CHAPTER
10

Alterations in the Immune Response

The human immune network is a multifaceted defense system that has evolved to protect against invading microorganisms, prevent the proliferation of cancer cells, and mediate the healing of damaged tissue. Under normal conditions, the immune response deters or prevents disease. However, occasionally the inadequate, inappropriate, or misdirected activation of the immune system can lead to debilitating or life-threatening illnesses, typified by allergic or hypersensitivity reactions, transplantation immunopathology, autoimmune disorders, and immunodeficiency states.

ALLERGIC AND HYPERSENSITIVITY DISORDERS

Hypersensitivity is defined as an exaggerated immune response to a foreign agent resulting in injury to the host.[1,2] Allergic or hypersensitivity disorders are caused by immune responses to environmental antigens that produce inflammation and cause tissue injury. In the context of an allergic response, these antigens usually are referred to as *allergens*. Allergens are any foreign substances capable of inducing an immune response. Many different chemicals of natural and synthetic origin are known allergens. Complex natural organic chemicals, especially proteins, are more likely to cause an immediate hypersensitivity response, whereas simple organic compounds, inorganic chemicals, and metals more commonly cause delayed hypersensitivity reactions. Exposure to the allergen can be through inhalation, ingestion, injection, or skin contact. Sensitization of a specific individual to a specific allergen is the result of a particular interplay between the chemical or physical properties of the allergen, the mode and quantity of exposure, and the unique genetic makeup of the person.

The manifestations of allergic responses reflect the effect of an immunologically induced inflammatory response in the organ or tissue involved. These manifestations usually are independent of the agent involved. For example, the symptoms of hay fever are the same whether the allergy is caused by ragweed pollen or mold spores. The diversity of allergic responses derives from the different immunologic effector pathways that are involved (*e.g.*, hay fever vs. allergic dermatitis).

Historically, hypersensitivity disorders have been categorized as four types: type I, IgE-mediated disorders; type II,

KEY CONCEPTS

ALLERGIC AND HYPERSENSITIVITY DISORDERS

- Allergic and hypersensitivity disorders result from immune responses to exogenous and endogenous antigens that produce inflammation and cause tissue damage.
- Type I hypersensitivity is an IgE-mediated immune response that leads to the release of inflammatory mediators for sensitized mast cells.
- Type II disorders involve humoral antibodies that participate directly in injuring cells by predisposing them to phagocytosis or lysis.
- Type III disorders result in generation of immune complexes in which humoral antibodies bind antigen and activate complement. The fractions of complement attract inflammatory cells that release tissue-damaging products.
- Type IV disorders involve tissue damage in which cell-mediated immune responses with sensitized T lymphocytes cause cell and tissue injury.

antibody-mediated (cytotoxic) disorders; type III, immune complex-mediated disorders; and type IV, cell-mediated hypersensitivity reactions (Table 10-1). Latex allergy is a newly emerging disorder that can result from an IgE-mediated or T-cell–mediated hypersensitivity response.

Type I, IgE-Mediated Disorders

Type I reactions are immediate-type hypersensitivity reactions that are triggered by binding of an allergen to a specific IgE that is found on the surface of mast cells or basophils. In addition to its role in allergic responses, IgE is involved in acquired immunity to parasitic infections.

The mast cells, which are tissue cells, and basophils, which are blood cells, are derived from hematopoietic (blood) precursor cells. Mast cells normally are distributed throughout connective tissue, especially in areas beneath the skin and mucous membranes of the respiratory, gastrointestinal, and genitourinary tracts, and adjacent to blood and lymph vessels.[3] This location places mast cells near surfaces that are exposed to environmental antigens and parasites. Mast cells and basophils have granules that contain potent mediators of allergic reactions. These mediators are preformed in the cell or activated through enzymatic processing. During the sensitization or priming stage, the allergen-specific IgE antibodies attach to receptors on the surface of mast cells and basophils. With subsequent exposure, the sensitizing allergen binds to the cell-associated IgE and triggers a series of events that ultimately lead to degranulation of the sensitized mast cells or basophils, causing release of their allergy-producing mediators (Fig. 10-1).

The primary (preformed) mediators of allergic reactions include histamine, acetylcholine, adenosine, chemotactic mediators, and neutral proteases that are released from mast cells. Histamine, the most important of these preformed mediators, is a potent vasodilator that increases the permeability of capillaries and venules, and causes bronchoconstriction and increased secretion of mucus. Acetylcholine produces bronchial smooth muscle contraction and dilation of small blood vessels. The proteases generate kinins and cleave complement components to produce additional chemotactic and inflammatory mediators. Secondary mediators include leukotrienes and prostaglandins that are generated from arachidonic acid in the mast cell membrane (see Chapter 9). The leukotrienes and prostaglandins produce responses similar to those of histamine and acetylcholine, although their effects are delayed and prolonged by comparison. Platelet-activating factor is another secondary mediator, resulting in platelet aggregation, histamine release, and bronchospasm. It also acts as a chemotactic factor for neutrophils and eosinophils. Mast cells also produce a number of cytokines that play a role in type I hypersensitivity responses through their ability to recruit and activate a variety of inflammatory cells.

Type I hypersensitivity reactions may present as a systemic disorder (anaphylaxis) or a localized reaction (atopy).[2]

Systemic Anaphylactic Reactions

Systemic anaphylactic disorders often result from injected allergens (*e.g.*, penicillin, radiographic contrast dyes, bee or wasp stings). More rarely, they may result from ingested allergens (seafood, nuts, legumes). In sensitized individuals, only a small amount of the allergen may be required to produce a

TABLE 10-1 Classification of Hypersensitivity Responses

Type	Mechanism	Examples
I — Anaphylactic (immediate) hypersensitivity	IgE-mediated—mast cell degranulation	Hay fever, asthma, anaphylaxis
II — Cytotoxic	Formation of antibodies (IgG, IgM) against cell surface antigens. Complement usually is involved.	Autoimmune hemolytic anemia, hemolytic disease of the newborn, Goodpasture's disease
III — Immune complex disease	Formation of antibodies (IgG, IgM, IgA) that interact with exogenous or endogenous antigens to form antigen- antibody complexes.	Arthus reaction, autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis), certain forms of acute glomerulosclerosis
IV — Cell-mediated (delayed-type) hypersensitivity	Sensitized T lymphocytes release cytokines and produce T-cell–mediated cytotoxicity.	Tuberculosis, contact dermatitis, transplant rejection

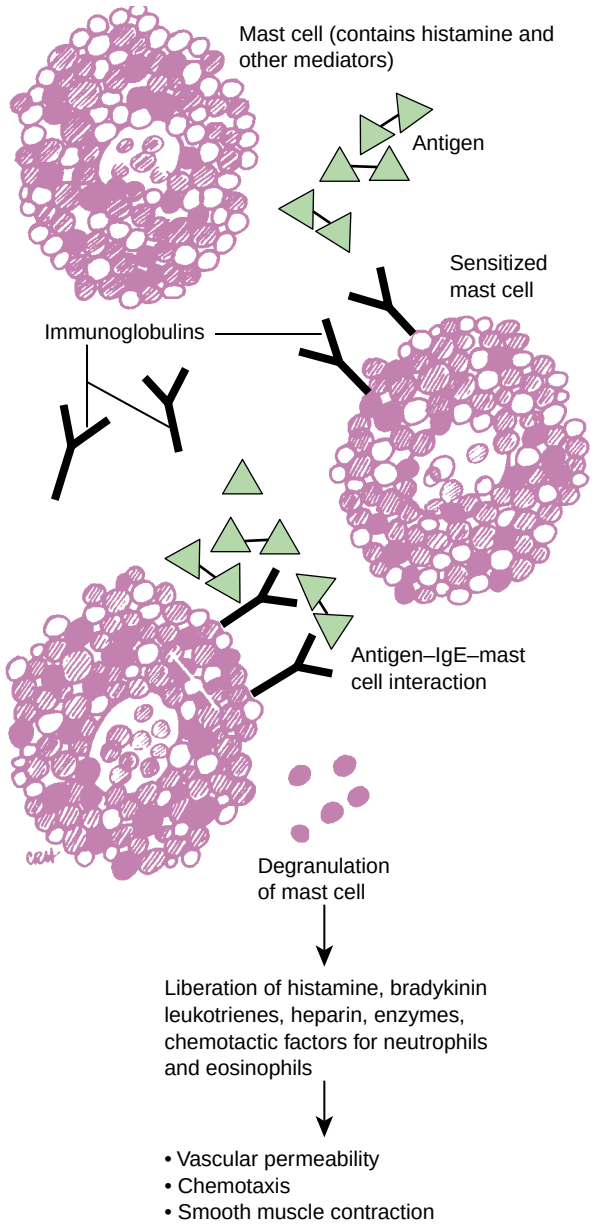


FIGURE 10-1 Type I, IgE-mediated hypersensitivity reaction. Exposure to the antigen causes sensitization of the mast cell; subsequent binding of the antigen to the sensitized degranulation of mast cell with release of potent inflammatory mediators, such as histamine, that are responsible for the hypersensitivity reactions.

reaction. Anaphylaxis has a rapid onset, often within minutes, of itching, urticaria (hives), gastrointestinal cramps, and difficulty breathing caused by bronchospasm. Angioedema (swelling of face and throat) may develop, causing upper airway obstruction. Massive vasodilation may lead to peripheral pooling of blood, a profound drop in blood pressure, and life-threatening circulatory shock (see Chapter 18).

Localized Atopic Disorders

Localized reactions generally occur when the antigen is confined to a particular site, usually related to the route of exposure. Localized type I hypersensitivity reactions appear to be genetically determined and the term *atopy* is often used to imply a hereditary predisposition to such reactions. Persons with atopic disorders commonly are allergic to more than one, and often many, environmental allergens. They tend to have high serum levels of IgE and increased numbers of basophils and mast cells. Although the IgE-triggered response is likely to be a key factor in the pathophysiology of the disorders, it is not the only factor. It is possible that persons with atopic disorders are exquisitely responsive to the chemical mediators of allergic reactions, rather than having a hyperactive IgE immune response.

Atopic disorders include food allergies, allergic rhinitis (hay fever), allergic dermatitis, and certain forms of bronchial asthma. The discussion in this section focuses on allergic rhinitis and food allergy. Allergic asthma is discussed in Chapter 21 and atopic dermatitis in Chapter 44.

