The immune system is a finely tuned network that protects the host against foreign antigens, particularly infectious agents. Sometimes this network breaks down, causing the immune system to react inappropriately. Inappropriate immune responses may be (1) exaggerated against environmental antigens (allergy); (2) misdirected against the host’s own cells (autoimmunity); (3) directed against beneficial foreign tissues, such as transfusions or transplants (alloimmunity); or (4) insufficient to protect the host (immune deficiency). All of these can be serious or life threatening. Exaggerated immune responses (allergy) are the most common, but they are usually the least life threatening.

**HYPERSENSITIVITY: ALLERGY, AUTOIMMUNITY, AND ALLOIMMUNITY**

Allergy, autoimmunity, and alloimmunity are classified as hypersensitivity reactions. **Hypersensitivity** is an altered immunologic response to an antigen that results in disease or damage to the individual. Allergy, autoimmunity, and alloimmunity (also termed isomimmunity) can be most easily understood in relationship to the source of the antigen against which the hypersensitivity response is directed (Table 7-1). **Allergy** refers to a hypersensitivity to environmental antigens. These can include medicines, natural products (e.g., pollens, bee stings), infectious agents, and any other antigen that is not naturally found in the individual.

**Autoimmunity** is a disturbance in the immunologic tolerance of self-antigens. The immune system normally does not strongly recognize the individual’s own antigens. Healthy individuals of all ages, but particularly the elderly, may produce low quantities of antibodies against their own antigens (autoantibodies) without developing overt autoimmune disease. Therefore, the presence of low quantities of autoantibodies does not necessarily indicate a disease state. Autoimmune diseases occur when the immune system reacts against self-antigens to such a degree that autoantibodies or autoreactive T cells damage the individual’s tissues. Many clinical disorders are associated with autoimmunity and are generally referred to as autoimmune diseases (Table 7-2).

**Alloimmune diseases** occur when the immune system of one individual produces an immunologic reaction against tissues of another individual. Alloimmunity can be observed during immunologic reactions against transfusions, transplanted tissue, or the fetus during pregnancy.

The mechanism that initiates the onset of hypersensitivity, whether allergy, autoimmunity, or alloimmunity, is not completely understood. It is generally accepted that genetic, infectious, and possibly environmental factors contribute to hypersensitivity.
Mechanisms of Hypersensitivity

Diseases caused by hypersensitivity reactions can be characterized also by the particular immune mechanism that results in the disease (see Table 7-1). These mechanisms are apparent in most hypersensitivity reactions and have been divided into four distinct types: type I (IgE-mediated reactions), type II (tissue-specific reactions), type III (immune complex-mediated reactions), and type IV (cell-mediated reactions) (Table 7-3). This classification is artificial and seldom is a particular disease associated with only a single mechanism. The four mechanisms are interrelated, and in most hypersensitivity reactions several mechanisms can be at work simultaneously or sequentially.

As with all immune responses, hypersensitivity reactions require sensitization against a particular antigen that results in a primary immune response. Disease symptoms appear after an adequate secondary immune response occurs. Hypersensitivity reactions are immediate or delayed, depending on the time required to elicit clinical symptoms after reexposure to the antigen. Reactions that occur within minutes to a few hours after exposure to antigen are termed immediate hypersensitivity reactions. Delayed hypersensitivity reactions may take several hours to appear and are at maximum severity days after reexposure to the antigen.

The most rapid and severe immediate hypersensitivity reaction is anaphylaxis. Anaphylaxis occurs within minutes of reexposure to the antigen and can be either systemic (generalized) or cutaneous (localized). Symptoms of systemic anaphylaxis include itching, erythema, vomiting, abdominal cramps, diarrhea, and breathing difficulties. Severe anaphylactic reactions may include contraction of bronchial smooth muscle, edema of the throat, breathing difficulties, decreased blood pressure, shock, and death. An example of systemic anaphylaxis is an allergic reaction to bee stings. Cutaneous anaphylaxis results in local symptoms, such as pain, swelling, and redness, which occur at the site of exposure to an antigen (e.g., a painful local reaction to an injected vaccine or drug).

Type I: IgE-mediated hypersensitivity reactions

Type I reactions are mediated by antigen-specific IgE and the products of tissue mast cells (Figure 7-1). Most common allergic reactions are type I reactions. In addition, most type I reactions occur against environmental antigens and are therefore allergic. Because of this strong association, many health care professionals use the term allergy to indicate only IgE-mediated reactions. However, IgE can contribute to some autoimmune and alloimmune diseases, and many common allergies (e.g., poison ivy) are not mediated by IgE.

IgE has a relatively short life span in the blood because it rapidly binds to Fc receptors on mast cells (see Figure 7-1). Unlike Fc receptors on phagocytes, which bind IgG that has reacted with antigen, the Fc receptors on mast cells specifically bind IgE that has not previously interacted with antigen. After a large amount of IgE has bound to the mast cell, an individual is considered sensitized. Further exposure of a sensitized individual to the allergen results in degranulation of the mast cell and the release of mast cell products (see Chapter 5).

Mechanisms of IgE-mediated hypersensitivity

The most potent mediator of IgE-mediated hypersensitivity is histamine, which affects several key target cells. Acting through H1 receptors, histamine contracts bronchial smooth muscles (bronchial constriction), increases vascular permeability (edema), and causes vasodilation (increased blood flow) (see Chapter 5). The interaction of histamine...
with H2 receptors results in increased gastric acid secretion. Some type I allergic responses can be controlled by blocking histamine receptors with antihistamines.

**CLINICAL MANIFESTATIONS**  The clinical manifestations of type I reactions are attributable mostly to the biologic effects of histamine. The tissues most commonly affected by type I responses contain large numbers of mast cells and are sensitive to the effects of histamine released from them. These tissues are found in the gastrointestinal tract, the skin, and the respiratory tract (Figure 7-2 and Table 7-4).
Gastrointestinal allergy is caused primarily by allergens that enter through the mouth—usually foods or medicines. Symptoms include vomiting, diarrhea, or abdominal pain. Foods most often implicated in gastrointestinal allergies are milk, chocolate, citrus fruits, eggs, wheat, nuts, peanut butter, and fish. When food is the allergen, the active immunogen may be an unidentifiable product of food breakdown by digestive enzymes. Sometimes the allergen is a drug, an additive, or a preservative in the food. For example, cows treated for mastitis with penicillin yield milk containing trace amounts of this antibiotic. Thus, hypersensitivity apparently caused by milk proteins may instead be the result of an allergy to penicillin.

**Urticaria**, or hives, is a dermal (skin) manifestation of allergic reactions (Figure 7-3). The underlying mechanism is the localized release of histamine and increased vascular permeability, resulting in limited areas of edema. Urticaria is characterized by white fluid-filled blisters (wheals) surrounded by areas of redness (flares). The **wheal and flare reaction** is usually accompanied by itching. Not all urticarial symptoms are caused by immunologic reactions. Some, termed nonimmunologic urticaria, result from exposure to cold temperatures, emotional stress, medications, systemic diseases, or malignancies (e.g., lymphomas).

Effects of allergens on the mucosa of the eyes, nose, and respiratory tract include conjunctivitis (inflammation of the membranes lining the eyelids) (see Figure 7-3), rhinitis (inflammation of the mucous membranes of the nose), and asthma (constriction of the bronchi). Symptoms are caused by vasodilatation, hypersecretion of mucus, edema, and swelling of the respiratory mucosa. Because the mucous membranes lining the respiratory tract are continuous, they are all adversely affected. The degree to which each is affected determines the symptoms of the disease.

The central problem in allergic diseases of the lung is obstruction of the large and small airways (bronchi) of the lower respiratory tract by bronchospasm (constriction of smooth muscle in airway walls), edema, and thick secretions. This leads to ventilatory insufficiency, wheezing, and difficult or labored breathing (see Chapter 26).

Certain individuals are genetically predisposed to develop allergies and are called **atopic**. In families in which one parent has an allergy, allergies develop in about 40% of the offspring. If both parents have allergies, the incidence may be as high as 80%. Atopic individuals tend to produce higher quantities of IgE and to have more Fc receptors for IgE on their mast cells. The airways and the skin of atopic individuals have increased responsiveness to a wide variety of both specific and nonspecific stimuli.

**EVALUATION AND TREATMENT** Allergic reactions can be life threatening; therefore, it is essential that severely allergic individuals be made aware of the specific allergen against which they are sensitized and instructed to avoid contact with that material. Several tests are available to evaluate allergic individuals. These include food challenges, skin tests with allergens, and laboratory tests for total IgE and allergen-specific IgE.

Clinical **desensitization** to allergens can be achieved in some individuals. Minute quantities of the allergen to which the person is sensitive are injected in increasing doses over a prolonged period. This procedure may reduce the severity of the allergic reaction in the treated individual. However, this form of therapy is associated with a risk of systemic anaphylaxis, which can be severe and life threatening.

**Type II: Tissue-specific hypersensitivity reactions**

Type II hypersensitivities are generally reactions against a specific cell or tissue. Cells express a variety of antigens on their surfaces, some of which are called tissue-specific antigens because they are expressed on the plasma membranes of only certain cells. Platelets, for example, have groups of antigens that are found on no other cells of the body. The symptoms of many type II diseases are determined by which tissue or organ expresses the particular antigen. Environmental antigens (e.g., drugs or their

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Rate of Development</th>
<th>Class of Antibody Involved</th>
<th>Principal Effector Cells Involved</th>
<th>Participation of Complement</th>
<th>Examples of Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IgE-mediated reaction</td>
<td>Immediate</td>
<td>IgE</td>
<td>Mast cells</td>
<td>No</td>
<td>Seasonal allergic rhinitis</td>
</tr>
<tr>
<td></td>
<td>Tissue-specific reaction</td>
<td>Immediate</td>
<td>IgG, IgM</td>
<td>Macrophages in tissues</td>
<td>Frequently</td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Autoimmune thrombocytopenic purpura,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Graves disease, autoimmune hemolytic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>anemia</td>
</tr>
<tr>
<td>III</td>
<td>Immune complex-mediated reaction</td>
<td>Immediate</td>
<td>IgG, IgM</td>
<td>Neutrophils</td>
<td>Yes</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>IV</td>
<td>Cell-mediated reaction</td>
<td>Delayed</td>
<td>None</td>
<td>Lymphocytes, Macrophages</td>
<td>No</td>
<td>Contact sensitivity to poison</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ivy and metals (jewelry)</td>
</tr>
</tbody>
</table>

**TABLE 7-3 Immunologic Mechanisms of Tissue Destruction**

The central problem in allergic diseases of the lung is obstruction of the large and small airways (bronchi) of the lower respiratory tract by bronchospasm (constriction of smooth muscle in airway walls), edema, and thick secretions. This leads to ventilatory insufficiency, wheezing, and difficult or labored breathing (see Chapter 26).

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metabolites) may bind to the plasma membranes of specific cells (especially erythrocytes and platelets) and function as targets of type II reactions.

The five general mechanisms by which type II hypersensitivity reactions can affect cells are shown in Figure 7-4. All of these mechanisms begin with antibody binding to tissue-specific antigens or antigens that have attached to particular tissues. First, the cell may be destroyed by antibody and complement. The antibody (IgM or IgG) reacts with an antigen on the surface of the cell, causing activation of the complement cascade through the classical pathway. Formation of the membrane attack complex (C5–9) damages the membrane and may result in lysis of the cell (see Figure 7-4, A). For example, erythrocytes are destroyed by complement-mediated lysis in individuals with autoimmune hemolytic anemia (see Chapters 20 and 21) or as a result of an alloimmune reaction to mismatched transfused blood cells.

Second, antibody may cause cell destruction through phagocytosis by macrophages. The antibody may additionally activate complement, resulting in the deposition of C3b on the cell surface. Receptors on the macrophage recognize and bind opsonins (e.g., antibody or C3b) and increase phagocytosis of the target cell (Figure 7-4, B, phagocytosis is illustrated in Chapter 5). For example, antibodies against platelet-specific antigens or against red blood cell antigens of the Rh system cause their removal by phagocytosis in the spleen.

The third mechanism involves toxic products produced by neutrophils. Soluble antigen such as medications, molecules

Figure 7-1 ■ Mechanism of Type I, IgE-Mediated Reactions. First exposure to an allergen stimulates B lymphocytes to mature into plasma cells that produce IgE. The IgE is adsorbed to the surface of the mast cell by binding with IgE-specific Fc receptors. When an adequate amount of IgE is bound the mast cell is “sensitized.” During a second exposure, the allergen cross-links the surface-bound IgE and causes degranulation of the mast cell. The initial phase is characterized by vasodilation, vascular leakage, and smooth muscle spasm or glandular secretions, usually within 5 to 30 minutes after exposure to antigen. The late phase occurs 2 to 8 hours later without additional exposure to antigen and results from infiltration of tissues with inflammatory cells, including eosinophils, neutrophils, and basophils. (See Chapter 5 for more details on the role of mast cells in inflammation.)

Figure 7-2 ■ Type I Hypersensitivity Reactions. Symptoms of type I allergic reactions are indicated.
released from infectious agents, or molecules released from an individual’s own cells may enter the circulation. In some instances, the antigens are deposited on the surface of tissues, where they bind antibody (see Figure 7-4, C). The antibody may activate complement, resulting in the release of C3a and C5a, which are chemotactic for neutrophils, and deposition of complement component C3b. Neutrophils are attracted, bind to the tissues through receptors for the Fc portion of antibody (Fc receptor) or for C3b, and release their granules onto the healthy tissue. The components of neutrophil granules, as well as the toxic oxygen products produced by these cells, will damage the tissue.

The fourth mechanism is antibody-dependent cell-mediated cytotoxicity (ADCC) (see Figure 7-4, D). This mechanism involves natural killer (NK) cells. Antibody on the target cell is recognized by Fc receptors on the NK cells, which release toxic substances that destroy the target cell.

The fifth mechanism does not destroy the target cell but rather causes the cell to malfunction. The antibody is usually directed against antigenic determinants associated with specific cell-surface receptors (see Figure 7-4, D). The antibody changes the function of the receptor by preventing interactions with their normal ligands, replacing the ligand and inappropriately stimulating the receptor, or destroying the receptor. For example, in the hyperthyroidism (excessive thyroid activity) of Graves disease, autoantibody binds to and activates receptors for thyroid-stimulating hormone (TSH) (a pituitary hormone that controls the production of the hormone thyroxine by the thyroid). In this way, the antibody stimulates the thyroid cells to produce thyroxine. Under normal conditions, the increasing levels of thyroxine in the blood would signal the pituitary to decrease TSH production, which would result in less stimulation of the TSH receptor in the thyroid and a concomitant decrease in thyroxine production. Increasing amounts of thyroxine in the blood have no effect on antibody levels, and thyroxine production continues to increase despite decreasing amounts of TSH (see Chapter 18).

