentially harmful experiment on a boy who managed to survive the procedure. What would happen if a would-be Jenner tried to do the same thing today in the United States?

2. Elena developed chicken pox when she was in first grade. Later in life, when her children developed chicken pox, she remained healthy even though she was exposed to countless virus particles daily. Explain why.

3. Before each flu season, you get a flu shot, an influenza vaccination. This year, you get "the flu" anyway. What happened? There are at least three explanations.

4. Monoclonal antibodies are made by immunizing a mouse with a particular antigen, then removing its spleen. Individual B cells producing mouse antibodies specific for the antigen are isolated from the mouse's spleen and fused with cancerous B cells from a myeloma cell line.

The resulting hybrid myeloma cells—hybridoma cells—are cloned, or grown in tissue culture as separate cell lines. Each line produces and secretes antibodies that recognize the antigen to which the mouse was immunized. These monoclonal antibodies can be purified and used for research or other purposes.

Monoclonal antibodies are sometimes used in passive immunization. They tend to be effective, but only in the immediate term. IgG produced by one's own immune system can last up to about six months in the bloodstream, but monoclonals delivered in passive immune therapy typically last for less than a week. Why the difference?