Allergic Rhinitis. Allergic rhinitis (*i.e.*, allergic rhinoconjunctivitis) is characterized by symptoms of sneezing, itching, and watery discharge from the eyes and nose. Allergic rhinitis not only produces nasal symptoms but also frequently is associated with other chronic airway disorders, such as sinusitis and bronchial asthma.[4] Severe attacks may be accompanied by systemic malaise, fatigue, and muscle soreness from sneezing. Fever is absent. Sinus obstruction may cause headache. Typical allergens include pollens from ragweed, grasses, trees, and weeds; fungal spores; house dust mites; animal dander; and feathers. Allergic rhinitis can be divided into perennial and seasonal allergic rhinitis, depending on the chronology of symptoms. Persons with the perennial type of allergic rhinitis experience symptoms throughout the year, but those with seasonal allergic rhinitis (*i.e.*, hay fever) are plagued with intense symptoms in conjunction with periods of high allergen (*e.g.*, pollens, fungal spores) exposure. Symptoms that become worse at night suggest a household allergen, and symptoms that disappear on weekends suggest occupational exposure.

Diagnosis depends on a careful history and physical examination, microscopic identification of nasal eosinophilia, and skin testing to identify the offending allergens.

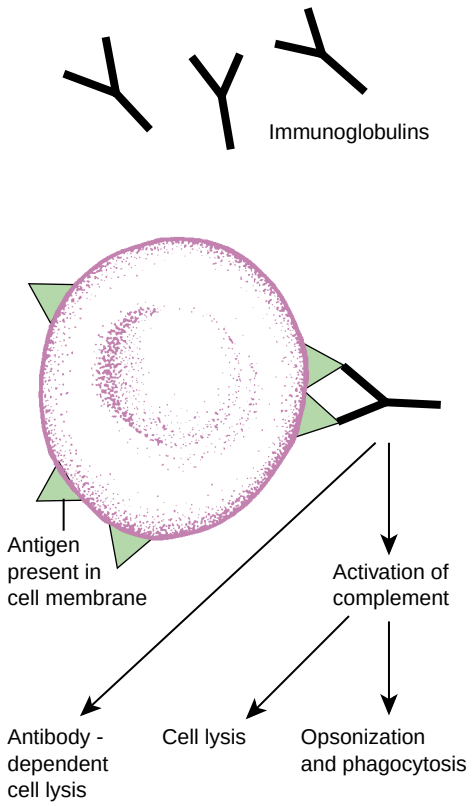
Treatment is symptomatic in most cases and includes the use of oral antihistamines and decongestants.[4] Intranasal corticosteroids often are effective when used appropriately. Intranasal cromolyn, a drug that stabilizes mast cells and prevents their degranulation, may be useful, especially when administered before expected contact with an offending allergen. The anticholinergic agent ipratropium, which is available as a nasal spray, also may be used. When possible, avoidance of the offending allergen is recommended.

Food Allergies. Virtually any food can produce atopic allergies. The primary target of food allergy may be the skin, the gastrointestinal tract, or the respiratory system. The foods most commonly causing these reactions in children are milk, eggs, peanuts, soy, tree nuts, fish, and shellfish foods (*i.e.*, crustaceans and mollusks).[5] In adults, such foods are peanuts, shellfish, and fish. The allergenicity of a food may be changed by heating or cooking. A person may be allergic to drinking milk but may not have symptoms when milk is included in cooked foods. Both acute reactions (*e.g.*, anaphylaxis) and chronic re-

actions (*e.g.*, asthma, atopic dermatitis, and gastrointestinal disorders) can occur. Anaphylaxis is a serious and sometimes fatal systemic reaction. The foods most responsible for anaphylaxis are peanuts, tree nuts (*e.g.*, walnuts, almonds, pecans, cashews, hazelnuts), and shellfish.

Although food allergies can occur at any age, they tend to manifest during childhood. The allergic response is thought to occur after contact between specific food allergens and IgE-sensitized mast cells found in the intestinal mucosa causes local and systemic release of histamine and other mediators of the allergic response. In this disorder, allergens usually are food proteins and partially digested food products. Carbohydrates, lipids, or food additives, such as preservatives, colorings, or flavorings, also are potential allergens. Closely related food groups can contain common cross-reacting allergens. For example, some persons are allergic to all legumes (*i.e.*, beans, peas, and peanuts).

Diagnosis of food allergies usually is based on careful food history and provocative diet testing. Provocative testing involves careful elimination of a suspected allergen from the diet for a period of time to see if the symptoms disappear and reintroducing the food to see if the symptoms reappear. Only one food should be tested at a time. Treatment focuses on avoidance of the food or foods responsible for the allergy. However, avoidance may be difficult for persons who are exquisitely sensitive to a particular food protein because foods may be contaminated with the protein during processing or handling of the food. For example, contamination may occur when chocolate candies without peanuts are processed with the same equipment used for making candies with peanuts. In predisposed persons, even using the same spatula to serve cookies with and without peanuts can cause enough contamination to produce a severe anaphylactic reaction.



■ **FIGURE 10-2** ■ Type II, cytotoxic hypersensitivity reactions involve formation of immunoglobulins (IgG and IgM) against cell surface antigens. The antigen-antibody response leads to (1) complement-mediated mechanisms of cell injury or to (2) antibody cytotoxicity that does not require the complement system.

Type II, Antibody-Mediated Cytotoxic Disorders

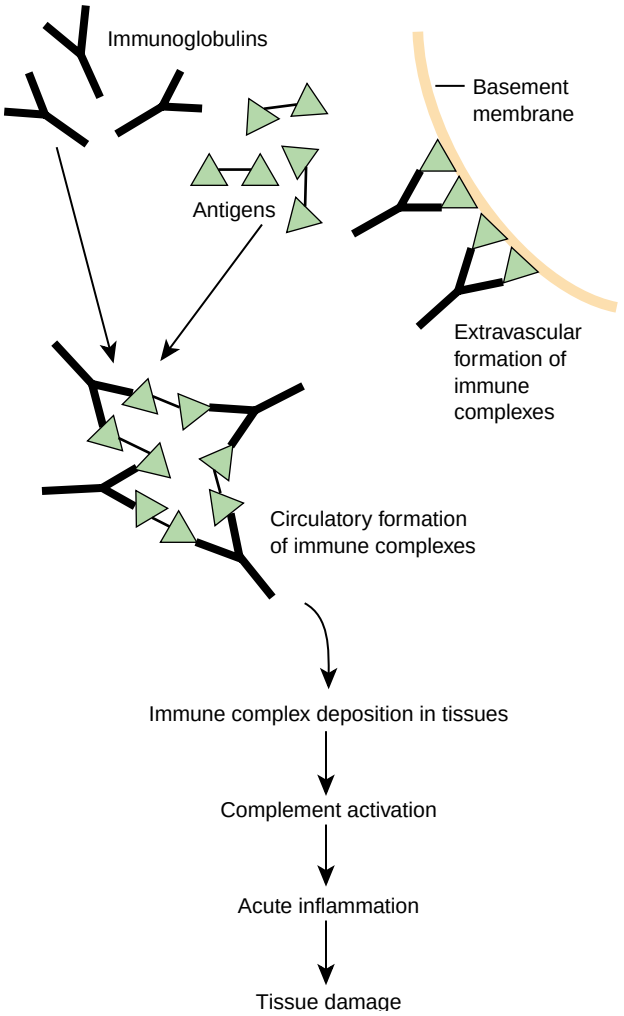
Type II (cytotoxic) hypersensitivity reactions are the end result of direct interaction between IgG and IgM class antibodies and tissue or cell surface antigens, with subsequent activation of complement- or antibody-dependent cell-mediated cytotoxicity (Fig. 10-2). Examples of type II reactions include mismatched blood transfusions, hemolytic disease of the newborn caused by ABO or Rh incompatibility, and certain drug reactions. In the latter, the binding of certain drugs to the surface of red or white blood cells elicits an antibody and complement response that lyses the drug-coated cell. Lytic drug reactions can produce transient anemia, leukopenia, or thrombocytopenia, which are corrected by the removal of the offending drug.

Type III, Immune-Complex Disorders

Immune complex disorders are mediated by the formation of insoluble antigen-antibody complexes that activate complement (Fig. 10-3). Activation of complement by the immune complex generates chemotactic and vasoactive mediators that cause tissue damage by a variety of mechanisms, including alterations in blood flow, increased vascular permeability, and the destructive action of inflammatory cells. The reaction occurs when the antigen combines with antibody, whether in the circulation (circulating immune complexes) or at extravascular sites where antigen may have been deposited. Immune complexes formed in the circulation produce damage when they come in contact with the vessel lining or are deposited in tissues, including the renal glomerulus, skin venules, the lung, and joint synovium. Once deposited, the immune complexes elicit an inflammatory response by activating complement, thereby leading to chemotactic recruitment of neutrophils and other inflammatory cells.

There are two general types of antigens that cause immune-complex mediated injury: (1) exogenous antigens such as viral and bacterial proteins and (2) endogenous antigens such as self-antigens associated with autoimmune disorders. Type III reactions are responsible for the acute glomerulonephritis that follows a streptococcal infection and the manifestations of autoimmune disorders such as systemic lupus erythematosus (SLE). Unlike type II reactions, in which the damage is caused by binding of antibody to body cells, the harmful effects of type III reactions are indirect (*i.e.*, secondary to the inflammatory response induced by activated complement).