**Type III: Immune complex–mediated hypersensitivity reactions**

**Mechanisms of type III hypersensitivity**

Most type III hypersensitivity diseases are caused by antigen-antibody (immune) complexes that are formed in the circulation and deposited later in vessel walls or other tissues (Figure 7-5). The primary difference between type II and type III mechanisms is that in type II hypersensitivity antibody binds to the antigen on the cell surface, whereas in type III the antibody binds to soluble antigen that was released into the blood or body fluids, and the complex is then deposited in the tissues. Type III reactions are not organ specific, and symptoms have little to do with the particular antigenic target of the antibody. The harmful effects of immune complex deposition are caused by complement activation, particularly through the generation of chemotactic factors for neutrophils. The neutrophils bind to antibody and C3b contained in the complexes and attempt to ingest the immune complexes. They are often unsuccessful because the complexes are bound to large areas of tissue. During the attempted phagocytosis, large quantities of lysosomal enzymes are released into the inflammatory site instead of into phagolysosomes. The attraction of neutrophils

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**TABLE 7-4 Causes of Clinical Allergic Reactions**

<table>
<thead>
<tr>
<th>Typical Allergen</th>
<th>Mechanism of Hypersensitivity</th>
<th>Clinical Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INGESTANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foods</td>
<td>Type I</td>
<td>Gastrointestinal allergy</td>
</tr>
<tr>
<td>Drugs</td>
<td>Types I, II, III</td>
<td>Urticaria, immediate drug reaction, hemolytic anemia, serum sickness</td>
</tr>
<tr>
<td><strong>INHALANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pollens, dust, molds</td>
<td>Type I</td>
<td>Allergic rhinitis, bronchial asthma</td>
</tr>
<tr>
<td><em>Aspergillus fumigatus</em></td>
<td>Types I, III</td>
<td>Allergic bronchopulmonary aspergillosis</td>
</tr>
<tr>
<td>Thermophilic actinomycetes*</td>
<td>Types III, IV</td>
<td>Extrinsic allergic alveolitis</td>
</tr>
<tr>
<td><strong>INJECTANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Types I, II, III</td>
<td>Immediate drug reaction, hemolytic anemia, serum sickness</td>
</tr>
<tr>
<td>Bee venom</td>
<td>Type I</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Type III</td>
<td>Localized Arthus reaction</td>
</tr>
<tr>
<td>Serum</td>
<td>Types I, III</td>
<td>Anaphylaxis, serum sickness</td>
</tr>
<tr>
<td><strong>CONTACTANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poison ivy, metals</td>
<td>Type IV</td>
<td>Contact dermatitis</td>
</tr>
</tbody>
</table>


*An order of fungi that is stimulated to grow by warmth.*
and the subsequent release of lysosomal enzymes cause most of the resulting tissue damage.

**Immune complex disease**

Two prototypic models of type III hypersensitivity help explain the variety of diseases in this category. Serum sickness is a model of systemic type III hypersensitivities, and the Arthus reaction is a model of localized or cutaneous reactions.

**Serum sickness**—type reactions are caused by the formation of immune complexes in the blood and their subsequent generalized deposition in target tissues. Typically affected tissues are the blood vessels, joints, and kidneys. Other symptoms include fever, enlarged lymph nodes, rash, and pain at sites of inflammation. Serum sickness was initially described as a complication of therapeutic administration of horse serum that contained antibody against tetanus toxin. Foreign serum generally is not administered to individuals today, although serum sickness reactions can be caused by the repeated intravenous administration of other antigens, such as drugs, and the characteristics of serum sickness are observed in systemic type III autoimmune diseases.

A form of serum sickness is **Raynaud phenomenon**, a condition caused by the temperature-dependent deposition of immune complexes in the capillary beds of the peripheral circulation. Certain immune complexes precipitate at temperatures below normal body temperature, particularly in the tips of the fingers, toes, and nose, and are called **cryoglobulins**. The precipitates block the circulation and cause localized pallor and numbness, followed by cyanosis (a bluish tinge resulting from oxygen deprivation) and eventually gangrene if the circulation is not restored.
An Arthus reaction is caused by repeated local exposure to an antigen that reacts with preformed antibody and forms immune complexes in the walls of the local blood vessels. Symptoms of an Arthus reaction begin within 1 hour of exposure and peak 6 to 12 hours later. The lesions are characterized by a typical inflammatory reaction, with increased vascular permeability, an accumulation of neutrophils, edema, hemorrhage, clotting, and tissue damage.

Arthus reactions may be observed after injection, ingestion, or inhalation of allergens. Skin reactions can follow subcutaneous or intradermal inoculation with drugs, fungal extracts, or antigens used in skin tests. Gastrointestinal reactions, such as gluten-sensitive enteropathy (celiac disease), follow ingestion of antigen, usually gluten from wheat products (see Chapter 35). Allergic alveolitis (farmer’s lung, pigeon breeder’s disease) is an Arthus-like acute hemorrhagic inflammation of the air sacs (alveoli) of the lungs resulting from inhalation of fungal antigens, usually particles from moldy hay or pigeon feces (see Chapter 26).

**Type IV: Cell-mediated hypersensitivity reactions**

Whereas types I, II, and III hypersensitivity reactions are mediated by antibody, type IV reactions are mediated by T lymphocytes and do not involve antibody (Figure 7-6). Type IV mechanisms occur through either cytotoxic T lymphocytes (Tc cells) or cytokine-producing Th1 cells. Tc cells attack and destroy cellular targets directly. Th1 cells produce cytokines that recruit and activate phagocytic cells, especially macrophages. Destruction of the tissue is usually caused by direct killing by Tc cells or the release of soluble factors, such as lysosomal enzymes and toxic reactive oxygen species, from activated macrophages.

Clinical examples of type IV hypersensitivity reactions include graft rejection, the skin test for tuberculosis, and allergic reactions resulting from contact with such substances as poison ivy and metals. A type IV component also may be present in many autoimmune diseases. For example, T cells against type II collagen (a protein present in joint tissues) contribute to the destruction of joints in rheumatoid arthritis; T cells against a thyroid cell surface antigen contribute to the destruction of the thyroid in autoimmune hypothyroiditis (Hashimoto disease); and T cells against an antigen on the surface of pancreatic beta cells (the cell that normally produces insulin) are responsible for beta cell destruction in insulin-dependent (type 1) diabetes mellitus.

In 1891, Ehrlich was the first to thoroughly describe a type IV hypersensitivity reaction in the skin, leading to the development of a diagnostic skin test for tuberculosis. The reaction follows an intradermal injection of tuberculin antigen into a suitably sensitized individual and is called a delayed hypersensitivity skin test because of its slow onset—24 to 72 hours to reach maximum intensity. The reaction site is infiltrated with T lymphocytes and macrophages, resulting in a clear hard center (induration) and a reddish surrounding area (erythema).

Allergic type IV reactions are elicited by some environmental antigens that are haptons (Chapter 6) that become immunogenic after binding to larger (carrier) proteins in the individual. In allergic contact dermatitis, the carrier protein is in the skin. The best-known example is poison ivy (Figure 7-7). The antigen is a plant catechol, urushiol, which reacts with normal skin proteins and evokes a cell-mediated immune response. Skin reactions to industrial
chemicals, cosmetics, detergents, clothing, food, metals, and topical medicines (such as penicillin) are elicited by the same mechanism. Contact dermatitis consists of lesions only at the site of contact with the allergen, such as a metal allergy to jewelry.

**QUICK CHECK 7-1**

1. Distinguish among the four types of hypersensitivity mechanisms.
2. What is the mechanism of anaphylaxis?
3. What are some clinical examples of type IV hypersensitivity?

---

**Antigenic Targets of Hypersensitivity Reactions**

**Allergy**

**Allergens**

Environmental antigens that cause allergic responses are called *allergens*. It is not known why some antigens are allergens and others are not. Typical allergens include pollens (e.g., ragweed), molds and fungi (e.g., *Penicillium notatum*), foods (e.g., milk, eggs, fish), animals (e.g., cat dander, dog dander), cigarette smoke, and components of house dust (e.g., fecal pellets of house mites). Often the allergen is contained within a particle that is too large to be phago-
cytosed or is surrounded by a protective nonallergenic coat. The actual allergen is released after enzymatic breakdown (e.g., by lysozyme in secretions) of the larger particle.

**Allergic disease: bee sting allergy**

Allergies are the most common hypersensitivity diseases. The majority of allergies are type I reactions that lead to annoying symptoms, including runny nose, sneezing, and other relatively mild reactions. In some individuals, however, these reactions can be excessive and life-threatening (anaphylaxis). Anaphylactic reactions have been described against peanuts and other nuts, shellfish, fish, milk, eggs, and some medications.

Bee venoms contain a mixture of enzymes and other proteins that may serve as allergens. About 1% of children may have an anaphylactic reaction to bee venom. Within minutes they may develop more than normal swelling (edema) at the bee sting site, followed by generalized hives, itching, and swelling in areas distal from the sting (e.g., eyes, lips), and other systemic symptoms including flushing, sweating, dizziness, and headache. The most severe symptoms may include gastrointestinal (e.g., stomach cramps, vomiting), respiratory (e.g., tightness in the throat, wheezing, difficulties breathing), and vascular (e.g., low blood pressure, shock) reactions. Severe respiratory and vascular reactions may lead to death.

For an individual with known bee sting hypersensitivity, lifestyle changes include avoidance of stinging or biting insects. If a child has had a previous anaphylactic reaction, the chance of having another is about 60%. Most individuals carry self-injectable epinephrine. The primary life-threatening symptoms result from contraction of respiratory smooth muscle. Autonomic nervous system mediators, such as epinephrine, bind to specific receptors on smooth muscle and reverse the effects of histamine and result in muscle relaxation. The administration of antihistamines will have little effect because histamine has already bound to H1 receptors and initiated severe bronchial smooth muscle contraction. Long-term protection may be afforded by desensitization in most individuals.

**Autoimmunity**

It is fairly well established that autoimmune diseases can be familial. Affected family members may not all develop the same disease, but several members may have different disorders characterized by a variety of hypersensitivity reactions, including autoimmune and allergic.

**Breakdown of tolerance**

An individual is usually tolerant to his or her own antigens. Tolerance is a state of immunologic control so that the individual does not make a detrimental immune response against his or her own cells and tissues. Autoimmune disease results from a breakdown of this tolerance.

Although many theories exist concerning the initial cause of autoimmune diseases, only one example is known: acute rheumatic fever. In a small number of individuals with group A streptococcal sore throats, the M proteins in the bacterial capsule mimic (antigenic mimicry) normal heart antigens and induce antibodies that also react with proteins in the heart valve, damaging the valve. Thus, rheumatic fever is a type II autoimmune hypersensitivity. Additionally, some streptococcal skin or throat infections release bacterial antigens into the blood that form circulating immune complexes. The complexes may deposit in the kidneys and initiate an immune complex glomerulonephritis (inflammation of the kidney). Thus, streptococcal antigens (an environmental antigen) may also cause a type III allergic hypersensitivity (poststreptococcal glomerulonephritis).

**Autoimmune disease: systemic lupus erythematosus**

Systemic lupus erythematosus (SLE) is the most common, complex, and serious of the autoimmune disorders. SLE is characterized by the production of a large variety of antibodies (autoantibodies) against self-antigens, including nucleic acids, erythrocytes, coagulation proteins, phospholipids, lymphocytes, platelets, and many other self-components. The most characteristic autoantibodies are against nucleic acids (e.g., single-stranded DNA, double-stranded DNA), histones, ribonucleoproteins, and other nuclear materials. The blood normally contains many of these products of cellular turnover and breakdown. Excessive levels of autoantibodies react with the circulating antigen and form circulating immune complexes. The deposition of circulating DNA/anti-DNA complexes in the kidneys can cause severe kidney inflammation. Similar reactions can occur in the brain, heart, spleen, lung, gastrointestinal tract, peritoneum, and skin. Thus, some of the symptoms of SLE result from a type III hypersensitivity reaction. Other symptoms, such as destruction of red blood cells (anemia), lymphocytes (lymphopenia), and other cells, may be type II hypersensitivity reactions.

SLE, like most autoimmune diseases, occurs more often in women (approximately a 10:1 predominance of females), especially in the 20- to 40-year-old age group. Blacks are affected more often than whites (about an eightfold increased risk). A genetic predisposition for the disease has been implicated on the basis of increased incidence in twins and the existence of autoimmune disease in the families of individuals with SLE.

Clinical manifestations of SLE include arthralgias or arthritis (90% of individuals), vasculitis and rash (70% to 80% of individuals), renal disease (40% to 50% of individuals), hematologic abnormalities (50% of individuals, with anemia being the most common complication), and cardiovascular diseases (30% to 50% of individuals). As with most autoimmune diseases, SLE is characterized by frequent remissions and exacerbations. Because the signs and symptoms affect almost every body system and tend to come and go, SLE is extremely difficult to diagnose. This has led to the development of a list of 11 common clinical findings. The serial or simultaneous presence of at least four of them indicates that the individual has SLE. The findings are as follows:

1. Malar (butterfly) rash
2. Photosensitivity
3. Oral ulcers
4. Arthritis
5. Pleuritis or pericarditis
6. Renal involvement
7. Neurologic abnormalities
8. Hematologic abnormalities
9. Disseminated lupus (SLE) arthritis
10. Cutaneous vasculitis
11. Hypertension

The serial or simultaneous presence of at least four of the 11 symptoms is diagnostic of SLE.
1. Facial rash confined to the cheeks (malar rash)
2. Discoid rash (raised patches, scaling)
3. Photosensitivity (skin rash developed as a result of exposure to sunlight)
4. Oral or nasopharyngeal ulcers
5. Nonerosive arthritis of at least two peripheral joints
6. Serositis (inflammation of membranes of lung [pleurisy] or heart [pericarditis])
7. Renal disorder (proteinuria of 0.5 g/day or cellular casts)
8. Neurologic disorders (seizures or psychosis)
9. Hematologic disorders (hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia)
10. Immunologic disorders (positive lupus erythematosus [LE] cell preparation, anti–double stranded DNA, anti-Smith [Sm] antigen, false-positive serologic test for syphilis, or antiphospholipid antibodies [anticardiolipin antibody or lupus anticoagulant])
11. Presence of antinuclear antibody (ANA)

**HEALTH ALERT**

**Autoimmune Diseases Affect Women More Than Men**

To explain why women are especially susceptible to autoimmune disorders, researchers are investigating whether the sex hormones estrogen and testosterone affect the immune system. Although inconclusive, there are several findings that support the idea that differences between gender are based on sex hormones. Disappointing, however, is that treating affected individuals with sex hormones have had inconclusive results. Other hormones may affect the progress of autoimmune diseases. In mice, the cells of males and females differ in how they process newly made proteins. These differences may also contribute to the increased susceptibility to autoimmune diseases in women.