Acute serum sickness is the prototype of a systemic immune complex disease. The term *serum sickness* was originally coined to describe a syndrome consisting of rash, lymphadenopathy, arthralgias, and occasionally neurologic disorders that appeared 7 or more days after injections of horse antisera for prevention of tetanus. Although this therapy is not used



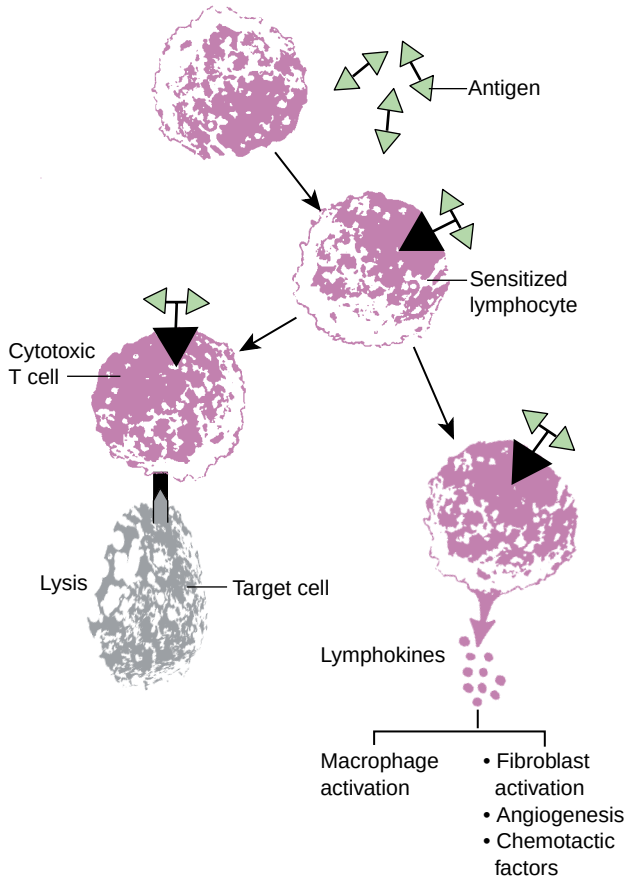
■ **FIGURE 10-3** ■ Type III, immune complex reactions involve complement-activating IgG and IgM immunoglobulins with formation of blood-borne immune complexes that are eventually deposited in tissues. Complement activation at the site of immune complex deposition leads to recruitment of leukocytes, which are eventually responsible for tissue injury.

today, the name remains. The most common contemporary causes of this allergic disorder include antibiotics (especially penicillin), various foods, drugs, and insect venoms. Serum sickness is triggered by the deposition of insoluble antigen-antibody (IgM and IgG) complexes in blood vessels, joints, heart, and kidney tissue. The deposited complexes activate complement, increase vascular permeability, and recruit phagocytic cells, all of which can promote focal tissue damage and edema. The signs and symptoms include urticaria, patchy or generalized rash, extensive edema (usually of the face, neck, and joints), and fever. In most cases, the damage is temporary, and symptoms resolve within a few days. However, a prolonged and continuous exposure to the sensitizing antigen can lead to irreversible damage. In previously sensitized persons, severe and even fatal forms of serum sickness may occur immediately or within several days after the sensitizing drug or serum is administered.

Type IV, Cell-Mediated Hypersensitivity Disorders

Unlike other hypersensitivity reactions, type IV, delayed hypersensitivity, is mediated by cells, not antibodies. Type IV hypersensitivity reactions usually occur 24 to 72 hours after exposure of a sensitized individual to the offending antigen. They are mediated by T lymphocytes that are directly cytotoxic ($CD8^+$ T cells) or that secrete inflammatory mediators ($CD4^+$ T cells) that cause tissue changes (Fig. 10-4). The reaction is initiated by antigen-specific $CD4^+$ helper T cells, which release numerous immunoregulatory and proinflammatory cytokines into the surrounding tissue. These substances attract antigen-specific and antigen-nonspecific T or B lymphocytes as well as monocytes, neutrophils, eosinophils, and basophils. Some of the cytokines promote differentiation and activation of macrophages that function as phagocytic and antigen-presenting cells (APCs). Activation of the coagulation cascade leads to formation and deposition of fibrin.

The best-known type of delayed hypersensitivity response is the reaction to the tuberculin test, in which inactivated tuberculin or purified protein derivative is injected under the skin. In a previously sensitized person, redness and induration of the area develop within 8 to 12 hours, reaching a peak in



■ **FIGURE 10-4** ■ Type IV, cell-mediated or delayed-type hypersensitivity reactions involve sensitization of T lymphocytes with the subsequent formation of cytotoxic T cells that lyse target cells or T cells that release cell-damaging lymphokines.

24 to 72 hours. A positive tuberculin test indicates that a person has had sufficient exposure to the *M. tuberculosis* organism to incite a hypersensitivity reaction; it does not mean that the person has tuberculosis. Certain types of antigens induce cell-mediated immunity with an especially pronounced macrophage response. This type of delayed hypersensitivity commonly develops in response to particulate antigens that are large, insoluble, and difficult to eliminate. The accumulated macrophages are often transformed into so-called *epithelioid cells* because they resemble epithelium. A microscopic aggregation of epithelioid cells, which usually are surrounded by a layer of lymphocytes, is called a *granuloma.* Inflammation that is characterized by this type of type IV hypersensitivity is called *granulomatous inflammation* (see Chapter 9).

Direct T-cell–mediated cytotoxicity, which causes necrosis of antigen-bearing cells, is believed to be important in the eradication of virus-infected cells, autoimmune diseases such as Hashimoto's thyroiditis, and host-versus-graft or graft-versus-host transplant rejection. Allergic contact dermatitis and hypersensitivity pneumonitis are presented as examples of cell-mediated hypersensitivity reactions.

Allergic Contact Dermatitis

Allergic contact dermatitis denotes an inflammatory response confined to the skin that is initiated by re-exposure to an allergen to which a person had previously become sensitized (*e.g.*, cosmetics, hair dyes, metals, topical drugs). Contact dermatitis usually consists of erythematous macules, papules, and vesicles (*i.e.*, blisters). The affected area often becomes swollen and warm, with exudation, crusting, and development of a secondary infection. The location of the lesions often provides a clue about the nature of the antigen causing the disorder. The most common form of this condition is the dermatitis that follows an intimate encounter with poison ivy or poison oak antigens, although many other substances can trigger a reaction.

The mechanism of events leading to prior sensitization to an antigen is not completely understood. It is likely that sensitization follows transdermal transport of an antigen, with subsequent presentation to T lymphocytes. Subpopulations of sensitized lymphocytes are distributed throughout the body so that subsequent cutaneous exposure to the offending antigen promotes a localized reaction regardless of the initial site of contact. The severity of the reaction associated with contact dermatitis ranges from mild to intense, depending on the person and the allergen. Because this condition follows the time course of a delayed hypersensitivity response, the reaction does not become apparent for at least 12 hours and usually more than 24 hours after exposure. Depending on the antigen and the duration of exposure, the reaction may last from days to weeks and is typified by erythematous, vesicular, or papular lesions associated with intense pruritus and weeping.

Diagnosis of contact dermatitis is made by observing the distribution of lesions on the skin surface and associating a particular pattern with exposure to possible allergens. If a particular allergen is suspected, a patch test can be used to confirm the suspicion. Treatment usually is limited to removal of the irritant and application of topical preparations (*e.g.*, ointments, corticosteroid creams) to relieve symptomatic skin lesions and prevent secondary bacterial infections. Severe reactions may require systemic corticosteroid therapy.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis or allergic alveolitis is associated with exposure to inhaled organic dusts or related occupational antigens. The disorder is thought to involve a susceptible host and activation of pulmonary T cells, followed by the release of cytokine mediators of inflammation.[6] The inflammatory response that ensues (usually several hours after exposure) produces labored breathing, dry cough, chills and fever, headache, and malaise. The symptoms usually subside within hours after the sensitizing antigens are removed. A primary example of hypersensitivity pneumonitis is "farmer's lung," a condition resulting from exposure to moldy hay. Other sensitizing antigens include tree bark, sawdust, animal danders, and *Actinomycetes* bacteria that are occasionally found in humidifiers, hot tubs, and swimming pools. Exposure to small amounts of antigen for a long period may lead to chronic lung disease with minimal reversibility. This can happen to persons exposed to avian or animal antigens or a contaminated home air humidifier.[6]

The most important element in the diagnosis of hypersensitivity pneumonitis is to obtain a good history (occupational and otherwise) of exposure to possible antigens. Skin tests, when available, and serum tests for precipitating antibody can be done. Occasionally, direct observation of the person's work and other environments may help to establish a diagnosis. Treatment consists of identifying and avoiding the offending antigens. Severe forms of the disorder may be treated with systemic corticosteroid therapy.

Latex Allergy

With the advent of the human immunodeficiency virus (HIV) and other blood-borne pathogens, the use of natural latex gloves has spiraled. Along with the expanded use of latex gloves have come increased reports of latex allergy among health care workers. Other persons at high risk of sensitization are those with prolonged exposure to latex, including persons who have undergone repeated surgeries. Exposure to latex may occur by cutaneous, mucous membrane, inhalation, internal tissue, or intravascular routes. Most severe reactions have resulted from latex proteins coming in contact with the mucous membranes of the mouth, vagina, urethra, or rectum. Children with meningomyelocele (spina bifida) who undergo frequent examinations and treatments involving the mucosal surface of the bladder or rectum are at particular risk for the development of latex allergy.[7,8] A large number of latex products are used in dentistry, and oral mucosal contact is common during dental procedures. Anaphylactic reactions have been caused by exposure of the internal organs to the surgeon's gloves during surgery.

Allergic reactions to latex products can be triggered by the latex proteins or by the additives used in the manufacturing process. Natural rubber latex is derived from the milky sap of the *Hevea brasiliensis* plant or rubber tree. Various accelerants, curing agents, antioxidants, and stabilizers are added to the liquid latex during the manufacturing process. Cornstarch powder is applied to the gloves during the manufacturing process to prevent stickiness and give the gloves a smooth feel. The cornstarch glove powder has an important role in the allergic response. Latex proteins are readily absorbed by glove powder and become airborne during removal of the gloves. Operating

rooms and other high exposure areas where powdered gloves are used contain sufficiently high levels of aerosolized latex to produce symptoms in sensitized persons.

Latex allergy can involve a type I, IgE-mediated hypersensitivity reaction, or a type IV, cell-mediated response. The distinction between the type I and type IV reactions to latex products is not always clear. Affected individuals may experience both types of reactions. Persons with latex allergy commonly show cross-sensitivity to bananas, avocado, kiwi, tomatoes, and chestnuts, probably because latex proteins are similar to the proteins in these foods.[7,8] These foods have been responsible for anaphylactic reactions in latex-sensitive persons.

The most common type of allergic reaction to latex gloves is a contact dermatitis caused by a type IV, delayed hypersensitivity reaction to rubber additives. It usually develops 48 to 96 hours after direct contact with latex additives. It often affects the dorsum of the hands and is characterized by a vesicular rash. When latex contact is continued, the area becomes crusted and thickened. The type I, IgE-mediated hypersensitivity reactions that occur in response to the latex proteins are less common but far more serious. They may manifest as urticaria, rhinoconjunctivitis, asthma, or anaphylaxis.

Diagnosis of latex allergy often is based on careful history and evidence of skin reactions caused by latex exposure. Symptoms after use of a rubber condom or diaphragm should raise suspicion of latex allergy. Because many of the reported reactions to latex gloves have been the result of a nonimmunologic dermatitis, it is important to differentiate between nonallergic and allergic types of dermatitis.

Treatment of latex allergy consists of avoiding latex exposure. Use of powder-free gloves can reduce the amount of airborne latex particles. Health care workers with severe and life-threatening allergy may be forced to change employment. Patients at high risk for latex allergy (*e.g.*, children with spina bifida, health care workers with atopic disorders) should be offered clinical testing for latex allergy before undergoing procedures that expose them to natural rubber latex. All surgical or other procedures on persons with latex allergy should be done in a latex-free environment.

In summary, hypersensitivity and allergic disorders are responses to environmental, food, or drug antigens that would not affect most of the population. There are four basic categories of hypersensitivity responses: type I responses such as allergic rhinitis, bronchial asthma, and food allergies, which are mediated by IgE-class immunoglobulins; type II cytotoxic reactions such as blood transfusion reactions, which result from immunoglobulin (IgG and IgM) activation of complement; type III reactions, which result from the formation of insoluble antigen-antibody complexes that become deposited in blood vessels or in the kidney and cause localized tissue injury; and type IV, cell-mediated responses which cause conditions such as allergic dermatitis and hypersensitivity pneumonitis. Latex allergy, which is becoming more common with the spiraling use of latex gloves to prevent transmission of blood-borne diseases, can involve a type I, IgE-mediated anaphylactic reaction or a type IV, T-cell–mediated contact dermatitis.

TRANSPLANTATION IMMUNOPATHOLOGY

Not long ago, transplantation of solid organs (*e.g.*, liver, kidney, heart) and bone marrow was considered experimental and reserved for persons for whom alternative methods of therapy were exhausted and survival was unlikely. However, with a greater understanding of humoral and cellular immune regulation, the development of immunosuppressive drugs such as cyclosporine, and an appreciation of the role of the major histocompatibility complex (MHC) antigens, transplantation has become nearly routine, and the subsequent success rate has been greatly enhanced.

The cell surface antigens that determine whether transplanted tissue is recognized as foreign are the MHC or *human leukocyte antigen* (HLA) (see Chapter 8). Transplanted tissue can be categorized as *allogeneic* if the donor and recipient are related or unrelated but share similar HLA types, *syngeneic* if the donor and recipient are identical twins, and *autologous* if donor and recipient are the same person. Donors of solid organ transplants can be living or dead (cadaver) and related or nonrelated (heterologous). When tissues bearing foreign MHC antigens are transplanted, the recipient's immune system attempts to eliminate the donor cells, a process referred to as *host-versus-graft* disease (HVGD). Conversely, the cellular immune system of the transplanted tissues can attack unrelated recipient tissue, causing a *graft-versus-host* disease (GVHD). The likelihood of rejection varies indirectly with the degree of HLA or MCH relatedness between donor and recipient.

Host-Versus-Graft Disease

In HVGD, the immune cells of the transplant recipient attack the donor cells of the transplanted organ. HVGD usually is limited to allogeneic organ transplants, although even HLA-identical siblings may differ in some minor HLA loci, which can evoke slow rejection. Rejection caused by HVGD is a complex process that involves cell-mediated and circulating antibodies. Although many cells may participate in the process of acute transplant rejection, only the T lymphocytes seem to be absolutely required.[2] The activation of $CD8^+$ cytotoxic T cells and $CD4^+$ helper T cells is triggered in response to the donor's HLA antigens. Activation of $CD4^+$ helper cells leads to proliferation of B-cell–mediated antibody production and a delayed-type hypersensitivity reaction. The initial target of the recipient antibodies is graft vasculature. The antibodies can produce injury to the transplanted organ by complement-mediated cytotoxicity, generation of antigen-antibody complexes, or through antibody-mediated cytolysis.[2]

There are three basic patterns of transplant rejection: hyperacute, acute, and chronic.[2] A hyperacute reaction occurs almost immediately after transplantation; in kidney transplants, it can often be seen at the time of surgery. As soon as blood flow from the recipient to the donor organ begins, it takes on a cyanotic, mottled appearance. Sometimes, the reaction takes hours to days to develop. The hyperacute response is produced by existing recipient antibodies to graft antigens that initiate a type III immune-complex reaction in the blood vessels of the graft. These antibodies usually have developed in response to pre-

vious blood transfusions, pregnancies in which the mother makes antibodies to fetal antigens, or infections with bacteria or viruses possessing antigens that mimic MHC antigens.

Acute rejection usually occurs within the first few months after transplantation. It also may occur suddenly months or even years later, after immunosuppression has been used and terminated. In the person with an organ transplant, acute rejection is evidenced by signs of organ failure. Acute rejection often involves both humoral and cell-mediated immune responses. Histologically, humoral rejection is associated with vasculitis, whereas a cell-mediated rejection response is marked by interstitial infiltration by mononuclear cells. Acute rejection vasculitis is mediated primarily by antidonor antibodies and is characterized by lesions that lead to arterial narrowing or obliteration.

Chronic HVGD occurs over a prolonged period. It is manifest by dense fibrosis of the intimal layer of blood vessels in the transplanted organ. In renal transplantation, it is characterized by a gradual rise in serum creatinine during a period of 4 to 6 months. The actual mechanism of this type of response is unclear but may include release of inflammatory mediators such as interleukin-1 and platelet-derived growth factor.

Graft-Versus-Host Disease

GVHD occurs mainly in patients who undergo bone marrow transplant and in severely immunocompromised patients who have received blood products containing HLA-incompatible lymphocytes.[1] Although GVHD occurs mainly in patients who undergo bone marrow transplant, it may also occur after transplantation of solid organs rich in lymphoid cells (*e.g.*, the liver) or transfusion of nonirradiated blood.[2] Three basic requirements are necessary for GVHD to develop: (1) the donor bone marrow must have a functional cellular immune component; (2) the recipient's tissue must bear antigens foreign to the donor tissue; and (3) the recipient's immunity must be compromised to the point that it cannot destroy the transplanted cells. The primary agents of GVHD are the donor T cells, and the antigens they recognize and attack are the host HLA. The greater the difference in tissue antigens between the donor and recipient, the greater is the likelihood of GVHD. Recipients of bone marrow transplants are usually immunodeficient, either because of the primary disease or prior treatment with immunosuppressant drugs or irradiation. When such recipients receive normal bone marrow cells from allogenic donors, the immunocompetent T cells derived from the donor recognize the recipient's HLA antigens as foreign and react against them.

If GVHD occurs, the primary targets of the acute illness are the skin, liver, intestine, and cells of the immune system. Acute GVHD is characterized by a pruritic, maculopapular rash, which begins on the palms and soles and frequently extends over the entire body, with subsequent desquamation. The epithelial layer is the primary site of injury. When the intestine is involved, symptoms include nausea, bloody diarrhea, and abdominal pain. GVHD of the liver can lead to bleeding disorders and coma. GVHD is considered chronic if symptoms persist or begin 100 days or more after transplantation. Chronic GVHD is characterized by abnormal humoral and cellular immunity, severe skin disorders, and liver disease.

Another type of GVHD has been recognized after the transplantation of genetically identical tissue (*i.e.*, syngeneic or autologous [from self]). This variety of GVHD stems from the pretreatment conditioning regimen (*e.g.*, total-body irradiation) or treatment with cytotoxic drugs. The conditioning therapy disrupts the normal immune surveillance system and allows "rogue" autoreactive T cells to proliferate and attack native tissue. This type of GVHD usually is self-limited and not severe.

GVHD can often be prevented by selectively blocking the mechanisms responsible for the rejection process. For example, donor T cells can be selectively removed from the transplanted tissue or destroyed using various treatments such as monoclonal antibodies with attached toxins, equivalent to heat-seeking missiles. Alternatively, immunosuppressive or anti-inflammatory drugs such as cyclosporine and tacrolimus or glucocorticoids can be used to block T-cell activation and the action of cytokines.

In summary, organ and bone marrow transplantation has been enhanced by a greater understanding of humoral and cellular immune regulation, the development of immunosuppressive drugs such as cyclosporine, and an appreciation of the role of the MHC antigens in transplant rejection. The likelihood of rejection varies with the degree of HLA (or MHC) relatedness between donor and recipient. A rejection can involve an attempt by the recipient's immune system to eliminate the donor cells, as in HVGD, or an attack by the cellular immunity of the transplanted tissue on the unrelated recipient tissue, as in GVHD.

AUTOIMMUNE DISORDERS

Autoimmune diseases represent a group of disorders that are caused by a breakdown in the ability of the immune system to differentiate between self- and nonself antigens. To function properly, the immune system must be able to differentiate foreign antigens from self-antigens. Normally, there is a high degree of immunologic tolerance to self-antigens, which prevents the immune system from destroying the host.

Autoimmune diseases can affect almost any cell or tissue in the body. Some autoimmune disorders, such as Hashimoto's thyroiditis, are tissue specific; others, such as SLE, affect multiple organs and systems. Chart 10-1 lists some of the probable autoimmune diseases. Many of these disorders are discussed elsewhere in this book.

Immunologic Tolerance

The ability of the immune system to differentiate self from nonself is called *self-tolerance*. It is the HLA antigens encoded by MHC genes that serve as recognition markers of self and nonself for the immune system (see Chapter 8). To elicit an immune response, an antigen must first be processed by an antigen-presenting cell (APC), such as a macrophage, which then presents the antigenic determinants along with an MHC II molecule to a $CD4^+$ helper T cell for binding to its T-cell receptor (TCR). It is the dual recognition of the MHC–antigen

CHART 10-1 Probable Autoimmune Disease*

Systemic

Mixed connective tissue disease
Polymyositis-dermatomyositis
Rheumatoid arthritis
Scleroderma
Sjögren's syndrome
Systemic lupus erythematosus

Blood

Autoimmune hemolytic anemia
Autoimmune neutropenia and lymphopenia
Idiopathic thrombocytopenic purpura

Other Organs

Acute idiopathic polyneuritis
Atrophic gastritis and pernicious anemia
Autoimmune adrenalitis
Goodpasture's syndrome
Hashimoto's thyroiditis
Insulin-dependent diabetes mellitus
Myasthenia gravis
Premature gonadal (ovarian) failure
Primary biliary cirrhosis
Sympathetic ophthalmia
Temporal arteritis
Thyrotoxicosis (Graves' disease)
Ulcerative colitis

*Examples are not inclusive.