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There is no cure for SLE or most other autoimmune diseases. The goals of treatment are to control symptoms and prevent further damage by suppressing the autoimmune response. Nonsteroidal antiinflammatory drugs, such as aspirin, ibuprofen, or naproxen, reduce inflammation and relieve pain. Corticosteroids are often prescribed for more serious active disease. Immunosuppressive drugs (e.g., methotrexate, azathioprine, or cyclophosphamide) are used to treat severe symptoms involving internal organs. Ultraviolet light can worsen symptoms (known as flares), and protection from sun exposure is helpful. Prolonged use of certain drugs can cause transient SLE-like symptoms, and the medication history is important for diagnostic evaluation. Improved outcomes may be available in the future with the continued advances in medical research and the use of stem cell treatments.

**Alloimmunity**

**Alloantigens**

Genetic diversity is the norm in humans. Diversity is also observed among self-antigens, so that two individuals may have different antigens on their tissues and, therefore, be able to make an immune response against each other’s tissues. Some self-antigens, such as the ABO blood group, have limited diversity with very few different antigens being expressed in the population, whereas others, such as the HLA system, have tremendous diversity.

**Alloimmune disease: transfusion reactions**

Red blood cells (erythrocytes) express several important surface antigens, known collectively as the blood group antigens, which can be targets of alloimmune reactions. More than 80 different red cell antigens are grouped into several dozen blood group systems. The most important of these, because they provoke the strongest humoral alloimmune response, are the ABO and Rh systems.

**ABO system.** The ABO blood group consists of two major carbohydrate antigens, labeled A and B (Figure 7-8), that are expressed on virtually all cells. These are codominant so that both A and B can be simultaneously expressed, resulting in an individual having any one of four different blood types. The erythrocytes of persons with blood type A have the type A carbohydrate antigen (i.e., carry the A antigen), those with blood type B carry the B antigen, those with blood type AB carry both A and B antigens, and those of blood type O carry neither the A nor the B antigen. A person with type A blood also has circulating antibodies to the B carbohydrate antigen. If this person receives blood from a type AB or B individual, a severe transfusion reaction occurs, and the transfused erythrocytes are destroyed by agglutination or complement-mediated lysis. Similarly, a type B individual (whose blood contains anti-A antibodies) cannot receive blood from a type A or AB donor. Type O individuals, who have neither antigen but have both anti-A and anti-B antibodies, cannot accept blood from any of the other three types. These naturally occurring antibodies, called isohemagglutinins, are IgM immunoglobulins and are induced early in life by similar antigens expressed on naturally occurring bacteria in the intestinal tract.

Because individuals with type O blood lack both types of antigens, they are considered universal donors, meaning that anyone can accept their red blood cells. Similarly, type AB individuals are considered universal recipients because they lack both anti-A and anti-B antibodies and can be transfused with any ABO blood type. Agglutination and lysis cause harmful transfusion reactions that can be prevented only by complete and careful ABO matching between donor and recipient.

**Rh system.** The Rh blood group is a group of antigens expressed only on red blood cells. This is most diverse group of red cell antigens, consisting of at least 45 separate antigens, although only one is considered very important. The most important is the D antigen. Individuals who express the D antigen on their red cells are Rh-positive, whereas
individuals who do not express the D antigen are Rh-negative. When discussing the gene for the Rh antigen, the letter d is used to indicate lack of D. Rh-positive individuals can have either a DD or Dd genotype, whereas Rh-negative individuals have the dd genotype. About 85% of North Americans are Rh positive. Rh-negative individuals can make an IgG antibody to the D antigen (anti-D) if exposed to Rh-positive erythrocytes.

A disease called hemolytic disease of the newborn was most commonly caused by IgG anti-D alloantibody produced by Rh-negative mothers against erythrocytes of their Rh-positive fetuses (see Chapter 21). The mother’s antibody crossed the placenta and destroyed the fetus’ red blood cells. The occurrence of this particular form of the disease has decreased dramatically because of the use of prophylactic anti-D immunoglobulin (i.e., Rhogam). By mechanisms that are still not completely understood, administration of anti-D antibody within a few days of exposure to RhD-positive erythrocytes completely prevents sensitization against the D antigen. Because hemolytic disease of the newborn related to the D antigen has been controlled, alloantibodies against the other Rh antigens have become more important. In general, these alloantibodies are associated with a less severe hemolytic disease.

**Alloimmune disease: transplant rejection**

**Major histocompatibility complex.** Molecules of the major histocompatibility complex (MHC) were discussed in Chapter 6 as antigen-presenting molecules. MHC molecules are also a major target of transplant rejection. As a result of studies of transplantation, the human MHC molecules are also referred to as human leukocyte antigens (HLA) and the different MHC genetic loci are commonly called HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ, and HLA-DP (Figure 7-9). Additional genes for complement components (e.g., C4, factor B) are also contained in the MHC and are referred to as class III loci. The class I (HLA-A, B, and C) and class II MHC loci (HLA-DR, DQ, and DP) are the most genetically diverse (polymorphic) of any human genetic loci. Within the human population, the numbers of possible different alleles (i.e., forms of the gene) expressed by each locus is astounding. For example, more than 300 different HLA-A antigens are expressed in the population. These numbers are based on the polymorphism of observed DNA sequences and may not reflect differences in function.

![Figure 7-8](image_url) **ABO Blood Types.** The relationship of antigens and antibodies associated with the ABO blood groups. The surfaces of erythrocytes of individuals with blood group A have the A antigenic carbohydrate. The blood of these individuals has IgM antibodies against the B antigen. In individuals with blood group B, the red blood cells have the B antigenic carbohydrate, and the blood contains IgM antibodies against the A antigen. In individuals of the blood group AB, the same cells have both the A and B antigens. These individuals do not have antibody to either A or B antigens. The erythrocytes of blood group O individuals have neither antigen, but their blood contains both antibodies to A and B.

![Figure 7-9](image_url) **Human Leukocyte Antigens (HLA).** The major histocompatibility complex (MHC) is located on chromosome 6 and contains genes that code for class I antigens, class II antigens, and class III proteins (i.e., complement proteins and cytokines). (From Mudge-Grout C: Immunologic disorders, St Louis, 1992, Mosby.)
Clearly, not every allele is expressed in the same individual. Humans have two copies of each MHC locus (one inherited from each parent) that are codominant so that molecules encoded by each parent’s genes are expressed on the cell surface. Within an individual, each locus will express only one allele. For instance, each person will have at most two different HLA-A proteins (one from each parent). However, with the tremendous number of possible alleles that can be expressed throughout the population, it is likely that any two unrelated individuals will have different MHC antigens and would reject organs transplanted from one to another.

**Transplantation.** The diversity of MHC molecules becomes clinically relevant during organ transplantation. The recipient of a transplant can mount an immune response against the foreign MHC antigens on the donor tissue, resulting in rejection. To minimize the chance of tissue rejection, the donor and recipient are often tissue-typed beforehand to identify differences in HLA antigens. Because of the large number of different alleles, it is highly unlikely that a perfect match can be found between someone who needs a transplant and a potential donor from the general population. The more similar two individuals are in their HLA tissue type, the more likely a transplant from one to the other will be successful. Clearly, the most successful transplants would be between identical twins because they are identical genetically.

The specific combination of alleles at the six major HLA loci on one chromosome (A, B, C, DR, DQ, and DP) is termed a haplotype. Each individual has two HLA haplotypes, one from the paternal chromosome 6 and another from the maternal chromosome (Figure 7-10). Each parent passes on one set of HLA antigens to each of his or her offspring, meaning that children usually share half their HLA antigens with each parent. Odds dictate that children will share one haplotype with half their siblings and either no haplotypes or both haplotypes with a quarter of their siblings. Thus, the chance of finding a match among siblings is much higher (25%) than the general population.

**Rejection.** Transplant rejection may be classified as hyperacute, acute, or chronic, depending on the amount of time that elapses between transplantation and rejection. **Hyperacute rejection** is immediate and rare. When the circulation is reestablished to the grafted area, the graft may immediately turn white (the so-called white graft) instead of a normal pink color. Hyperacute rejection usually occurs because of preexisting antibody (type II reaction) to antigens on the vascular endothelial cells in the grafted tissue.

**Acute rejection** is a cell-mediated immune response that occurs within days to months after transplantation. This type of rejection occurs when the recipient develops an immune response against unmatched HLAs after transplantation. A biopsy of the rejected organ usually shows an infiltration of lymphocytes and macrophages characteristic of a type IV reaction.

**Chronic rejection** may occur after a period of months or years of normal function. It is characterized by slow, progressive organ failure. Chronic rejection may result from a weak cell-mediated (type IV) reaction against minor histocompatibility antigens on the grafted tissue.

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**QUICK CHECK 7-2**

1. Why do certain drugs become immunogenic to the host?
2. Why is SLE considered an autoimmune disease?
3. Define the different types of graft rejection.

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**Figure 7-10** Inheritance of HLA. HLA alleles are inherited in a codominant fashion; both maternal and paternal antigens are expressed. Specific HLA alleles are commonly given numbers to indicate different antigens. In this example, the mother has linked genes for HLA-A3 and HLA-B12 on one chromosome 6 and genes for HLA-A10 and HLA-B5 on the second chromosome 6. The father has HLA-A28 and HLA-B7 on one chromosome and HLA-A1 and HLA-B35 on the second chromosome. The children from this pairing may have one of four possible combinations of maternal and paternal HLA.
INFECTION

Modern health care has shown great progress in preventing and treating infectious diseases. In developed countries, sanitary living conditions, clean water, uncontaminated food, vaccinations, and antimicrobials make death from infectious disease most common only among those with debilitating diseases or immunosuppression. In the United States, heart disease and malignancies greatly surpass infectious disease as major causes of death.

However, infectious diseases remain the number one cause of death worldwide (causing 26% of all deaths in 2005). In Africa, 62% of deaths in 2005 were attributable to infection. The infectious cause of death may be underestimated because many deaths related to cancer are the result of secondary infections because the immune system can be severely depressed both the cancer itself and by many of the treatments used to treat the cancer.

Developing countries with dense populations and poor sanitation are victims of plague, cholera, malaria, tuberculosis, leprosy, and schistosomiasis. Only smallpox has been eradicated worldwide by vaccination. Although vaccines and antimicrobials have altered the prevalence of some infectious diseases, mutant strains of bacteria and viruses have emerged with resistance to protection provided by drug therapy. The emergence of new diseases, such as West Nile virus, severe acute respiratory syndrome (SARS), Lyme disease, Hantavirus, and drug-resistant tuberculosis are examples of the current intense challenges being faced in the struggle to prevent and control infectious disease.

Microorganisms and Humans: A Dynamic Relationship

For many microorganisms, the human body is a very hospitable site to grow and flourish. The microorganisms are provided with nutrients and appropriate conditions of temperature and humidity. In many cases a mutual relationship exists, in which humans and the microorganisms benefit (Box 7-1). For instance, the human gut is colonized by a large variety of microorganisms that make up normal human flora. The normal floras of different body areas are summarized in Table 7-5. These bacteria are provided with nutrients from ingested food, and in exchange they produce enzymes that facilitate the digestion and utilization of many molecules in the human diet, produce antibacterial factors that prevent colonization by pathogenic microorganisms (see Chapter 5), and produce usable metabolites (e.g., vitamin K, B vitamins). This relationship normally is maintained through the physical integrity of the skin and mucosal epithelium and other mechanisms that guarantee that the immune and inflammatory systems do not attack these symbiotes (see Box 7-1). If those systems are compromised, many microorganisms will leave their normal sites and cause infection. Individuals with deficiencies in their immune system become easily infected with opportunistic microorganisms—those that normally would not cause disease but seize the opportunity provided by the person’s decreased immune or inflammatory responses.

True pathogens have devised means to circumvent the normal controls provided by the host’s main defensive barriers, the inflammatory system, and the immune system. Infection by a pathogen is influenced by several factors:

- **Mechanism of action.** Direct damage of cells, interference with cellular metabolism, and rendering a cell dysfunctional because of the accumulation of pathogenic substances and toxin production
- **Infectivity.** Ability of the pathogen to invade and multiply in the individual—for example, coagulase (an enzyme) that causes coagulation and allows some microorganisms, such as Staphylococcus, to clot and form a sticky layer around themselves, protecting themselves against host defenses
- **Pathogenicity.** Ability of an agent to produce disease—success depends on its speed of reproduction, extent of tissue damage, and production of toxins
- **Virulence.** Potency of a pathogen measured in terms of the number of microorganisms or micrograms of toxin required to kill a host—for example, measles is of low virulence; the rabies virus is highly virulent
- **Immunogenicity.** Ability of pathogens to induce an immune response
- **Toxigenicity.** A factor important in determining a pathogen’s virulence, such as production of soluble toxins or endotoxin

The portal of entry for pathogenic microorganisms may be by direct contact, inhalation, ingestion, or the bite of animals or insects. Spread of infection is facilitated by the ability of pathogens to attach to cell surfaces, release enzymes that dissolve protective barriers, escape the action of phagocytes, or resist the effect of low pH. After penetrating protective barriers, pathogens then spread through the lymph and blood for invasion of tissues and organs, where they multiply and cause disease. In humans the route of entrance of many pathogenic microorganisms also becomes the site of shedding of new infectious agents to other individuals, completing a cycle of infection (Figure 7-11).
### TABLE 7-5
Normal Indigenous Flora of the Human Body

<table>
<thead>
<tr>
<th>Location</th>
<th>Microorganisms</th>
</tr>
</thead>
</table>
| Skin          | Predominantly gram-positive cocci and rods  
Staphylococcus epidermidis, corynebacteria, mycobacteria, and streptococci are primary inhabitants;  
Staphylococcus aureus in some people; also yeasts (Candida, Pityrosporum) in some areas of skin  
Numerous transient microorganisms may become temporary residents  
In moist areas, gram-negative bacteria  
Around sebaceous glands, Propionibacteria and brevibacteria  
The mite Demodex folliculorum lives in hair follicles and sebaceous glands around the face |
| Nose          | Predominantly gram-positive cocci and rods, especially S. epidermidis  
Some people are nasal carriers of pathogenic bacteria, including S. aureus, ß-hemolytic streptococci, and Corynebacterium diphtheriae |
| Mouth         | A complex of bacteria that includes several species of streptococci, Actinomyces, lactobacilli, and Haemophilus  
Anaerobic bacteria and spirochetes colonize the gingoval crevices |
| Pharynx       | Similar to flora in mouth plus staphylococci, Neisseria, and diphtheroids  
Some asymptomatic persons also harbor the pathogens pneumococcus, Haemophilus influenzae, Neisseria meningitidis, and C. diphtheriae |
| Distal intestine | Enterococci, lactobacilli, clostridia, Salmonella, Shigella, Klebsiella, Proteus, Pseudomonas, enterococci and other streptococci, bacilli, and Escherichia coli |
| Colon         | Typical bacteria found on the skin, especially S. epidermidis and diphtheroids; also lactobacilli and nonpathogenic streptococci |
| Distal urethra | Birth to 1 mo: similar to adult  
1 mo to puberty: S. epidermidis, diphtheroids, E. coli, and streptococci  
Puberty to menopause: Lactobacillus acidophilus, diphtheroids, staphylococci, streptococci, and a variety of anaerobes  
Postmenopause: similar to prepubescence |


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**Figure 7-11** - The Spread of Infection. (Redrawn from Mims CA et al: *Medical microbiology*, St Louis, 1993, Mosby.)
**Classes of Infectious Microorganisms**

Infectious disease can be caused by microorganisms that range in size from 20 nanometers (nm) (poliovirus) to 10 meters (m) (tapeworm). Classes of pathogenic microorganisms and their characteristics are summarized in Table 7-6. Some mechanisms of tissue damage caused by microorganisms are summarized in Table 7-7.