KEY CONCEPTS

IMMUNOLOGIC TOLERANCE AND AUTOIMMUNE DISEASE

- Immunologic tolerance is the ability of the immune system to differentiate self from nonself.
- Central tolerance involves the elimination of self-reactive T and B cells in the central lymphoid organs. Self-reactive T cells are deleted in the thymus and self-reactive B cells in the bone marrow.
- Peripheral tolerance derives from the deletion or inactivation of self-reactive T and B cells that escaped deletion in the central lymphoid organs.
- Autoimmune disorders result from the breakdown in the integrity of immune tolerance such that a humoral or cellular immune response can be mounted against host tissue or antigens, leading to localized or systemic injury.

complex by the TCR that acts as a security check that affects all T cells, including $CD4^+$ helper T cells, which orchestrate T- and B-cell immune responses, and cytotoxic T cells, which act directly to destroy target cells. A number of chemical messengers (*e.g.*, interleukins) and costimulatory signals are essential to the activation of immune responses and the preservation of self-tolerance.

Several mechanisms have been postulated to explain the tolerant state, including central tolerance and peripheral tolerance.[9] Central tolerance refers to the elimination of self-reactive T cells in the thymus and B cells in the bone marrow. Peripheral tolerance refers to the deletion or inactivation of autoreactive T cells or B cells that escaped elimination in the central lymphoid organs. Autoreactive B cells are deleted in the spleen and lymph nodes. Autoreactive T cells may undergo activation-induced cell death, be rendered inactive to the extent that they cannot recognize self antigens, or their activity may be suppressed by other regulatory T cells.[2]

Mechanisms of Autoimmune Disease

There are multiple explanations for the loss of self-tolerance and formation of autoantibodies or failure to recognize host antigens as self. Among the possible mechanisms responsible for development of autoimmune disease are aberrations in immune cell function or antigen structure. Heredity and gender may play a role in the development of autoimmunity. Because of the complexity of the immune system, it seems unlikely that autoimmune disorders arise from a single defect.

Heredity and Gender

Genetic factors can increase the incidence and severity of autoimmune diseases,[10] as shown by the familial clustering of several autoimmune diseases and the observation that certain inherited HLA types occur more frequently in persons with a variety of immunologic and lymphoproliferative disorders. For example, 90% of persons with ankylosing spondylitis carry the HLA-B27 antigen. Other HLA-associated diseases are Reiter's syndrome and HLA-B27, rheumatoid arthritis and HLA-DR4, and systemic lupus erythematosus (SLE) and HLA-DR3 (see Chapter 44). The molecular basis for these associations is unknown. Because autoimmunity does not develop in all persons with genetic predisposition, it appears that other factors, such as a "trigger event," interact to precipitate the altered immune state. The event or events that trigger the development of an autoimmune response are unknown. It has been suggested that the trigger may be a virus or other microorganism, a chemical substance, or a self-antigen from a body tissue that has been hidden from the immune system during development.

A number of autoimmune disorders such as SLE occur more commonly in women than men, suggesting that estrogens may play a role in the development of autoimmune disease. Evidence suggests that estrogens stimulate and androgens suppress the immune response.[11] For example, estrogen stimulates a DNA sequence that promotes the production of interferon-γ, which is thought to assist in the induction of an autoimmune response.

Failure of Self-tolerance

Autoimmune disorders can result from one or more mechanisms of self-tolerance. Immunologic cells are undoubtedly involved in the tissue injury that results, but the precise mecha-

nisms involved in initiating the response are largely unknown. More than one defect might be present in each disease, and each mechanism may be involved in more than one disease. Among the proposed mechanisms involved in loss of self-tolerance are: failure of T-cell–mediated suppression, breakdown of T-cell anergy, disorders of MHC–antigen receptor/complex interactions, release of sequestered antigens, molecular mimicry, and superantigens.

Failure of T-cell–Mediated Suppression. Disorders of immune regulatory or surveillance function can result from failure to delete autoreactive immune cells or suppress the immune response.[2] Because T cells regulate the immune response, an increasing ratio of helper T to suppressor T cells may lead to the development of autoimmune disorders.

Breakdown in T-cell Anergy. Anergy involves the prolonged or irreversible inactivation of T cells under certain conditions. Activation of antigen-specific $CD4^+$ T cells requires two signals: recognition of the antigen in association with class II MHC molecules on the surface of the APCs and a set of costimulatory signals provided by the APCs. If the second costimulatory signal is not delivered, the T cell becomes anergic. Most normal tissues do not express the costimulatory molecules and thus are protected from autoreactive T cells. This protection can be broken if the normal cells that do not normally express the costimulatory molecules are induced to do so. Some inductions can occur after an infection, or in situations where there is tissue necrosis and local inflammation. For example, up-regulation of the costimulator molecule B7-1 has been observed in the central nervous system of persons with multiple sclerosis, in the synovium of persons with rheumatoid arthritis, and in the skin of persons with psoriasis.[2]

Disorders in MHC–Antigen Complex/Receptor Interactions. The immune system recognizes antigen in the context of MHC–antigen complex and TCR interactions. Aberrations in any of these three stages of the immune response—antigen structure, TCR recognition of antigen, or MHC antigen presentation—have the potential for initiating an autoimmune response.

There are many ways in which chemical or microbial antigens can be modified to evoke an altered immune response, leading to an autoimmune disorder. Autoantigenic drugs and viruses can be complexed to a carrier that is recognized by nontolerant $CD4^+$ helper T cells as foreign. Virus-encoded antigens expressed on the cell surface can serve as carriers for self-antigens. In this case, the self-antigen would appear as a hapten for which an immune response could be induced.

Partial degradation of self-antigens also may occur. For example, partially degraded collagen or enzymatically altered thyroglobulin or gamma globulin may be sufficiently foreign to promote an autoimmune response.

Release of Sequestered Antigens. Normally the body does not produce antibodies against self-antigens. Thus, any self-antigen that was completely sequestered during development and then reintroduced to the immune system is likely to be regarded as foreign. Among the sequestered tissues that could be regarded as foreign are spermatozoa and ocular antigens such as those found in uveal tissue. Post-traumatic uveitis and orchiditis after vasectomy may fall into this category.

Molecular Mimicry. It is possible that certain autoimmune disorders are caused by molecular mimicry, in which a foreign antigen so closely resembles a self-antigen that antibodies produced against the former react with the latter.[12,13] A humoral or cellular response can be mounted against antigenically altered or injured tissue, creating an immune process. For example, in rheumatic fever and acute glomerulonephritis, a protein in the cell wall of group A β-hemolytic streptococci has considerable similarity with antigens in heart and kidney tissue, respectively. After infection, antibodies directed against the microorganism cause a classic case of mistaken identity, which leads to inflammation of the heart or kidney. Certain drugs, when bound to host proteins or glycoproteins, form a complex to which a humoral response is directed with substantial cross-reactivity to the original self-protein. The antihypertensive agent methyldopa can bind to surface antigens on red cells to induce an antibody-mediated hemolytic anemia.

Not everyone exposed to group A β-hemolytic streptococci has an autoimmune reaction. The reason that only certain persons are targeted for autoimmune reactions to a particular self-mimicry molecule may be determined by differences in HLA types. The HLA type determines exactly which fragments of a pathogen are displayed on the cell surface for presentation to T cells. One individual's HLA may bind self-mimicry molecules for presentation to T cells, and another's HLA type may not. In the spondyloarthropathies, particularly Reiter's syndrome and reactive arthritis, there is a clear relationship between arthritis and a prior bacterial infection, combined with the inherited HLA-B27 antigens.[13]

Superantigens. Superantigens are a family of related substances, including staphylococcal and streptococcal exotoxins, that can short-circuit the normal sequence of events in an immune response, leading to inappropriate activation of $CD4^+$ helper T cells. Superantigens do not require processing and presentation of antigen by APCs to induce a T-cell response.[14] Instead, they are able to interact with a TCR outside the normal antigen-binding site. Normally, only a small percentage (0.01%) of the T-cell population is stimulated by the presence of processed antigens on the surface of macrophages; however, superantigens can interact with 5% to 30% of T cells.[14] Superantigens directly link the MHC II complex molecules of APCs such as macrophages to TCRs, causing a massive release of T-cell inflammatory cytokines, primarily interleukin-2 and tumor necrosis factor, and an uncontrolled proliferation of T cells. At least one disease in adults, toxic shock syndrome, is mediated by superantigens (see Chapter 18). Kawasaki's disease in children (see Chapter 17) probably has a similar cause.

Diagnosis and Treatment

Suggested criteria for determining that a disorder is an autoimmune disorder are evidence of an autoimmune reaction, determination that the immunologic findings are not secondary to another condition, and the lack of other identifiable causes for the disorder. Currently, the diagnosis of autoimmune disease is based primarily on clinical findings and serologic testing. The basis for most serologic assays is the demonstration of

antibodies directed against tissue antigens or cellular components. For example, a serological assay for antinuclear antibodies is used in the diagnosis of SLE.

Treatment of autoimmune disease is based on the tissue or organ that is involved, the effector mechanism involved, and the magnitude and chronicity of the effector processes. Ideally, treatment should focus on the mechanism underlying the autoimmune disorder.

In summary, autoimmune diseases represent a disruption in self-tolerance that results in damage to body tissues by the immune system. Autoimmune diseases can affect almost any cell or tissue of the body. The ability of the immune system to differentiate self from nonself is called *self-tolerance.* Normally, self-tolerance is maintained through central and peripheral mechanisms that delete autoreactive B or T cells or otherwise suppress or inactivate immune responses that would be destructive to host tissues. Defects in any of these mechanisms could impair self-tolerance and predispose to development of autoimmune disease.

The ability of the immune system to differentiate foreign from self-antigens is the responsibility of HLA encoded by MHC genes. Antigen is presented to receptors of T cells in combination with MHC molecules. Among the possible mechanisms responsible for the development of autoimmune disease are failure of T-cell–mediated immune suppression; aberrations in MHC-antigen-TCR interactions; molecular mimicry; and superantigens.