**Pathogenic Defense Mechanisms**

Our multiple layers of defense against infection were described in Chapters 5 and 6. True pathogens have devised ways of circumventing these barriers. For example, some bacteria produce thick capsules of carbohydrate or protein that are antiphagocytic, preventing efficient phagocytosis. Others defend themselves by producing toxins that kill neutrophils. Because the primary immune response may take a week to develop adequately, some pathogens proliferate at rates that surpass the development of a protective response. Table 7-8 contains examples of microorganisms that fight off the immune system or cause it to attack the host.

Viral pathogens bypass many defense mechanisms by hiding within cells and away from normal inflammatory or immune responses. In many cases, however, because viral agents must spread from cell to cell, the developing immune response eventually cures the infection so the disease is self-limiting. However, many viruses (e.g., measles, herpes) are inaccessible to antibodies after initial infection because they do not circulate in the bloodstream but instead remain inside infected cells, spreading by direct cell-to-cell contact. Antibodies that block a virus from attaching to a target cell (neutralizing antibodies) are most effective in preventing the initial infection. Other viruses, such as polio and influenza, spread through the blood, are more susceptible to the effects of circulating antibodies, and can be controlled by antibodies even after the initial infection.

Some viruses can elude the immune response by undergoing antigenic variation. The virus can change its appearance by altering surface antigens. Influenza infection provides an example of how this occurs. The “flu” virus undergoes yearly antigenic drift resulting from mutations in key surface antigens, hemagglutinin (H antigen) and neuraminidase (N antigen), allowing the emergence of new strains of influenza virus. Thus, immunity against the previous year’s viruses is no longer completely protective, thus creating the need for new vaccines every year. Antigenic shifts are major changes in antigenicity that occur from recombination of genes for H and N among different strains of viruses and can result in major worldwide pandemics. Other pathogens, such as some parasitic microorganisms, use a similar approach and change surface antigens by gene switching. A parasite (i.e., African trypanosomes) may carry thousands of genes for different surface molecules that the parasite can switch on and off at frequent intervals. Consequently, the immune system is always trying to catch up by generating new antibodies and T cells against the new antigens.

**Infection and Injury**

**Bacterial disease**

Bacteria are prokaryocytes (lacking a discrete nucleus) and are relatively small. They can be aerobic or anaerobic and motile or immotile. Spherical bacteria are called cocci, rod-like forms are called bacilli, and spiral forms are termed spirochetes. Gram stain and acid-fast stain are important for differentiating gram-positive or gram-negative types of bacteria. The different types of gram-positive and gram-negative bacteria are reviewed in Figure 7-12. The general structure of bacteria is reviewed in Figure 7-13.

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**TABLE 7-6**

<table>
<thead>
<tr>
<th>Class</th>
<th>Size</th>
<th>Examples of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viruses</td>
<td>20–30 nm</td>
<td>Measles, Hepatitis B, Pneumonitis</td>
</tr>
<tr>
<td>Bacteria</td>
<td>0.8–15 µm</td>
<td>Staphylococcal wound infection, Cholera, Streptococcal pneumonia</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>200–1000 nm</td>
<td>Trachoma, Rocky Mountain spotted fever</td>
</tr>
<tr>
<td>Rickettsiae</td>
<td>300–1200 nm</td>
<td>Mycoplasma pneumonia, Tuberculosis</td>
</tr>
<tr>
<td>Mycoplasma</td>
<td>125–350 nm</td>
<td>Tinea pedis (athlete’s foot), Thrush (Candida)</td>
</tr>
<tr>
<td>Mycobacterium</td>
<td>1–10 µm</td>
<td>Histoplasmosis, Giardiasis, Malaria</td>
</tr>
<tr>
<td>Fungi</td>
<td>2–200 µm</td>
<td>Trichinosis, Filariasis</td>
</tr>
<tr>
<td>Protozoa</td>
<td>1–360 µm</td>
<td></td>
</tr>
<tr>
<td>Helminths</td>
<td>3 mm to 10 m</td>
<td></td>
</tr>
</tbody>
</table>
Bacterial survival and growth depend on the effectiveness of the body’s defense mechanisms and on the bacterium’s ability to resist these defenses. Many pathogens have devised ways of preventing destruction by the inflammatory and immune systems. For example, some bacteria produce thick capsules of carbohydrate or protein that are antiphagocytic, preventing efficient opsonization and phagocytosis. Such coatings include the thick polysaccharide covering of the pneumococcus and the waxy capsule surrounding the tubercle bacillus. The long M protein on the cell wall of the streptococcus suppresses complement activation.

Other bacteria survive and proliferate in the body by producing exotoxins and endotoxins that injure cells and tissues. Exotoxins are proteins released during bacterial growth. They are usually enzymes and have highly specific effects on host cells; they include cytotoxins, neurotoxins, pneumotoxins, enterotoxins, and hemolysins. Exotoxins can damage cell membranes, activate second messengers, and inhibit protein synthesis. Exotoxins are immunogenic.
and elicit the production of antibodies known as antitoxins. Consequently, vaccines are available for many of the exotoxins (i.e., tetanus, diphtheria, and pertussis). Some strains of toxin-producing group A streptococci cause destructive skin infections (e.g., flesh-eating bacteria syndrome, or necrotizing fasciitis) and pneumonia that may kill an individual within 2 days.

Endotoxins (lipopolysaccharides [LPS]) are contained in the cell walls of gram-negative bacteria and are released during lysis, or destruction, of the bacteria. Endotoxin may be released also from the membrane of the bacteria during bacterial growth or during treatment with antibiotics, which therefore cannot prevent the toxic effects of the endotoxin. Bacteria that produce endotoxins are called pyrogenic bacteria because they activate the inflammatory process and produce fever. The innermost part of the lipopolysaccharide, lipid A, is made of polysaccharide and fatty acids and is responsible for the substance’s toxic effects.

Inflammation is the body’s initial response to the presence of the bacteria. Vascular permeability is increased, allowing blood-borne substances (i.e., the complement system) involved in bacterial destruction to access the site of infection. Endotoxins increase capillary permeability further by activating the anaphylatoxins (C5a and C3a) of the complement cascade. Capillary permeability may increase sufficiently to permit the escape of large volumes of plasma, contributing to hypotension and, in severe cases, cardiovascular shock (see Chapter 23). Endotoxin also can activate the coagulation cascade, leading to the syndrome of disseminated (or diffuse) intravascular coagulation (see Chapter 20).

Septicemia (bacteremia) is the presence of bacteria in the blood and is caused by a failure of the body’s defense mechanisms. The usual cause is proliferation of gram-negative bacteria, although a few gram-positive bacteria and fungi can cause it. Symptoms of gram-negative septic shock are produced by endotoxins. Once in the blood, endotoxins cause the release of vasoactive peptides and cytokines that affect blood vessels, producing vasodilation, which reduces blood pressure, causes decreased oxygen delivery, and produces subsequent cardiovascular shock (see Chapter 23). Sepsis is diagnosed from evaluation of blood cultures.

Endotoxic shock is a complication of sepsis and can be fatal to the individual. The cytokine TNF-α plays a pivotal role in the pathogenesis of endotoxic shock. TNF-α is produced by activated macrophages on exposure to endotoxin from gram-negative bacterial infections. It is sometimes called cachectin because of its role in promoting cachexia in individuals with cancer. (Cachexia is discussed in Chapter 10; cytokines are discussed in Chapters 5 and 6; types of shock are discussed in Chapter 23.)

<table>
<thead>
<tr>
<th>TABLE 7-8</th>
<th>Examples of Mechanisms Used by Pathogens to Resist the Immune System</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanisms</strong></td>
<td><strong>Effect on Immunity</strong></td>
</tr>
<tr>
<td><strong>DESTROYS OR BLOCKS COMPONENT OF IMMUNE SYSTEM</strong></td>
<td></td>
</tr>
<tr>
<td>Produce toxins</td>
<td>Kills phagocyte or interferes with chemotaxis</td>
</tr>
<tr>
<td>Produce antioxidants (e.g., catalase, superoxide dismutase)</td>
<td>Prevents phagocytosis by inhibiting fusion between phagosome and lysosomal granules</td>
</tr>
<tr>
<td>Produce protease to digest IgA</td>
<td>Prevents killing by O2-dependent mechanisms Promotes bacterial attachment</td>
</tr>
<tr>
<td>Produce surface molecules that mimic Fc receptors and bind antibody</td>
<td>Prevents activation of complement system Prevents antibody functioning as opsonin</td>
</tr>
<tr>
<td><strong>MIMIC SELF-ANTIGENS</strong></td>
<td></td>
</tr>
<tr>
<td>Produce surface antigens (e.g., M protein, red blood cell antigens) that are similar to self-antigens</td>
<td>Pathogen resembles the individual’s own tissue; in some individuals, antibodies can be formed against the self-antigen, leading to hypersensitivity disease (e.g., antibody to M protein also reacts with cardiac tissue, causing rheumatic heart disease; antibody to red blood cell antigens can cause anemia)</td>
</tr>
<tr>
<td><strong>CHANGE ANTIGENIC PROFILE</strong></td>
<td></td>
</tr>
<tr>
<td>Undergo mutation of antigens or activate genes that change surface molecules</td>
<td>Immune response delayed because of failure to recognize new antigen</td>
</tr>
</tbody>
</table>
**Viral disease**

Viral diseases are the most common afflictions of humans and include a variety of diseases ranging from the common cold and the “cold sore” of herpes simplex to several types of cancers and AIDS. Viruses are very simple microorganisms consisting of nucleic acid (the viral genome) protected from the environment by a layer or layers of proteins. They are sensitive to many environmental factors and cannot survive for long outside a cell.

**Viral replication**

Virions (viral particles) do not possess any of the metabolic organelles found in prokaryotes (e.g., bacteria) or eukaryotes (e.g., human cells). Thus, viruses have no metabolism. Unlike bacteria, viruses are incapable of independent reproduction. Their replication depends totally on their ability to infect a permissive host cell—a cell that cannot resist viral invasion and replication. The replication cycle of most viruses can be divided into six distinct phases: adsorption, penetration, uncoating, replication, assembly, and release. Infection with a virus begins with a virion binding to a specific receptor on the plasma membrane of

**Figure 7-13** General Structure of Bacteria. A, The structure of the bacterial cell wall determines its staining characteristics with gram stain. A gram-positive bacterium has a thick layer of peptidoglycan (left). A gram-negative bacterium has a thick peptidoglycan layer and an outer membrane (right). B, Example of a gram-positive (darkly stained microorganisms, arrow) group A Streptococcus. This microorganism consists of cocci that frequently form chains. C, Example of a gram-negative (pink microorganisms, arrow) Neisseria meningitides in cerebrospinal fluid. Neisseria form complexes of two cocci (diplococci). (From Murray PR et al: Medical microbiology, ed 4, St Louis, 2002, Mosby.)

A host cell (Figure 7-14). The specificity of this virus-receptor interaction dictates the range of host cells that a particular virus will infect and therefore the clinical symptoms, which reflect the alteration of the function of the infected cells. For example, the influenza virus binds to a receptor on respiratory epithelial cells, causing symptoms of an upper respiratory tract infection. Once bound, the virion penetrates the plasma membrane by one of several means: by receptor-mediated endocytosis, by viral envelope fusion with the plasma membrane, or by directly crossing the plasma membrane.

**Figure 7-14** Stages of Viral Infection of a Host Cell. The virion (1) becomes attached to the cell’s plasma membrane by adsorption; (2) releases enzymes that weaken the membrane and allow it to penetrate the cell; (3) uncoats itself; (4) replicates; and (5) matures and escapes from the cell by budding from the plasma membrane. The infection then can spread to other host cells.

Viruses contain their genetic information in either DNA or ribonucleic acid (RNA). The viral genetic material is protected by a protein coat that must be removed in the cytoplasm of the infected host cell (uncoating). The viral genetic material may be processed by one of several paths, depending on the particular virus. Generally, all RNA viruses, except influenza and retroviruses, replicate their genetic material in the cytoplasm of the infected cell, and all DNA viruses, except poxviruses, require the DNA to enter the nucleus and use the cell’s DNA polymerases to replicate. Poxviruses provide their own DNA polymerase and replicate their DNA in the cytoplasm of the infected cell. Retroviruses generally convert their RNA genetic information to DNA using an enzyme contained in the virion—reverse transcriptase.

After infection, viruses usually make multiple copies of their genetic material and produce the necessary viral proteins for replication. New virions are assembled in the host cell’s cytoplasm and are released from the cell for transmission of the viral infection to other host cells. This cycle is referred to as the productive or lytic cycle because a large number of progeny are produced, and the result is often the destruction of the host cell.