Suggested criteria for determining that a disorder results from an autoimmune disorder are evidence of an autoimmune reaction, determination that the immunologic findings are not secondary to another condition, and the lack of other identifiable causes for the disorder.

IMMUNODEFICIENCY DISORDERS

Immunodeficiency can be defined as an abnormality in one or more branches of the immune system that renders a person susceptible to diseases normally prevented by an intact immune system. Two major categories of immune mechanisms defend the body against infectious or neoplastic disease: humoral or antibody-mediated immunity (*i.e.,* B lymphocytes) and cell-mediated immunity (*i.e.,* T lymphocytes and lymphokines).

Abnormalities of the immune system can be classified as primary (*i.e.,* congenital or inherited) or secondary if the immunodeficiency is acquired later in life. Secondary immunodeficiencies are more common than primary disorders of genetic origin. Secondary deficiencies in humoral immunity can develop as a consequence of selective loss of immunoglobulins through the gastrointestinal or genitourinary tracts. Secondary deficiencies of T-cell function have been described in conjunction with acute viral infections (*e.g.,* measles virus, cytomegalovirus) and with certain malignancies (*e.g.,* Hodgkin's disease and other lymphomas). HIV/AIDS (to be discussed) is the most devastating example of a secondary immunodeficiency. Regardless of the cause, primary and secondary deficiencies can produce the same spectrum of disease. The severity and symptomatology of the various immunodeficiencies depend on the disorder and extent of immune system involvement.

Primary Immunodeficiency Disorders

Until recently, little was known about the causes of primary immunodeficiency diseases. As a result of recent advances in mapping the human genome, the genetic origin of many of the defects has been identified.[15] In addition, previous classifications of the disorders were based on specific clinical manifestations and alterations in immune function. Advances in molecular genetics now allow many of these disorders to be grouped according to the types of genetically altered molecules that are involved. Although genes essential to immune function are located throughout the genome, a large number are located on the X chromosome. Thus, there is a clear dominance of X-linked immunodeficiencies in males who have only one X chromosome and a single copy of these genes.[15] In addition, spontaneous mutations in these X-linked genes are relatively common.

Humoral (B-Cell) Immunodeficiencies

Humoral immunodeficiency can range from a transient decrease in immunoglobulin levels during early infancy to inherited disorders that interrupt the production of one or all of the immunoglobulins. During the first few months of life, infants are protected from infection by immunoglobulin G (IgG) class

KEY CONCEPTS

PRIMARY IMMUNODEFICIENCY DISORDERS

- Primary immunodeficiency disorders are congenital or inherited abnormalities of immune function that render a person susceptible to diseases normally prevented by an intact immune system.
- Disorders of B-cell function impair the ability to produce antibodies and defend against microorganisms and toxins that circulate in body fluids (IgM and IgG) or enter the body through the mucosal surface of the respiratory or gastrointestinal tract (IgA). Persons with primary B-cell immunodeficiency are particularly prone to infections due to encapsulated organisms.
- Disorders of T-cell function impair the ability to orchestrate the immune response ($CD4^+$ helper T cells) and to protect against fungal, protozoan, viral, and intracellular bacterial infections ($CD8^+$ cytotoxic T cells).
- Combined T-cell and B-cell immunodeficiency states affect all aspects of immune function. Severe combined immunodeficiency represents a life-threatening absence of immune function that requires bone marrow transplantation for survival.

antibodies that have been transferred from the maternal circulation during fetal life. IgA, IgM, IgD, and IgE do not normally cross the placenta (see Chapter 9). An infant's level of maternal IgG gradually declines during a period of approximately 6 months. Concomitant with the loss of maternal antibody, the infant's immature humoral immune system begins to function, and between the ages of 1 and 2 years, the child's antibody production reaches that of adult levels.

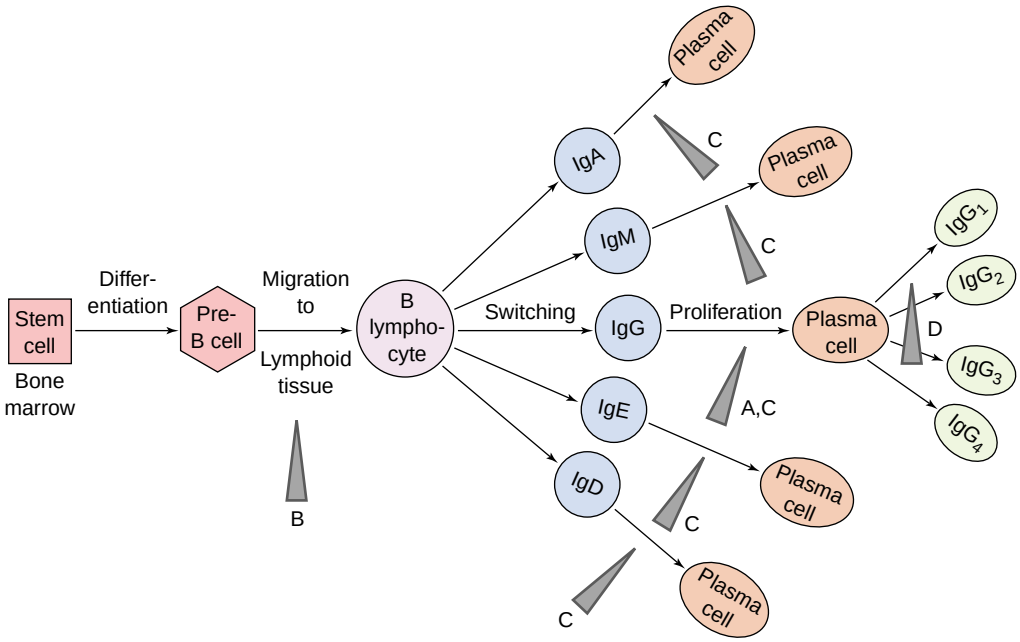
Any abnormality that blocks or prevents the maturation of B-lymphocyte stem cells can produce a state of immunodeficiency. For example, certain infants experience a delay in the maturation process of B cells that leads to a prolonged deficiency in IgG levels (IgM and IgA levels are normal) beyond 6 months of age. The total number and antigenic response of circulating B cells is normal, but the chemical communication between B and T cells that leads to clonal proliferation of antibody-producing plasma cells seems to be reduced.[16] This condition is referred to as *transient hypogammaglobulinemia of infancy*. The result of this condition usually is limited to repeated bouts of upper respiratory and middle ear infections. This condition usually resolves by the time the child is 2 to 4 years of age.

Primary B-cell immunodeficiencies are genetic disorders of B lymphocyte maturation. They account for 70% of primary immunodeficiencies and are manifested by decreased IgG production.[17] Antibody production depends on the differentiation of B-lymphocyte stem cells in the bone marrow to mature, immunoglobulin-producing plasma cells. This maturation cycle initially involves the production of surface IgM, migration from the marrow to the peripheral lymphoid tissue, and switching to the specialized production of IgG, IgA, IgD, IgE, or IgM antibodies after antigenic stimulation (Fig. 10-5).

Defects in B-cell function increase the risk of recurrent pyogenic infections, including those caused by *Streptococcus pneumoniae, Haemophilus influenzae,* and *Staphylococcus aureus,* and by gram-negative organisms such as *Pseudomonas* species. Humoral immunity usually is not as important in defending against intracellular bacteria (mycobacteria), fungi, and protozoa. Viruses usually are handled normally, except for the enteroviruses that cause gastrointestinal infections.

X-linked Agammaglobulinemia. *X-linked* or *Bruton's agammaglobulinemia* is a recessive trait that affects only males.[15–18] As the name implies, persons with this disorder have essentially undetectable levels of all serum immunoglobulins. Therefore, they are susceptible to meningitis and recurrent otitis media and to sinus and pulmonary infections with encapsulated organisms such as *S. pneumoniae, H. influenzae* type b, *S. aureus,* and *Neisseria meningitidis.*[15] Many boys with this disorder have severe tooth decay.

The central defect in this syndrome is a genetic mutation that blocks the differentiation of pre-B cells, creating an absence of mature circulating B cells and plasma cells. However, T lymphocytes are normal in number and function. Symptoms of the disorder usually coincide with the loss of maternal antibodies at about 6 months of age. A clue to the presence of the disorder is failure of an infection to respond completely and promptly to antibiotic therapy. Diagnosis is based on demonstration of low or absent serum immunoglobulins. Therapy consists of prophylaxis with intravenous immunoglobulin and prompt antimicrobial therapy for suspected infections. The prognosis of this condition depends on the prompt recognition and treatment of infections. Chronic pulmonary disease is an ever-present danger.



■ **FIGURE 10-5** ■ Stem cells to mature immunoglobulin-secreting plasma cells. *Arrows* indicate the stage of the maturation process that is interrupted in (**A**) transient hypoglobulinemia, (**B**) X-linked hypogammaglobulinemia, (**C**) common variable immunodeficiency, and (**D**) IgG subclass deficiency.

Common Variable Immunodeficiency. Another disorder of B-cell maturation, which is similar to X-linked agammaglobulinemia, is a condition called *common variable immunodeficiency.* In this syndrome, the terminal differentiation of mature B cells to plasma cells is blocked. The result is markedly reduced serum immunoglobulin levels, normal numbers of circulating B lymphocytes, and a complete absence of germinal centers and plasma cells in lymph nodes and the spleen.

The symptomatology of common variable immunodeficiency is similar to that of X-linked agammaglobulinemia (*i.e.*, recurrent otitis media and sinus and pulmonary infections with encapsulated organisms), but the onset of symptoms occurs much later, usually between the ages of 15 and 35 years, and distribution of disease between the sexes is equal. Persons with late-onset hypogammaglobulinemia also have an increased tendency toward development of chronic lung disease, autoimmune disorders, hepatitis, gastric carcinoma, and chronic diarrhea with associated intestinal malabsorption. Approximately one half of persons with the disorder have evidence of abnormal T-cell immunity, suggesting that this syndrome is a complex immunodeficiency. Treatment methods for late-onset hypogammaglobulinemia are similar to those used for X-linked hypogammaglobulinemia.

Selective Immunoglobulin A Deficiency. Selective IgA deficiency is the most common type of immunoglobulin deficiency, affecting 1 in 400 to 1 in 1000 persons.[15] The syndrome is characterized by moderate to marked reduction in levels of serum and secretory IgA. It is likely that the cause of this deficiency is a block in the pathway that promotes terminal differentiation of mature B cells to IgA-secreting plasma cells.