Some viruses will not be productive initially but instead initiate a latency phase, during which the host cell is transformed. During this phase, the viral DNA may be integrated into the DNA of the host cell and become a permanent passenger in that cell and its progeny. In response to stimuli, such as stress, hormonal changes, or disease, the virus may exit latency and enter a productive cycle.
**Cellular effects of viruses**

Besides taking over the host cell’s metabolic machinery, viral infection can injure cells. In some viral infections, cellular destruction results from large quantities of virus being released from the cell’s plasma membrane. Alteration of the plasma membrane by the expression of new antigens as a result of viral infection can incite an immune response against the individual’s infected cells (e.g., hepatitis B virus). Once inside the cell, virions have many harmful effects, including the following:

1. The cessation of DNA, RNA, and protein synthesis (e.g., herpes virus)
2. Disruption of lysosomal membranes, resulting in release of “digestive” lysosomal enzymes that can kill the cell (e.g., herpes virus)
3. Fusion of host cells, producing multinucleated giant cells (e.g., respiratory syncytial virus)
4. Alteration of the antigenic properties, or “identity” of the infected cell, causing the individual’s immune system to attack the cell as if it were foreign (e.g., hepatitis B virus)
5. Transformation of host cells into cancerous cells, resulting in uninhibited and unregulated growth (e.g., human papilloma virus)

6. Promotion of secondary bacterial infection in tissues damaged by viruses

Examples of human diseases caused by specific viruses are listed in Table 7-9.

Viral pathogens bypass many defense mechanisms by developing intracellularly, thus hiding within cells and away from normal inflammatory or immune responses. In many cases, however, because viral agents must spread from cell to cell, the developing immune response eventually cures the infection so the disease is usually self-limiting, in that it resolves without the need for medications. Some viruses will persist, and a state of unapparent infection may result. In persistent infections, cellular injury may be minimal, and the virus persists until it is activated to replicate (e.g., the cold sores of herpesvirus infection). Immunity may limit recurrent outbreaks and protect the individual from an acute exacerbation only or may be sufficiently strong to prevent disease.

**Fungal disease**

Fungi are relatively large microorganisms with thick walls that grow as either single-celled yeasts (spheres) or multicelled molds (filaments or hyphae) (Figure 7-15). Some fungi can exist in either form and are called dimorphic.

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**TABLE 7-9**

**List of DNA and RNA Viruses of Human Importance**

<table>
<thead>
<tr>
<th>DNA VIRUSES</th>
<th>RNA VIRUSES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family</strong></td>
<td><strong>Family</strong></td>
</tr>
<tr>
<td>Adenoviridae</td>
<td>Arenaviridae</td>
</tr>
<tr>
<td></td>
<td>Astroviridae</td>
</tr>
<tr>
<td></td>
<td>Bunyaviridae</td>
</tr>
<tr>
<td>Hepadnaviridae</td>
<td>Caliciviridae</td>
</tr>
<tr>
<td></td>
<td>Coronavirusidae</td>
</tr>
<tr>
<td>Herpesvirdae</td>
<td>Flaviviridae</td>
</tr>
<tr>
<td></td>
<td>Filoviridae</td>
</tr>
<tr>
<td>Papillomaviridae</td>
<td>Orthomyxoviridae</td>
</tr>
<tr>
<td>Paroviridae</td>
<td>Paramyxoviridae</td>
</tr>
<tr>
<td>Polyomaviridae</td>
<td>Picornaviridae</td>
</tr>
<tr>
<td>Poxviridae</td>
<td>Retroviridae</td>
</tr>
</tbody>
</table>

**Viral Members**

- Human adenoviruses
- Hepatitis B virus
- Herpes simplex 1 and 2 varicella zoster virus cytomegalovirus, Epstein-Barr virus, human herpes-viruses 6, 7, and 8
- Human papilloma viruses
- Parvovirus B-19
- BK and JC-polyomaviruses
- Variola, vaccinia, orf, molluscum contagiosum, monkeypox
- Lymphocytic choriomeningitis virus, Lassa fever virus
- Gastroenteritis-causing astroviruses
- Arboviruses including California encephalitis and LaCrosse viruses; nonarboviruses including sin nombre and related hantaviruses
- Noroviruses and hepatitis E virus
- Coronavirus, including SARS coronavirus
- Ebola and Marburg hemorrhagic fever viruses
- Arboviruses including yellow fever, dengue, West Nile, Japanese encephalitis, and St. Louis encephalitis viruses, nonarboviruses including hepatitis C virus
- Influenza A, B, and C viruses
- Parainfluenza viruses, mumps virus, measles virus, respiratory syncytial virus, metapneumovirus, Nipah virus
- Polio viruses, coxsackie A viruses, coxsackie B viruses, echoviruses, enteroviruses 68–71, enterovirus, 72 (hepatitis A virus), rhinoviruses
- Rotavirus, Colorado tick fever virus
- Human immunodeficiency viruses (HIV-1 and HIV-2), human T-lymphotropic viruses (HTLV-1 and HTLV-2)
- Rabies virus
- Eastern, Western and Venezuela equine encephalitis, viruses, rubella virus

fungi. The cell walls of fungi are rigid and multilayered. The wall is composed of polysaccharides different from the peptidoglycans of bacteria. The lack of peptidoglycans allows fungi to resist the action of bacterial cell wall inhibitors such as penicillin and cephalosporin. In contrast to bacteria, the cytosols of fungi contain organelles: mitochondria, ribosomes, Golgi apparatus, microtubules, microvesicles, endoplasmic reticulum, and nuclei. Molds are aerobic, and yeasts are facultative anaerobes, which adapt to, but do not require, anaerobic conditions. They usually reproduce by simple division or budding.

Pathologic fungi cause disease by adapting to the host environment. Fungi that colonize the skin can digest keratin. Other fungi can grow with wide temperature variations in lower oxygen environments. Still other fungi have the capacity to suppress host immune defenses. Phagocytes and T lymphocytes are important in controlling fungi, and low white blood cell counts promote fungal infection. Fungi have two basic structures: hyphae and yeasts. Hyphae have branching, tubular filaments. Yeasts are singular spherical cells.

Diseases caused by fungi are called mycoses. Mycoses can be superficial, deep, or opportunistic. Superficial mycoses occur on or near skin or mucous membranes and usually produce mild and superficial disease. Fungi that invade the skin, hair, or nails are known as dermatophytes. The diseases they produce are called tinea (ringworm), for example, tinea capitis (scalp), tinea pedis (feet), and tinea cruris (groin). Superficial dermatophytes grow in a ringlike, erythematous patch with a raised border. Itching often is intense, and cracking of tissue can occur and lead to secondary bacterial infection. Infections of the scalp are accompanied by scaling and hair loss. (Chapter 39 discusses the various skin disorders caused by fungi.)

Deep infections involving internal organs can be life threatening and are most common in association with other diseases or as an opportunistic infection in immunosuppressed individuals. Fungi causing deep infection enter the body through inhalation or through open wounds. Filamentous forms can multiply extracellularly, but the spherical yeasts multiply within cells, including white blood cells. Some fungi are a part of the normal body flora and become pathologic only when immunity is compromised, allowing exaggerated growth and translocation. For example, Candida albicans is normally found in the mouth, gastrointestinal tract, and vagina of normal individuals. Changes in pH and use of antibiotics that kill bacteria that normally inhibit Candida growth permit rapid proliferation and overgrowth, which can lead to superficial or deep infection. Common pathologic fungi are summarized in Table 7-10.

Fungi are diagnosed by microscopic observation of specimens treated with potassium hydroxide and stained to enhance visualization of spheres and filaments. Specimens also can be cultured. Skin tests are available for species of Aspergillus. No vaccines are available to prevent fungal disease effectively. Many of the antifungal drugs (e.g., amphotericin B, ketoconazole, fluconazole) used to treat deep or systemic infections are toxic to the host because the fungal cell composition is similar to the host cell.

**Figure 7-15** Types of Fungi. (From Mims CA et al: Medical microbiology, ed 3, London, 2004, Mosby.)

<table>
<thead>
<tr>
<th>TABLE 7-10</th>
<th>Common Pathologic Fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fungus</strong></td>
<td><strong>Growth Form</strong></td>
</tr>
<tr>
<td><strong>SUPERFICIAL</strong></td>
<td></td>
</tr>
<tr>
<td>Microsporum spp.</td>
<td>Filament</td>
</tr>
<tr>
<td>Epidermophyton floccosum</td>
<td>Filament</td>
</tr>
<tr>
<td>Malassezia furfur</td>
<td>Sphere</td>
</tr>
<tr>
<td><strong>DEEP</strong></td>
<td></td>
</tr>
<tr>
<td>Pneumocystis carinii</td>
<td>Sphere</td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
<td>Sphere</td>
</tr>
<tr>
<td>Aspergillus fumigatus</td>
<td>Filament</td>
</tr>
<tr>
<td>Coccidioides immitis</td>
<td>Unusual form</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>Sphere</td>
</tr>
</tbody>
</table>
Clinical Manifestations of Infection

The progression from infection to infectious disease follows predictable stages (infection, incubation, symptoms, shedding of the microorganism) as demonstrated by the pathogenesis of measles illustrated in Figure 7-16. Clinical manifestations of infectious disease vary, depending on the pathogen and the organ system affected. Manifestations can arise directly from the infecting microorganism or its products; however, the majority of the clinical symptoms result from the host’s inflammatory and immune responses (see Chapters 5 and 6). Infectious diseases typically begin with the nonspecific or general symptoms of fatigue, malaise, weakness, and loss of concentration. Generalized aching and loss of appetite are common complaints. However, the hallmark of most infectious diseases is fever.

Fever

Fever resulting from cytokines has been discussed in Chapter 5. Exogenous pyrogens produced by infectious agent may not cause fever directly but induce the production of endogenous pyrogens during inflammation. Endogenous pyrogens include interleukin-1 (IL-1), interleukin-6 (IL-6), interferon, tumor necrosis factor-alpha (TNF-α), and other cytokines. It is generally accepted that fever has a beneficial effect against infection, although the mechanisms have not been fully established.

Countermeasures Against Pathogenic Defenses

The body’s innate and acquired responses against microorganisms are numerous and involve an interaction between the immune and inflammatory systems. Pathogenic microorganisms, however, have developed means of circumventing the individual’s protective defenses. Therefore, prophylactic or interventive procedures have been developed either to prevent the pathogen from initiating disease (vaccines) or to destroy the pathogen once the disease process has started (antimicrobials). Most vaccine development has focused on preventing the most severe and common infections. With the initial success of antibiotic therapy, there was no perceived need for vaccination against many common and non-life-threatening infections. The increasing problem of antibiotic-resistant pathogens, however, has forced a reappraisal of that strategy, and a greater emphasis now is being placed on the development of new vaccines.

Vaccines

The purpose of vaccination is to induce long-lasting protective immune responses under conditions that will not result in disease in a healthy recipient of the vaccine. The primary immune response from vaccination is generally short lived; therefore, booster injections are used to push the immune response through multiple secondary responses resulting in large numbers of memory cells and sustained protective levels of antibody or T cells, or both.

Development of a successful vaccine is costly and depends on several factors. These include identification of the protective immune response and the appropriate antigen to induce that response. For instance, individuals with ongoing HIV infection produce a great deal of antibody against several HIV antigens. But, for development of a successful vaccine, we must first understand which antibody will protect against an initial infection.

Once a good candidate antigen is identified, it must be developed into an effective, cost-efficient, stable, and safe vaccine. For instance, most vaccines against viral infection (measles, mumps, rubella, varicella [chickenpox]) contain live viruses that are weakened (attenuated) so they continue to express appropriate antigens but establish only a limited and easily controlled infection. For most common vaccines against viral infections, limited replication of the virus appears to afford better long-term protection than using viral antigen. One current exception is the hepatitis B vaccine, which uses a recombinant viral protein. The hepatitis A vaccine is an inactivated (killed) virus and normally should not cause an infection.

Even attenuated viruses can establish life-threatening infections in individuals whose immune system is congenitally deficient or suppressed. The risk of infection by
the vaccine strain of virus is extremely small, but it may affect the choice of recommended vaccines. For instance, two different vaccines were developed against polio. The Sabin vaccine was an attenuated virus that was administered orally. It provided systemic protection and induced a secretory immune response to prevent growth of the poliovirus in the intestinal tract. Being a live virus, the vaccine could cause polio in some children who had unsuspected immune deficiencies (about 1 case in 2.4 million doses). The Salk vaccine was a completely inactivated virus administered by injection. It induced protective systemic immunity but did not provide adequate secretory immunity. Therefore, even if the individual was protected from systemic infection by poliovirus, the virus could transiently infect their intestinal mucosa, be shed, and spread to others. When polio was epidemic, the oral vaccine was preferred. Vaccination has been extremely effective: 2525 cases of paralytic polio were reported in the United States in 1960, 61 cases were reported in 1965, and no cases of polio since 1979. In 1994, the disease polio was declared officially eradicated in all the Americas. The goal of the World Health Organization (WHO) is to eradicate polio worldwide in the next few years (Figure 7-17). However, the live attenuated vaccine itself caused about 8 cases of paralytic polio per year in the United States in individuals with inadequate immune systems. As a result, the current recommendation of the Centers for Disease Control and Prevention (CDC) is vaccination with the killed virus.

Some common bacterial vaccines are killed microorganisms or extracts of bacterial antigens. The vaccine against pneumococcal pneumonia consists of a mixture of capsular polysaccharides from 10 strains of Streptococcus pneumoniae. Of the more than 90 known strains of this microorganism, only these 10 cause the most severe illnesses. However, the capsular vaccine is not very immunogenic in young children. A conjugated vaccine is available that contains capsular polysaccharides from 7 strains that are conjugated to carrier proteins in order to increase immunogenicity. A similar vaccine is available for Haemophilus influenzae type b (Hib).

Some bacterial pathogens are not invasive, but do colonize mucosal membranes or wounds and release potent toxins that act locally or systemically. These include the bacteria that cause diphtheria, cholera, and tetanus. Vaccination against systemic toxins (e.g., diphtheria, tetanus) has been achieved using toxoids—purified toxins that have been chemically detoxified without loss of immunogenicity. Pertussis (whooping cough) vaccine has been changed from a killed whole-cell vaccine to cellular extract (acellular) vaccine that contains the pertussis toxin and additional bacterial antigens. This change has dramatically reduced adverse side effects (fever, local inflammatory reactions, and others).

Additional difficulties associated with vaccination include allergic reactions to the vaccine antigen itself or other components of the preparation. For instance, some viral vaccines are grown in chicken eggs and many elicit a reaction in individuals who are allergic to eggs. The preservative thimerosal has been removed from vaccines. Thimerosal is a mercury-containing compound that has been used as a preservative since the 1930s. Although no cases of mercury toxicity have been reported secondary to vaccination, it was recommended that thimerosal be removed from vaccines. (See Chapter 3.)

A more common problem is compliance of the susceptible population. Depending on the microorganism, a certain percentage of the population should be immunized to protect the total population. If this level of immunization is not achieved, outbreaks of infection can occur. For instance, an effective measles vaccine was made available in 1963 and resulted in a dramatic decrease in the number of measles cases. Many parents became complacent and did not obtain measles vaccination for their preschool children. As a result, a large increase in the number of cases and deaths in 1989 and 1990 occurred, which initiated a reemphasis on complete immunization before children could start school. Even with successful development of a vaccine, however, a certain percentage of the population will be genetically unresponsive to vaccination and therefore will not produce a protective immune response. With most vaccines, the percentage of unresponsive individuals is low, and they will benefit from successful immunization of the rest of the population.

Many vaccines are used in the United States to protect against pathogens. The vaccines recommended in childhood are listed in Table 7-11.

**Antimicrobials**

Since initiation of the widespread use of penicillin during World War II, antibiotics have had the greatest impact on successful resistance to infection. Antibiotics are natural products of fungi, bacteria, and related microorganisms.
### TABLE 7-11

**Immunization Schedule: Range of Ages for Routine Immunizations**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Birth</th>
<th>1 Mo</th>
<th>2 Mo</th>
<th>4 Mo</th>
<th>6 Mo</th>
<th>12 Mo</th>
<th>15 Mo</th>
<th>18 Mo</th>
<th>24 Mo</th>
<th>4 to 6 Yr</th>
<th>11 to 12 Yr</th>
<th>13 to 14 Yr</th>
<th>15 Yr</th>
<th>16 to 18 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>DTaP</td>
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<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
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</tr>
<tr>
<td>Hib</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<td>IPV</td>
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<td>1</td>
<td>2</td>
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<tr>
<td>PCV</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<td></td>
<td></td>
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<tr>
<td>FLU</td>
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<td></td>
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</tr>
<tr>
<td>HepA</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>HPV*</td>
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<td>2</td>
<td>3</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>RV*</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td></td>
<td></td>
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</tbody>
</table>

Modified from Centers for Disease Control and Prevention: *Recommended childhood and adolescent immunization schedule, United States, 2006*; available at [www.cdc.gov/nip/recs/child-schedule.htm](http://www.cdc.gov/nip/recs/child-schedule.htm).

* Provisional recommendation. HBV, hepatitis B virus: causes cirrhosis of the liver and liver cancer; the vaccine is a recombinant viral protein. DTaP, combination of (D), Diphtheria: a bacterial infection of the throat; produces a toxin that can lead to heart failure or paralysis; the vaccine is an inactivated form of diphtheria toxin (toxoid); (T), tetanus: a bacterial infection that produces a toxin that attacks the nervous system and may cause death; the vaccine is an inactivated form of the tetanus toxin (toxoid); and (aP), pertussis (acellular pertussis), or whooping cough: a bacterial infection that causes severe coughing in children younger than 5 years; the vaccine is an inactivated toxin and other bacterial antigens. Hib, *Haemophilus influenzae* type b: a bacterial infection that is commonly contracted by children younger than 5 years and infects the blood, joints, bones, and membrane covering the heart; most common cause of serious bacterial meningitis in children; the vaccine is an extracted bacterial antigen conjugated to a protein carrier. IPV, polio: polio is a viral infection that causes paralysis and death; the vaccine is an inactivated virus. MMR, combination of (MM), measles and mumps viruses that cause fever and rash (measles) or inflammation of the salivary glands (mumps); mumps also may cause meningitis; both vaccines are attenuated live viruses; and (R), rubella or German measles: a viral infection that causes fever and rash; may cause severe birth defects in pregnant women infected in the first trimester. VAR, varicella-zoster: a virus that causes chickenpox; vaccine is an attenuated live virus. MCV4, meningococcal: *Neisseria meningitides* is a major bacterial cause of meningitis, particularly in young adults; the vaccine contains four different extracted capsular polysaccharides. PCV, pneumococcal: *Streptococcus pneumoniae* is a bacteria that causes pneumonia, particularly in the elderly; the childhood vaccine is a protein conjugate with 7 different capsular antigens; the adult vaccine is a mixture of 10 extracted capsular polysaccharides. FLU, influenza: a virus that causes severe upper respiratory tract infections; the most common vaccine is an inactivated virus. HepA, Hepatitis A virus: a virus that causes liver disease; recommended in selected states and regions; vaccine is an inactivated virus. HPV, Human papillomavirus: a virus that causes genital warts and cervical cancer; (*) provisional recommendation for females; vaccine is quadrivalent non-infectious HPV-like particles made from capsid antigen. RV, Rotavirus: a virus that causes diarrheal disease; (*) provisional recommendation; vaccine is an attenuated live virus.
and kill or inhibit the growth of other microorganisms. Numerous chemicals or antimicrobials have been identified that either prevent the growth of microorganisms or directly destroy them (Table 7-12). Antibiotics generally act by preventing the function of enzymes or cell structures that are unique to the infecting agent. Because viruses use the enzymes of the host’s cells, there has been far less success in developing antiviral antibiotics.

**Recent pathogenic adaptations**

Microbial pathogens have emerged that have developed mechanisms for circumventing the most modern techniques for destroying or controlling infection. These include microorganisms that attack the immune system (e.g., HIV) and those that are resistant to multiple antibiotics (e.g., *Mycobacterium tuberculosis*). HIV is one of the few microorganisms that directly attacks the central processes involved in the development of an immune response and will be discussed later in this chapter.

Many pathogens have mutated and developed resistance to particular antibiotics. Resistance occurs primarily through inactivation of the drug, alteration of the bacterial membrane that prevents the antibiotic from being taken up, alteration of the target molecule, or reduced uptake or active efflux of the antibiotic. These changes result from genetic mutations and can be transmitted directly to neighboring microorganisms. Penicillin resistance, for example, results from the production of an enzyme (β-lactamase) that breaks down the antibiotic. Zidovudine (azidothymidine, AZT) is an antibiotic that suppresses the enzymatic activity of reverse transcriptase, a viral-specific enzyme responsible for the replication of viral RNA and a DNA strand. HIV frequently mutates and produces an AZT-resistant reverse transcriptase.

A rapid emergence of multiple antibiotic-resistant bacteria has been observed. These microorganisms are resistant to almost all currently available antibiotics. For example, *Streptococcus pneumoniae*, which causes pneumonia, menigitis, and acute otitis media (ear infections), was once routinely susceptible to penicillin. Since the 1980s, however, the incidence of penicillin-resistant microorganisms has risen to 30% or more in some populations. Many of these are resistant also to multiple antibiotics. In some areas, more than 20% of tuberculosis cases are caused by multiple antibiotic-resistant *M. tuberculosis*. Also, the incidence of drug-resistant gonorrhea, malaria, pneumococcal disease, salmonellosis, shigellosis, and staphylococcal infections has increased dramatically.

**Why have multiple antibiotic-resistant microorganisms appeared?** Overuse of antibiotics can lead to the destruction of the normal flora, allowing the selective overgrowth of antibiotic-resistant strains or pathogens that had previously been kept under control. For example, after treatment with the antibiotic clindamycin, the normal intestinal flora can become compromised, allowing the overgrowth of *Clostridium difficile* and the development of pseudomembranous colitis. Also, individuals commonly do not comply with the instructions of health care providers concerning the necessity of completing the therapeutic regimen with antibiotics. This practice allows the selective resurgence of microorganisms that are relatively resistant to the antibiotic.

### Quick Check 7-3

1. How do antigenic changes in viral pathogens promote disease?
2. What are three mechanisms pathogens use to block the immune system?
3. What is the difference between endotoxin and exotoxin?

### Deficiencies in Immunity

An immune deficiency is the failure of the immune or inflammatory response to function normally, resulting in increased susceptibility to infections. Primary (congenital) immune deficiency is caused by a genetic defect, whereas secondary (acquired) immune deficiency is caused by another condition, such as cancer, infection, or normal physiologic changes, such as aging. Acquired forms of immune deficiency are far more common than the congenital forms.

**Table 7-12**

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibits synthesis of cell wall</td>
<td>Penicillins, cephalosporins, monobactams,</td>
</tr>
<tr>
<td></td>
<td>carbapenems, vancomycin, bacitracin,</td>
</tr>
<tr>
<td></td>
<td>cyclosinerine, fosfomycin</td>
</tr>
<tr>
<td>Damages cytoplasmic membrane</td>
<td>Polymyxins, polyene antifungals, imidazoles</td>
</tr>
<tr>
<td>Alters metabolism of nucleic acid</td>
<td>Quinolones, rifampin, nitrofurans,</td>
</tr>
<tr>
<td>Inhibits protein synthesis</td>
<td>nitroimidazoles</td>
</tr>
<tr>
<td>Alters energy metabolism</td>
<td>Aminoglicosides, tetracyclines, chloramphenicol, macrolides, clindamycin, spectinomycin, sulfonamides</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim, dapsone, isoniazid</td>
</tr>
</tbody>
</table>

Initial Clinical Presentation

The clinical hallmark of immune deficiency is a tendency to develop unusual or recurrent, severe infections. Preschool and school-age children normally may have 6 to 12 infections per year, and adults may have 2 to 4 infections per year. Most of these are not severe and are limited to viral infections of the upper respiratory tract, recurrent streptococcal pharyngitis, or mild otitis media (ear infections).

Potential immune deficiencies should be considered if the individual has had severe, documented bouts of pneumonia, otitis media, sinusitis (sinus infection), bronchitis, septicemia (blood infection), or meningitis or infections with opportunistic microorganisms that normally are not pathogenic (e.g., Pneumocystis carinii). Infections are generally recurrent with only short intervals of relative health, and multiple simultaneous infections are common. Individuals with immune deficiencies often have eight or more ear infections, two or more serious sinus infections, and two or more pneumonias, recurrent abscesses, or persistent fungal infections (particularly thrush) within a year. Recurrent internal infections, such as meningitis, osteomyelitis, or sepsis, are common. Prolonged antibiotic use is commonly ineffective (e.g., rubella). Some complement deficiencies, however, are suggested if the individual has documented, recurrent infections with microorganisms that require opsonization (e.g., encapsulated bacteria) or viruses against which humoral immunity is normally effective (e.g., rubella). Some complement deficiencies resemble defects in antibody or phagocyte function, but others are commonly associated with disseminated infections with bacteria of the genus Neisseria (Neisseria meningitides and Neisseria gonorrhoeae).

Primary (Congenital) Immune Deficiencies

Most primary immune deficiencies are the result of a single gene defect (Table 7-13). Generally, the mutations are sporadic and not inherited: a family history exists in only about 25% of individuals. The sporadic mutations occur before birth, but the onset of symptoms may be early or later, depending on the particular syndrome. In some instances, symptoms of immune deficiency appear within the first 2 years of life. Other immune deficiencies are progressive, with the onset of symptoms appearing in the second or third decade of life.

Many immune deficiencies also are associated with other characteristic defects, some of which appear to be unrelated to the immune system yet may be life threatening by themselves. Examples are given in the following discussion.

These associated symptoms can be useful diagnostically and can clarify the pathophysiology of the disease.

Individually, primary immune deficiencies are rare. For instance, only 30 to 50 new cases of severe combined immune deficiency (SCID) are diagnosed in the United States yearly. However, more than 70 different deficiencies have been identified. Together, primary immune deficiencies are more common than cystic fibrosis, hemophilia, childhood leukemia, or many other well-known diseases. The distribution of male and female is about even, although some specific diseases have a male or female predominance. The three most commonly diagnosed deficiencies are common variable immune deficiency (34%), selective IgA deficiency (24%), and IgG subclass deficiency (17%).

Primary immune deficiencies are classified into five groups, based on which principal component of the immune or inflammatory systems is defective: defects of B lymphocytes, T lymphocytes, both B and T lymphocytes (combined), phagocytes, or complement.

B lymphocyte deficiencies

B lymphocyte deficiencies result from defects in B cell immune responses. Because T cell immunity rarely depends on competent B cell responses, T cell immune responses are not affected in pure B lymphocyte deficiencies. The results are lower levels of circulating immunoglobulins (hypogammaglobulinemia) or occasionally totally or nearly absent immunoglobulins (agammaglobulinemia).

Some defects may involve a particular class of antibody, such as selective IgA deficiency. This occurs in 1 in 700 to 1 in 400 individuals. Individuals with this deficiency produce other classes of immunoglobulins but not IgA. This suggests a failure to class-switch to IgA and mature into IgA-producing plasma cells. Many individuals are asymptomatic, although others have a history of severe, recurring sinus, lung, and gastrointestinal infections. Individuals with IgA deficiency often have chronic intestinal candidiasis (infection with C. albicans). (The secretory, or mucosal, immune system is described in Chapter 6.) Complications of IgA deficiency include severe atopic disease and autoimmune diseases. Studies of these individuals show that secretory IgA normally may prevent the uptake of allergens from the environment. Therefore, IgA deficiency may lead to increased allergen uptake and a more intense challenge to the immune system because of prolonged exposure to environmental antigens.

Stem cells mature in the central or primary lymphoid organs (thymus and bursal-equivalent tissue). Bruton agammaglobulinemia is caused by blocked development of mature B cells in bursal-equivalent tissue. There are few or no circulating B cells, although T cell number and function are normal, resulting in repeated infections, such as otitis media, sore throat, and conjunctivitis, and more serious conditions, such as septicemia.

T lymphocyte deficiencies

T lymphocyte deficiencies are defects in the development and function of T lymphocytes. Because helper T cells...
are obligatory in the development of many B lymphocyte responses, antibody production is often diminished, although the B cells are fully capable of producing an adequate antibody response. Immunodeficiency of T cell function contributes to failure to thrive, oral infections (e.g., candidiasis), chronic diarrhea, pneumonia, and skin rashes.

Some immune deficiencies are characterized by a defect in the capacity to produce an immune response against a particular antigen. In chronic mucocutaneous candidiasis, the T lymphocytes cannot respond to a specific infectious agent, C. albicans. These individuals usually have mild to extremely severe recurrent Candida infections involving the mucous membranes and skin.