Approximately two thirds of persons with selective IgA deficiency have no overt symptoms, presumably because IgG and IgM levels are normal and compensate for the defect. At least 50% of affected children overcome the deficiency by the age of 14 years. Persons with markedly reduced levels of IgA often experience repeated upper respiratory and gastrointestinal infections and have increased incidence of allergies such as asthma and autoimmune disorders. It has been estimated that as many as 50% of persons with selective IgA deficiency have some form of allergy.[19] It has been suggested that the lack of IgA allows inhaled and ingested antigens to cross the mucosal epithelium and elicit antibody responses in the gastrointestinal and bronchial lymphoid tissues. Persons with IgA deficiency also can develop antibodies against IgA, which can lead to an anaphylactic response when blood components containing IgA are given.[18]

There is no treatment available for selective IgA deficiency unless there is a concomitant reduction in IgG levels. Administration of IgA is of little benefit because it has a short half-life and is not secreted across the mucosa. There also is the risk associated with IgA antibodies.

Immunoglobulin G Subclass Deficiency. An IgG subclass deficiency can affect one or more of IgG subtypes, despite normal levels or elevated serum concentrations of IgG. As discussed in Chapter 9, IgG immunoglobulins can be divided into four subclasses (IgG1 through IgG4) based on structure and function. Most circulating IgG belongs to the IgG1 (70%) and IgG2 (20%) subclasses. In general, antibodies directed against protein antigens belong to the IgG1 and IgG3 subclasses, and antibodies directed against carbohydrate and polysaccharide antigens are primarily IgG2 subclass. As a result, persons who are deficient in IgG2 subclass antibodies can be at greater risk for development of sinusitis, otitis media, and pneumonia caused by polysaccharide-encapsulated microorganisms such as *S. pneumoniae, H. influenzae* type b, and *N. meningitidis.* Children with mild forms of the deficiency can be treated with prophylactic antibiotics to prevent repeated infections. Intravenous immune globulin can be given to children with severe manifestations of this deficiency. The use of polysaccharide vaccines conjugated to protein carriers can provide protection against some of these infections because protein conjugated to protein carriers stimulates an IgG1 response.

Cellular (T-Cell) Immunodeficiencies

There are few primary forms of T-cell immunodeficiency, probably because persons with defects in this branch of the immune response rarely survive beyond infancy or childhood. However, exceptions are being recognized as newer T-cell defects, such as X-linked immunodeficiency with hyper IgM and CD2, are being identified. Other primary T-cell immunodeficiency disorders result from defective expression of the T-cell receptor complex, defective cytokine production, and defects in T-cell activation.

Unlike the B-cell lineage, in which a well-defined series of differentiation steps ultimately leads to the production of immunoglobulins, mature T lymphocytes are composed of distinct subpopulations whose immunologic assignments are diverse. T cells can be functionally divided into helper and cytotoxic subtypes and a population of T cells that promote delayed hypersensitivity reactions. Collectively, T lymphocytes protect against fungal, protozoan, viral, and intracellular bacterial infections; control malignant cell proliferation; and are responsible for coordinating the overall immune response.

DiGeorge Syndrome. DiGeorge syndrome stems from a developmental defect that occurs during the time (*i.e.*, before the 12th week of gestation) when the thymus gland, parathyroid gland, and parts of the head, neck, and heart are developing. The disorder affects both sexes. Formerly thought to be caused by a variety of factors, including extrinsic teratogens, this defect has been traced to a gene on chromosome 22 (22q11).[18–20]

Infants born with this defect have partial or complete failure of development of the thymus and parathyroid glands and have congenital defects of the head, neck, and heart. The extent of immune and parathyroid abnormalities is highly variable, as are the other defects. Occasionally, a child has no heart defect. In some children, the thymus is not absent but is in an abnormal location and is extremely small. These infants can have partial DiGeorge syndrome, in which hypertrophy of the thymus occurs with development of normal immune function. The facial disorders can include hypertelorism (*i.e.*, increased distance between the eyes); micrognathia (*i.e.*, fish mouth); low-set, posteriorly angulated ears; split uvula; and high-arched palate. Urinary tract abnormalities also are common. The most common presenting sign is hypocalcemia and tetany that develops during the first 24 hours of life. It is caused by the absence of the parathyroid gland and is resistant to standard therapy.

Children who survive the immediate neonatal period may have recurrent or chronic infections because of impaired T-cell immunity. Children also may have an absence of immunoglobulin production, caused by a lack of helper T-cell function. For children who do require treatment, thymus transplantation can be performed to reconstitute T-cell immunity. Bone marrow transplantation also has been successfully used to restore normal T-cell populations. If blood transfusions are needed, as during corrective heart surgery, special processing is required to prevent graft-versus-host disease.

X-Linked Immunodeficiency With Hyper-IgM. The X-linked immunodeficiency of hyper-IgM, also known as the *hyper-IgM syndrome*, is characterized by low IgG and IgA levels with normal or, more frequently, high IgM concentrations. Being X-linked, the disorder is confined to males. Formerly classified as a B-cell defect, it now has been traced to a T-cell defect. The disorder results from the inability of T cells to signal B cells to undergo isotype switching to IgG and IgA; thus, they produce only IgM.[18]

Like boys with X-linked agammaglobulinemia, affected boys become symptomatic during the first and second years of life. They have recurrent pyogenic infections, including otitis media, sinusitis, tonsillitis, and pneumonia. They are also more susceptible to *Pneumocystis carinii* infection. Thymic-dependent lymphoid tissues and T-cell function usually are normal, as are B-cell counts. Hemolytic anemia and thrombocytopenia may occur, and transient, persistent, or cyclic neutropenia is a common feature. The occurrence of concomitant autoimmune disorders is higher than with other immunoglobulin deficiency disorders.[18]

Combined T-Cell and B-Cell Immunodeficiencies

Disorders of the immune response that have elements of T-cell and B-cell dysfunction fall under the broad classification of combined immunodeficiency syndrome (CIDS) and include a spectrum of inherited (autosomal recessive and X-linked) conditions. A single mutation in any one of the many genes that influence lymphocyte development or response, including lymphocyte receptors, cytokines, or major histocompatibility antigens, could lead to combined immunodeficiency. Regardless of the affected gene, the net result is a disruption in the normal communication system of T and B lymphocytes and deregulation of the immune response. The spectrum of disease resulting from CIDS ranges from mild to severe to ultimately fatal forms.

Severe Combined Immunodeficiency. The most severe form of T- and B-cell deficiency often is referred to as *severe combined immunodeficiency syndrome* (SCIDS). SCIDS is caused by diverse genetic mutations that lead to absence of all immune function.[18,19] A family history of similarly affected relatives occurs in approximately 50% of cases.[19] Both autosomal recessive and X-linked inheritance are involved. Infants with SCIDS have a disease course that resembles acquired immunodeficiency syndrome (AIDS), with failure to thrive, chronic diarrhea, and opportunistic infections that usually lead to death by the age of 2 years. If recognized at birth or within the first 3 months of life, 95% of infants can be successfully treated with human leukocyte antigen (HLA)-identical or T-cell–depleted bone marrow stem cell transplantation.[18]

Approximately 50% of persons with the autosomal recessive form of SCIDS have an associated deficiency in the enzyme adenosine deaminase (ADA).[16] Absence of this enzyme leads to accumulation of toxic metabolites that kill dividing and resting T cells. Bone marrow and stem cell transplantation has been successful in treating children with ADA-negative SCIDS.[18,21] Enzyme replacement therapy also may be used in the care of persons with this form of SCIDS.[21]

Acquired Immunodeficiency Syndrome

AIDS is an infectious disease of the immune system caused by the HIV retrovirus. First described in June 1981, the disease is prevalent worldwide and is one of the leading causes of death among young adults in the United States. At the end of 2000, nearly 36.1 million people worldwide were living with HIV/AIDS, 22 million had died of the infection, and 5.3 million people had become newly infected during the year.[22] Most of the new infections are in people younger than 25 years who live in developing countries. Sub-Saharan Africa has been hardest hit by HIV, with close to 70% of the world's infections, although it is home to only 10% of the world's population.[22]

The virus responsible for most HIV infection worldwide is called *HIV type 1*. A second type of human immunodeficiency, *HIV type 2* (HIV-2) is endemic in many countries in West Africa but generally much more rare in other parts of the world.[23] HIV-2 appears to be transmitted in the same manner as HIV-1. HIV-2 can also cause immunodeficiency evidenced by a reduction in the number of $CD4^+$ T cells and the development of AIDS. Although the spectrum of disease for HIV-2 is similar to that of HIV-1, it spreads more slowly and causes disease more slowly than HIV-1.[23] Long-term consequences of HIV-2 will depend on its spread in the population.

KEY CONCEPTS

ACQUIRED IMMUNODEFICIENCY SYNDROME

- AIDS is a secondary immunodeficiency disorder that results from HIV infection, which is transmitted from one person to another through blood, semen, or vaginal fluids.
- The main effect of HIV infection is the destruction of $CD4^+$ T cells, which constitutes an attack on the entire immune system, because this subset of T cells exerts critical regulatory and effector functions involving both cellular and humoral immunity.
- The three phases of HIV are primary HIV, latency, and overt AIDS. The classification of HIV/AIDS is based on laboratory counts of $CD4^+$ T cells and the manifestations of the immunodeficiency state (development of opportunistic infections, neoplasms, and other related problems).

Transmission of HIV Infection

Human immunodeficiency virus is transmitted from one person to another through sexual contact, blood, or perinatally. Transmission can occur when infected blood, semen, or vaginal secretions from one person are deposited onto a mucous membrane or into the bloodstream of another person.

HIV is transmitted most frequently via sexual contact. Worldwide, 75% to 85% of HIV infections are transmitted through unprotected sex.[24] HIV is present in semen and vaginal fluids. There is risk of transmitting HIV when these fluids come in contact with a part of the body that lets them enter the bloodstream. This can include the vaginal mucosa, anal mucosa, and wounds or a sore on the skin.[24] Contact with semen occurs during vaginal and anal sexual intercourse, oral sex (*i.e.*, fellatio), and donor insemination. Exposure to vaginal or cervical secretions occurs during vaginal intercourse and oral sex (*i.e.*, cunnilingus). Condoms are highly effective in preventing transmission of HIV. Evidence increasingly shows that people with other sexually transmitted diseases (STDs) are at increased risk for HIV infection. The risk of HIV transmission is further increased in the presence of STDs with genital ulcerations (*i.e.*, syphilis, herpes simplex virus infection, and chancroid) as well as nonulcerative STDs (*i.e.*, gonorrhea, chlamydial infection, and trichomoniasis).