DiGeorge syndrome (congenital thymic aplasia or hypoplasia and diminished parathyroid gland development) is caused by the lack or partial lack of the thymus, resulting in greatly decreased T cell numbers and function. The cause is defective development of several tissues originating from the third and fourth pharyngeal pouches during embryo development. Lack of the parathyroid gland causes inability to regulate calcium. Low blood calcium levels cause the development of tetany or involuntary rigid muscular contraction. DiGeorge syndrome is frequently associated with abnormal facial development, including low set ears, fish-shaped mouth, and other altered features (Figure 7-18).

**Combined deficiencies**

Combined deficiencies result from defects that directly affect the development of both T and B lymphocytes. Some combined deficiencies result in major defects in both the

<table>
<thead>
<tr>
<th>Classification</th>
<th>Example</th>
<th>Immune Deficiency</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B LYMPHOCYTE DEFICIENCIES</strong></td>
<td>Bruto agammaglobulinemia</td>
<td>Lack of B cells, little or no antibody production</td>
<td>Recurrent, life-threatening bacterial infections</td>
</tr>
<tr>
<td>Defective development of B cells in central lymphoid organ (bone marrow)</td>
<td>Selective IgA deficiency</td>
<td>Little or no production of IgA, with normal production of other classes of antibody</td>
<td>Mild infections of gastrointestinal and respiratory tracts</td>
</tr>
<tr>
<td>Defect in class switch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T LYMPHOCYTE DEFICIENCIES</strong></td>
<td>DiGeorge syndrome</td>
<td>Lack of T cells</td>
<td>Recurrent, life-threatening fungal and viral infections</td>
</tr>
<tr>
<td>Defective development of T cells in central lymphoid organ (thymus)</td>
<td>Chronic mucocutaneous candidiasis</td>
<td>Lack of T cell response to Candida</td>
<td>Recurrent and disseminated infections with the fungus Candida albicans</td>
</tr>
<tr>
<td>Defect in development of cellular immunity against a specific antigen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>COMBINED IMMUNE DEFICIENCIES</strong></td>
<td>Severe combined immunodeficiencies (SCID)</td>
<td>Lack of both T and B cells, little or no antibody production or cellular immunity</td>
<td>Recurrent, life-threatening infections with a variety of microorganisms</td>
</tr>
<tr>
<td>Defective development of both B and T cells</td>
<td>Bare lymphocyte syndrome</td>
<td>No antigen presentation because of lack of MHC class I or MHC class II molecules on the cell surface</td>
<td>Recurrent, life-threatening infections with a variety of microorganisms</td>
</tr>
<tr>
<td>Defects in cooperation among B cells, T cells, and antigen-presenting cells</td>
<td>Wiskott-Aldrich syndrome</td>
<td>Cytoskeletal defect resulting in selective decrease in IgM production</td>
<td>Recurrent infections with select groups of microorganisms</td>
</tr>
<tr>
<td>A large variety of defects that affect the function of B or T cells</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>COMPLEMENT DEFICIENCIES</strong></td>
<td>C3 deficiency</td>
<td>Little or no C3 produced</td>
<td>Recurrent, life-threatening bacterial infections</td>
</tr>
<tr>
<td>Defective production of one early component of the complement system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defective production of a component of the membrane attack complex</td>
<td>C6 deficiency</td>
<td>Little or no C6 produced</td>
<td>Recurrent disseminated infections with Neisseria gonorrhoeae or N. meningitidis</td>
</tr>
<tr>
<td><strong>PHAGOCYTE DEFICIENCIES</strong></td>
<td>Severe congenital neutropenia</td>
<td>Lack of neutrophils</td>
<td>Recurrent, life-threatening bacterial infections</td>
</tr>
<tr>
<td>Defects in production of neutrophils</td>
<td>Chronic granulomatous disease</td>
<td>Lack of production of oxygen products (e.g., hydrogen peroxide)</td>
<td>Recurrent infections with bacteria that are sensitive to killing by oxygen-dependent mechanisms</td>
</tr>
<tr>
<td>Defects in bacterial killing</td>
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</tr>
</tbody>
</table>
T and B cell immune responses, whereas others are “partial” and more adversely affect T cells than B cells. The most severe are called severe combined immunodeficiencies (SCID). Most individuals with SCID have few detectable lymphocytes in the circulation and secondary lymphoid organs (spleen, lymph nodes). The thymus usually is underdeveloped because of the absence of T cells. Immunoglobulin levels, especially IgM and IgA, are absent or greatly reduced. Several forms of SCID are caused by autosomal recessive enzymatic defects that result in the accumulation of toxic metabolites to which rapidly dividing cells, such as lymphocytes, are especially sensitive. Deficiency of adenosine deaminase (ADA deficiency) results in the accumulation of toxic purines. Even if nearly adequate numbers of B and T cells are produced, their cooperation may be defective. The bare lymphocyte syndrome is an immune deficiency characterized by an inability of lymphocytes and macrophages to produce MHC class I or class II molecules. Without MHC molecules, antigen presentation and intercellular cooperation cannot occur effectively. Children with this deficiency develop serious, life-threatening infections and usually die before the age of 5 years.

Some combined immune deficiencies result in depressed development of a small portion of the immune system. For instance, an individual can be unable to produce a certain class of antibody, as in Wiskott-Aldrich syndrome (an X-linked recessive disorder). Here IgM antibody production is greatly depressed, and therefore antibody responses against antigens that elicit primarily an IgM response, such as polysaccharide antigens from bacterial cell walls (e.g., of P. aeruginosa, S. pneumoniae, Haemophilus influenzae, and other microorganisms with polysaccharide outer capsules), are deficient. In addition, there are defects in platelets presumably because of the absence of certain glycoproteins. Clinical manifestations include bleeding because of decreases in circulating platelets, eczema, and recurrent infections (e.g., otitis media, pneumonia, herpes simplex, cytomegalovirus).

Complement deficiencies

Many complement deficiencies have been described. C3 deficiency is the most severe defect. C3 unites all pathways of complement activation, and complement component C3b is a major opsonin. Persons with C3 deficiency are at risk for recurrent life-threatening infections with encapsulated bacteria (e.g., Hemophilus influenzae and Streptococcus pneumoniae) at an early age. Deficiencies of terminal components of the complement cascade (C5, C6, C7, C8, or C9 deficiencies) are associated with increased infections with only one group of bacteria; those of the genus Neisseria (Neisseria meningitides or N. gonorrhoeae). Neisseria usually cause localized infections (meningitis or gonorrhea), but those with terminal pathway defects have more than an 8000-fold increased risk for systemic infections with atypical strains of these microorganisms.

Phagocytic deficiencies

Phagocytic deficiencies usually result in recurrent infections with the same group of microorganisms (encapsulated bacteria) associated with antibody and complement deficiencies. A variety of defects in killing of microorganisms have been described. Chronic granulomatous disease (CGD) is a severe defect in the myeloperoxidase-hydrogen peroxide system. A major means of bacterial killing uses the enzyme myeloperoxidase, halides (e.g., chloride ion), and hydrogen peroxide (H₂O₂). As a result of phagocytosis, neutrophils and other phagocytes switch much of their glucose metabolism to the hexose-monophosphate shunt. A by-product of this pathway is the conversion of molecular oxygen by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase into highly reactive oxygen derivatives, including hydrogen peroxide. Mutations in NADPH oxidase result in deficient production of hydrogen peroxide and other oxygen products. Thus, individuals have adequate myeloperoxidase and halide but lack the necessary hydrogen peroxide. Individuals with CGD have recurrent severe pneumonias, tumor-like granulomas in lungs, skin, and bones, and other infections with some normal, relatively innocuous microorganisms, such as Staphylococcus aureus, Serratia marcescens, Aspergillus spp., and others.
Secondary (Acquired) Immune Deficiencies

Secondary, or acquired, immune and inflammatory deficiencies are far more common than primary deficiencies. These deficiencies are not related to genetic defects but are complications of other physiologic or pathophysiologic conditions. Some conditions that are known to be associated with acquired deficiencies include the following:

Normal physiologic conditions
- Pregnancy
- Infancy
- Aging

Psychologic stress
- Emotional trauma
- Eating disorders

Dietary insufficiencies
- Malnutrition caused by insufficient intake of large categories of nutrients, such as protein or calories
- Insufficient intake of specific nutrients, such as vitamins, iron, or zinc
- Infections
- Congenital infections, such as rubella, cytomegalovirus, hepatitis B
- Acquired infections, such as AIDS

Malignancies
- Malignancies of lymphoid tissues, such as Hodgkin disease, acute or chronic leukemia, or myeloma
- Malignancies of nonlymphoid tissues, such as sarcomas and carcinomas

Physical trauma
- Burns

Medical treatments
- Stress caused by surgery
- Anesthesia
- Immunosuppressive treatment with corticosteroids or antilymphocyte antibodies
- Splenectomy
- Cancer treatment with cytotoxic drugs or ionizing radiation

Other diseases or genetic syndromes
- Diabetes
- Alcoholic cirrhosis
- Sickle cell disease
- SLE
- Chromosome abnormalities, such as Down syndrome

Although secondary deficiencies are common, many are not clinically relevant. In many cases, the degree of the immune deficiency is relatively minor and without any apparent increased susceptibility to infection. Alternatively, the immune system may be substantially suppressed, but only for a short duration, thus minimizing the incidence of clinically relevant infections. Some secondary immune deficiencies, however, are extremely severe and may result in recurrent life-threatening infections.

Acquired immunodeficiency syndrome (AIDS)

The human immune deficiency virus (HIV) infects and destroys the helper T cell, which is necessary for the development of both plasma cells and cytotoxic T cells. Therefore, HIV suppresses the immune response against itself and secondarily creates a generalized immune deficiency by suppressing the development of immune responses against other pathogens and opportunistic microorganisms, leading to the development of acquired immunodeficiency syndrome (AIDS).

Despite major efforts by health care agencies around the world, the number of cases and deaths from HIV infection and AIDS (HIV/AIDS) continues to increase. The number of people living with HIV/AIDS worldwide is estimated at 40 million, of which 2.5 million are under the age of 15. The rate of spread of the disease is still out of control: the number of people newly infected with HIV is estimated at 5 million yearly, with 700,000 being under the age of 15. Deaths from AIDS are about 3 million yearly. Since the end of 1998, more than 13 million people have died of HIV/AIDS.

The majority of cases are still in sub-Saharan Africa, but the epidemic is worldwide, and the number of new cases is increasing rapidly, particularly in Asia. As an example of the prevalence of HIV/AIDS, in the African country of Zambia it is estimated that 30% of the women age 30 to 34 years are HIV infected. In South Africa, about 35% of the pregnant women age 23 to 29 are HIV infected.

In the United States, the spread of HIV/AIDS remains somewhat stable. The Centers for Disease Control and Prevention (CDC) estimates that since the year 2000 the rate of new cases of HIV/AIDS has remained at about 31,000 per year. The number of deaths related to HIV/AIDS continues at about 18,000 per year (Figure 7-19). The total number of HIV/AIDS-related deaths in the United States is in excess of 550,000, and more than 400,000 individuals are currently living with AIDS.

Before the implementation of massive public health campaigns and the use of antiviral drugs in the United States, the progression from HIV infection to AIDS and death was unrelenting. In 1995, AIDS became the number one killer of individuals between the ages of 25 and 44 years of age. With the advent of effective therapy in the mid-1990s, HIV infection has become a chronic disease in the United States, with many fewer deaths.

Epidemiology HIV is a blood-borne pathogen with the typical routes of transmission: blood or blood products, intravenous drug abuse, both heterosexual and homosexual activity, and maternal-child transmission before or during birth (Figure 7-20). Although the disease first gained attention in the United States as being related to sexual transmission between males, the most common route worldwide is through heterosexual activity. Worldwide, women make up more than half of those living with HIV/AIDS. In the United States, as in the rest of the world,
HIV is a member of a family of viruses called retroviruses, which carry genetic information in the form of RNA rather than DNA (Figure 7-21). Retroviruses use a viral enzyme, reverse transcriptase, to convert RNA into double-stranded DNA. Using a second viral enzyme, an integrase, the new DNA is inserted into the infected cell’s genetic material, where it may remain dormant. If the cell is activated, translation of the viral information may be initiated, resulting in the formation of new virions, lysis and death of the infected cell, and shedding of infectious HIV particles. If, however, the cell remains relatively dormant, the viral genetic material may remain latent for years and is probably present for the life of the individual.

The primary surface receptor on HIV is the envelope protein gp120, which binds to the molecule CD4 on the surface of helper T cells. Several other necessary coreceptors have been identified on target cells. Thus, the major immunologic finding in AIDS is the striking decrease in the number of CD4+ Th cells (Figure 7-22). Individuals who are not HIV-infected typically have 800 to 1000 CD4+ cells per cubic millimeter of blood, with a range from 600/mm³ to 1200/mm³.

### PATHOGENESIS

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### HEALTH ALERT

**Risk of HIV Transmission Associated With Sexual Practices**

**High Risk (in descending order of risk)**
- Receptive anal intercourse with ejaculation (no condom)
- Receptive vaginal intercourse with ejaculation (no condom)
- Insertive anal intercourse (no condom)
- Insertive vaginal intercourse (no condom)
- Insertive anal intercourse with withdrawal before ejaculation
- Insertive anal intercourse with withdrawal before ejaculation
- Insertive vaginal intercourse with withdrawal before ejaculation
- Insertive anal intercourse (with spermicidal foam but no condom)
- Insertive vaginal intercourse (with spermicidal foam but no condom)
- Insertive anal or vaginal intercourse (with a condom)*
- Insertive anal or vaginal intercourse (with a condom)*

**Some Risk (in descending order of risk)**
- Oral sex with men with ejaculation
- Oral sex with women
- Oral sex with men with preejaculation fluid (precum)
- Oral sex with men, no ejaculation or precum
- Oral sex with men (with a condom)

**Some Risk (depending on situation, intactness of mucous membranes, etc.)**
- Mutual masturbation with external or internal touching
- Sharing sex toys
- Anal or vaginal fisting

**No Risk**
- Masturbating with another person without touching one another
- Hugging/massage/dry kissing
- Frottage (rubbing genitals while remaining clothed)
- Masturbating alone
- Abstinence

**Unresolved Issues**
- The role of precum in transmission
- The protection offered by covering female genitals with a dental dam during oral sex on the women
- The risk of transmission from wet kissing


*Risk lower if no ejaculation or if spermicidal foam is used.

### CLINICAL MANIFESTATIONS

Depletion of CD4+ cells has a profound effect on the immune system, causing a severely diminished response to a wide array of infectious pathogens and malignant tumors (Box 7-2). At the time of diagnosis, the individual may present with one of several different conditions: serologically negative (no detectable antibody), serologically positive (positive for antibody against HIV) but asymptomatic, early stages of HIV disease, or AIDS (Figure 7-23).

The presence of circulating antibody against the HIV indicates infection by the virus, although many of these
Life Cycle and Possible Sites of Therapeutic Intervention of Human Immunodeficiency Virus (HIV)

The HIV virion consists of a core of two identical strands of viral RNA encased in a protein structure with viral proteins gp41 and gp120 on its surface (envelope). HIV infection begins when a virion binds to CD4 and chemokine coreceptors on a susceptible cell and follows the process described here. The provirus may remain latent in the cell’s DNA until it is activated (e.g., by cytokines). The HIV life cycle is susceptible to blockage at several sites (see the text for further information), including entrance inhibitors, reverse transcriptase inhibitors, integrase inhibitors, and protease inhibitors. (Modified from Kumar V, Abbas A, Fausto N: Robbins and Cotran pathologic basis of disease, ed 7, Philadelphia, 2005, Saunders.)

Proportion of AIDS Cases Among Adults and Adolescents, by Exposure Category and Year of Diagnosis, in the United States (1985–2004). Worldwide, AIDS is primarily spread by heterosexual transmission. In the United States, the predominant route was by male-to-male sexual contact. The trend, however, is toward increasing heterosexual transmission. Transmission by injected drug use has remained relatively stable, as has the number of cases where both male-to-male sexual activity and injected drug use risk factors occur in the same individual. (Redrawn from Centers for Disease Control website, 2005; available at www.cdc.gov/hiv/topics/surveillance/resources/slides/index.htm.)

Figure 7-20

Figure 7-21

Individuals are asymptomatic. Antibody appears rather rapidly after infection through blood products, usually within 4 to 7 weeks. After sexual transmission, however, the individual can be infected yet seronegative for 6 to 14 months or, in at least one case, for years. The period between infection and the appearance of antibody is referred to as the window period. Although a person may not have antibody, he or she may have virus growing, have virus in the blood and body fluids, and be infectious to others.

Those with the early stages of HIV disease (early-stage disease) usually present with relatively mild symptoms resembling influenza, such as night sweats, swollen lymph glands, diarrhea, or fatigue. The early stage may last as long as 10 years. Although individuals appear to be in clinical latency, the virus is actively proliferating in lymph nodes (Figure 7-24).

The currently accepted definition of AIDS relies on both laboratory tests and clinical symptoms. The most common laboratory test is for antibodies against HIV. If the individual is seropositive, the diagnosis of AIDS is made in association with various clinical symptoms (see Box 7-2) (Figure 7-25). The symptoms include atypical or opportunistic infections and cancers, as well as indications of
debilitating chronic disease (e.g., wasting syndrome, recurrent fevers). Most commonly, new cases of AIDS are diagnosed initially by decreased CD4$^+$ T cell numbers. The average time from infection to development of AIDS has been estimated at just over 10 years. Some estimates are that approximately 99% of untreated HIV-infected individuals would eventually progress to AIDS.

**TREATMENT AND PREVENTION** The current regimen for treatment of HIV infection is a combination of drugs, termed **highly active antiretroviral therapy (HAART)**. The combination includes inhibitors of reverse transcriptase (reverse transcriptase inhibitors) and of the viral protease (protease inhibitors) (see Figure 7-21). The clinical benefits of HAART are profound and durable. Death from
AIDS-related diseases has been reduced significantly since the introduction of HAART. However, resistant variants to these drugs have been identified. Drug therapy for AIDS is difficult because, like most retroviruses, the AIDS virus incorporates into the genetic material of the host and may never be removed by antimicrobial therapy. Therefore, drug administration to control the virus may have to continue for the lifetime of the individual. Additionally, HIV may persist in regions where the antiviral drugs are not as effective, such as the CNS. Inhibitors of the initial viral entrance into the target cell (entrance inhibitors) and inhibitors of the viral integrase (integrase inhibitors) have undergone clinical trials and are being added to the combination.

Vaccine development is probably the most effective means of preventing HIV infection and may be useful in treating preexisting infection. Most of the common viral vaccines (e.g., rubella, mumps, influenza) induce protective antibodies that block the initial infection. Only one vaccine (rabies) is used after the infection has occurred. That approach is successful because the rabies virus proliferates and spreads very slowly. Whether an HIV vaccine would successfully prevent or treat HIV infection is questionable for several reasons. First, the AIDS virus is genetically and antigenically variable, like the influenza virus, so that a vaccine created against one variant may not provide protection against another variant. Second, although individuals with AIDS have high levels of circulating antibodies against the virus, these antibodies do not appear to be protective. Therefore, even if a circulating antibody response can be induced by vaccination, that response might not be effective. A vaccine may have to induce both circulating and secretory (to prevent initial infection of the mucosal T cell) antibody and Tc cells.

**Evaluation and Care of Those With Immune Deficiency**

Routine care of individuals with primary or secondary immune deficiencies must be tempered with the knowledge that the immune system may be totally ineffective. It may be unsafe to administer conventional immunizing agents or blood products to many of these individuals because of the risk that the immunizing agent will cause an uncontrolled infection. Uncontrolled infection is a problem when attenuated vaccines that contain live but weakened microorganisms are used (e.g., live polio vaccine, vaccines against measles, mumps, and rubella).

The most common presenting symptom of immune deficiencies is recurrent severe infections. Significant information on the specific immune deficiency can be obtained by noting certain characteristics of the individual, including the presence of any associated anomalies, age, gender, the types of infections (bacterial, viral, or fungal, and the specific microorganisms involved), family history, and risk factors associated with secondary immune deficiencies.
A variety of laboratory tests are available to evaluate specific immune deficiencies (Table 7-13). The choice of which particular tests to perform is determined on the characteristics described here. A basic screening test is a complete blood count (CBC) with a differential. The CBC provides information on the numbers of red cells, white cells, and platelets, and the differential indicates the quantities of lymphocytes, granulocytes, and monocytes in the blood. Quantitative determination of immunoglobulins (IgG, IgM, IgA) is a screening test for antibody production, and an assay for total complement (total hemolytic complement, CH50) is useful if a complement defect is suspected. Further testing is described in Table 7-14.

**Replacement Therapies for Immune Deficiencies**

Many immune deficiencies can be successfully treated by replacing the missing component of the immune system. Individuals with B cell deficiencies that cause hypogammaglobulinemia or agammaglobulinemia usually are treated with administration of gamma globulins, which are antibody-rich fractions prepared from plasma pooled from large numbers of donors. Administration of gamma globulin temporarily replaces the individual’s antibodies. Antibodies from these preparations are removed slowly from the person’s blood, with half of the antibodies being removed by 3 to 4 weeks. Thus, individuals must be treated repeatedly to maintain a protective level of antibodies in the blood.

Defects in lymphoid cell development in the primary lymphoid organs (e.g., SCID, Wiskott-Aldrich syndrome, leukocyte adhesion defect) can sometimes be treated by replacement of stem cells through transplantation of bone marrow, umbilical cord cells, or other cell populations that are rich in stem cells. Thymic defects (e.g., DiGeorge syndrome, ataxia-telangiectasia, or chronic mucocutaneous candidiasis) may be treated with transplantation of fetal thymus tissue or thymic epithelial cells (the cells that produce the thymic hormones). However, in most cases improvement is only temporary.

Enzymatic defects that cause SCID (e.g., adenosine deaminase deficiency) have been treated successfully with transfusions of glycerol frozen-packed erythrocytes. The donor erythrocytes contain the needed enzyme and can, at least temporarily, provide sufficient enzyme for normal
lymphocyte function. The first successful gene therapy was performed in ADA deficiency, resulting in reconstitution of the immune systems.

Individuals with immune deficiencies are at risk for graft-versus-host disease (GVHD). This occurs if T cells in a transplanted graft (e.g., transfused blood, bone marrow transplants) are mature and therefore capable of the cell-mediated immunity against the recipient’s HLA. The primary targets for GVHD are the skin (e.g., rash, loss or increase of pigment, thickening of skin), liver (e.g., damage to bile duct, hepatomegaly), mouth (e.g., dry mouth, ulcers, infections), eyes (e.g., burning, irritation, dryness), and gastrointestinal tract (e.g., severe diarrhea), and the disease may lead to death from infections. GVHD is not a problem when the recipient is immunocompetent—that is, has an immune system that can control the donor’s lymphocytes. If, however, the recipient’s immune system is deficient, the grafted T cells remain unchecked and attack the recipient’s tissues. Most GVHD should be prevented by the current practices of treating blood with irradiation to kill white blood cells before transfusion or removal of mature T cells from tissue used to treat individuals with immune deficiencies.

Quick Check 7-4

1. Why is the development of recurrent or unusual infections the clinical hallmark of immunodeficiency?
2. Compare and contrast the most common infections in individuals with defects in cell-mediated immune response and those with defects in humoral immune response.
3. What are the new treatments for HIV?
1. Hypersensitivity is an inappropriate immune response misdirected against the host’s own tissues (autoimmunity) or directed against beneficial foreign tissues, such as transfusions or transplants (alloimmunity); or it can be exaggerated responses against environmental antigens.

2. Mechanisms of hypersensitivity are classified as type I (IgE-mediated) reactions, type II (tissue-specific) reactions, type III (immune-complex-mediated) reactions, and type IV (cell-mediated) reactions.

3. Hypersensitivity reactions can be immediate (developing within seconds or hours) or delayed (developing within hours or days).

4. Anaphylaxis, the most rapid immediate hypersensitivity reaction, is an explosive reaction that occurs within minutes of reexposure to the antigen and can lead to cardiovascular shock.

5. Allergens are antigens that cause allergic responses.

6. Type I (IgE-mediated) reactions occur after antigen reacts with IgE on mast cells, leading to mast cell degranulation and the release of histamine and other inflammatory substances.

7. Type II (tissue-specific) reactions are caused by four possible mechanisms: complement-mediated lysis, opsonization and phagocytosis, antibody-dependent cell-mediated cytotoxicity, and modulation of cellular function.

8. Type III (immune complex-mediated) reactions are caused by the formation of immune complexes that are deposited in target tissues, where they activate the complement cascade, generating chemotactic fragments that attract neutrophils into the inflammatory site.
Did You Understand?—Cont’d

9. Immune-complex disease can be a systemic reaction, such as serum sickness (e.g., Raynaud phenomenon), or localized, such as the Arthus reaction.
10. Type IV (cell-mediated) reactions are caused by specifically sensitized T cells, which either kill target cells directly or release lymphokines that activate other cells, such as macrophages.
11. Allergies can be mediated by any of the four mechanisms of hypersensitivity.
12. Clinical manifestations of allergic reactions are usually confined to the areas of initial intake or contact with the allergen. Ingested allergens induce gastrointestinal symptoms, airborne allergens induce respiratory or skin manifestations, and contact allergens induce allergic responses at the site of contact.
13. Atopic individuals are genetically predisposed to the development of allergies.
14. Alloimmunity is the immune system’s reaction against antigens on the tissues of other members of the same species.
15. Alloimmune disorders include transient neonatal disease, in which the maternal immune system becomes sensitized against antigens expressed by the fetus, and transplant rejection and transfusion reactions, in which the immune system of the recipient of an organ transplant or blood transfusion reacts against foreign antigens on the donor’s cells.

Infection
1. Bacteria injure cells by producing exotoxins or endotoxins. Exotoxins are enzymes that can damage the plasma membranes of host cells or can inactivate enzymes critical to protein synthesis, and endotoxins activate the inflammatory response and produce fever.
2. Septicemia is the proliferation of bacteria in the blood. Endotoxins released by blood-borne bacteria cause the release of vasoactive enzymes that increase the permeability of blood vessels. Leakage from vessels causes hypotension that can result in septic shock.
3. Viruses enter host cells and use the metabolic processes of host cells to proliferate.
4. Viruses that have invaded host cells may decrease protein synthesis, disrupt lysosomal membranes, form inclusion bodies where synthesis of viral nucleic acids is occurring, fuse with host cells to produce giant cells, alter antigenic properties of the host cell, and transform host cells into cancerous cells.
5. Diseases caused by fungi are called mycoses, and they occur in two forms: yeasts (spheres) and molds (filaments or hyphae).
6. Dermatophytes are fungi that infect skin, hair, and nails with diseases such as ringworm and athlete’s foot.
7. Fungi release toxins and enzymes that are damaging to tissue.

Deficiencies in Immunity
1. Immunodeficiency is the failure of mechanisms of self-defense to function in their normal capacity.
2. Immunodeficiencies are either congenital (primary) or acquired (secondary). Congenital immunodeficiencies are caused by genetic defects that disrupt lymphocyte development, whereas acquired immunodeficiencies are secondary to disease or other physiologic alterations.
3. The clinical hallmark of immunodeficiency is a propensity to unusual or recurrent severe infections. The type of infection usually reflects the immune system defect.
4. The most common infections in individuals with defects of cell-mediated immune response are fungal and viral, whereas infections in individuals with defects of the humoral immune response or complement function are primarily bacterial.
5. Severe combined immunodeficiency (SCID) is a total lack of T cell function and a severe (either partial or total) lack of B cell function.
6. DiGeorge syndrome (congenital thymic aplasia or hypoplasia) is characterized by complete or partial lack of the thymus (resulting in depressed T cell immunity), the parathyroid glands (resulting in hypocalcemia), and cardiac anomalies.
7. Defects in B cell function are diverse, ranging from a complete lack of the human bursal equivalent, the lymphoid organs required for B cell maturation (as in Bruton agammaglobulinemia), to deficiencies in a single class of immunoglobulins (e.g., selective IgA deficiency).
8. Acquired immunodeficiencies are caused by superimposed conditions, such as malnutrition, medical therapies, physical or psychologic trauma, or infections.
9. AIDS is an acquired dysfunction of the immune system caused by a retrovirus (HIV) that infects and destroys CD4+ lymphocytes (helper T cells).
10. Immunodeficiency syndromes usually are treated by replacement therapy. Deficient antibody production is treated by replacement of missing immunoglobulins with commercial gamma-globulin preparations. Lymphocyte deficiencies are treated with the replacement of host lymphocytes with transplants of bone marrow, fetal liver, or fetal thymus from a donor.
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