Because HIV is found in blood, the use of needles, syringes, and other drug injection paraphernalia is a direct route for transmission. HIV-infected injecting drug users can pass the virus to their needle-sharing and sex partners and, in the case of pregnant women, to their offspring. Although alcohol, cocaine, and other noninjected drugs do not directly transmit infection, their use alters perception of risk and reduces inhibitions about engaging in behaviors that pose a high risk of transmitting HIV infection.

Transfusions of whole blood, plasma, platelets, or blood cells before 1985 resulted in the transmission of HIV. Since 1985, all blood donations in the United States have been screened for HIV so the risk of transmission has virtually been eliminated. The clotting factor used by persons with hemophilia is derived from the pooled plasma of hundreds of donors. Before HIV testing of plasma donors was implemented in 1985, the virus was transmitted to persons with hemophilia through infusions of these clotting factors.

HIV may be transmitted from infected women to their offspring in utero, during labor and delivery, or through breastfeeding. Transmission from mother to infant is the most common way that children become infected with HIV. Ninety percent of infected children acquired the virus from their mother. The risk of transmission of HIV from mother to infant is approximately 25%, with estimates ranging from 15% to 45%, depending on the country in which they reside.[25]

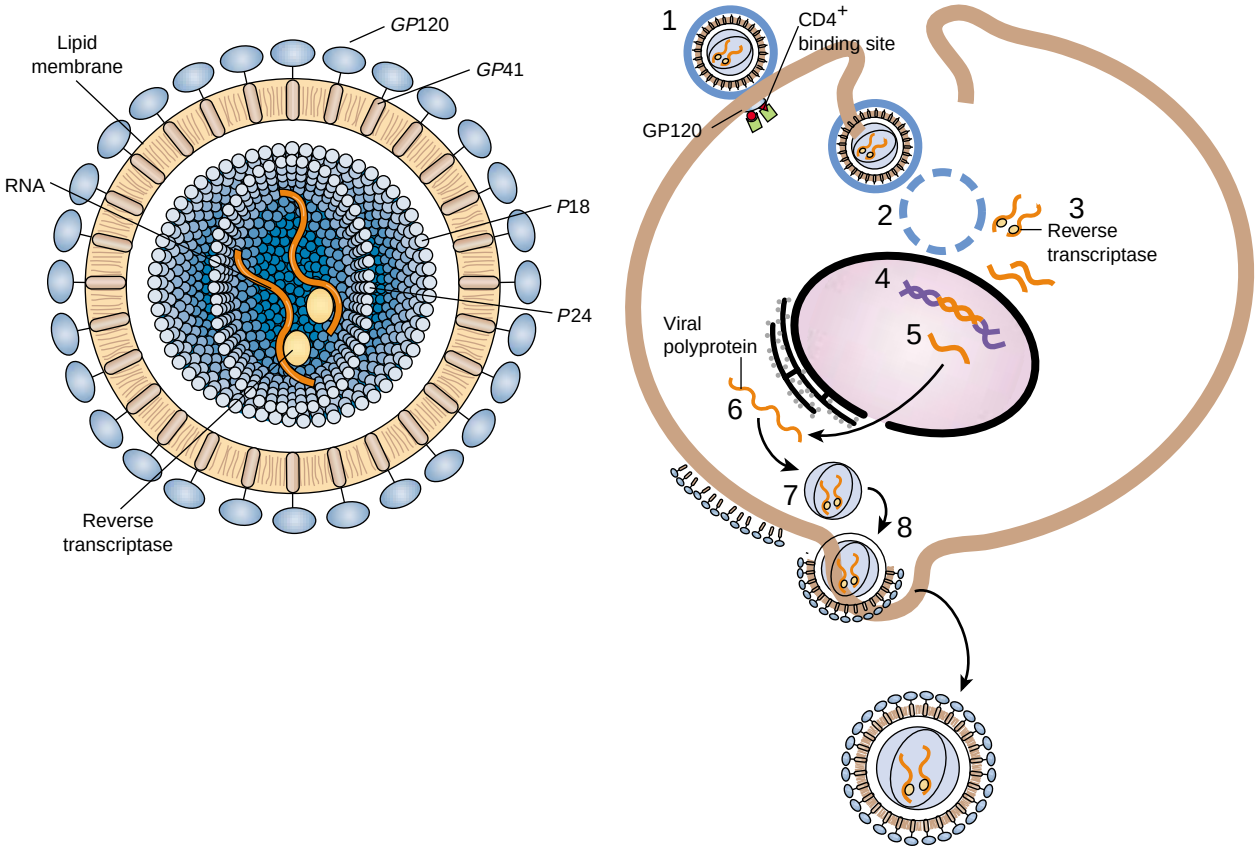
Occupational HIV infection among health care workers is uncommon.[26] Universal Blood and Body Fluid Precautions should be used in encounters with all patients in the health care setting because HIV status is not always known. The occupational risk of infection for health care workers most often is associated with percutaneous inoculation (*i.e.*, needle stick) of blood from a patient with HIV.

The HIV-infected person can transmit the virus even when no symptoms are present and the antibody test is negative. The point at which an infected person converts from being negative for the presence of HIV antibodies in the blood to being positive is called *seroconversion.* Seroconversion typically occurs within 1 to 3 months after exposure to HIV but can take up to 6 months.[27] The time after infection and before seroconversion is known as the *window period.* During the window period, an HIV-infected person could transmit the virus through the blood. Blood collection centers have implemented more stringent processes to avoid HIV transmission from a donor who has not seroconverted. Potential donors are now screened through interviews designed to identify risk behaviors for HIV infection, and blood is tested for the HIV antibody as well as viral nucleic acid.

Pathophysiology of AIDS

HIV belongs to a class of viruses called retroviruses, which carry their genetic information in ribonucleic acid (RNA), rather than deoxyribonucleic acid (DNA). HIV infects a limited number of cell types in the body, including a subset of lymphocytes called *CD4*$^+$ T helper cells and macrophages. The CD4$^+$ T cells are necessary for normal immune function (see Chapter 8). Among other functions, the CD4$^+$ T cell recognizes foreign antigens and infected cells and helps activate antibody-producing B lymphocytes. The CD4$^+$ T cells also orchestrate cell-mediated immunity, in which cytotoxic CD8$^+$ T cells and natural killer cells directly destroy viral infected cells and foreign antigens. Phagocytic monocytes and macrophages are also activated by CD4$^+$ T cells.

Viral Replication. Replication of HIV has been divided into eight steps (Fig. 10-6). Each of these steps provides insights into the development of methods for preventing and treating HIV infection. The *first step* involves the binding of the virus to the CD4$^+$ T cell. Once the HIV has entered the bloodstream, it attaches to the surface of a CD4$^+$ T cell by binding to the CD4 molecule and a chemokine coreceptor.[2] This is known as *attachment.* The *second step* allows for the internalization of the virus. Binding to the coreceptor allows the virus to be internalized into the cell, where it releases its coat along with two single strands of viral RNA that carry the instructions for producing more HIV. This is called *uncoating.* The *third step* consists of DNA synthesis. In order for the HIV to reproduce, it must change its RNA into DNA. It does this by using an enzyme called *reverse transcriptase.* Reverse transcriptase makes a copy of the viral RNA, and then in reverse order makes another mirror image copy. The result is double-stranded DNA. The *fourth step* is called *integration.* It involves the entry of the double stranded viral DNA into the nucleus of the CD4$^+$ T cell and, with the help of the enzyme *integrase,* insertion of the HIV DNA into the cell's original DNA. The *fifth step* involves transcription of the double stranded viral DNA to form a single stranded messenger RNA (mRNA) with the instructions for building new viruses. Transcription involves activation of the T cell and induction of host cell transcription factors. The *sixth step* includes the translation of mRNA. During *translation,* the ribosomal RNA (rRNA) uses the instructions in viral mRNA to create a chain of proteins and enzymes called a *polyprotein.* These polyproteins are the components for the new viruses that are formed. The *seventh step* is called cleavage. During the cleavage stage, *protease,* one of the enzymes in the polypeptide chain, cuts the chain into individual proteins, which will make up the



■ **FIGURE 10-6** ■ Life cycle of the HIV-1: (**1**) Attachment of the HIV virus to $CD4^+$ receptor; (**2**) internalization and uncoating of the virus with viral RNA and reverse transcriptase; (**3**) reverse transcription, which produces a mirror image of the viral RNA and double-stranded DNA molecule; (**4**) integration of viral DNA into host DNA using the integrase enzyme; (**5**) transcription of the inserted viral DNA to produce viral messenger RNA; (**6**) translation of viral messenger RNA to create viral polyprotein; (**7**) cleavage of viral polyprotein into individual viral proteins that make up the new virus; and (**8**) assembly and release of the new virus from the host cell.

new HIV viruses. Finally, during the *eighth step*, the proteins and the new RNA are assembled into new HIV viruses and released from the cell.

Viral Latency and Activation. In some $CD4^+$ T cells, the infection enters a latent phase that serves as a reservoir from which the virus can continue to be released for several years. In other $CD4^+$ T cells, the virus replicates, killing the cell and releasing copies of HIV into the bloodstream. These viral particles, or *virions*, invade other $CD4^+$ T cells, allowing the infection to progress. Initially, the infected cells are replaced and the viral particles destroyed. However, with time the $CD4^+$ T-cell count gradually decreases and the viral count detected in the blood increases. The initiation of viral replication in latent HIV infection is critically dependent on host proteins and transcription factors that are present during T-cell activation. These factors may be activated by proteins produced by other viruses known to affect persons with AIDS, such as herpes viruses, Epstein-Barr virus, adenovirus, and cytomegalovirus.[2] Thus, activation of the immune system by a variety of infectious agents may promote HIV replication.

Until the $CD4^+$ T-cell count falls to a very low level, infected persons can remain symptom free, although there is active viral replication, and serologic tests can identify antibodies to HIV. Unfortunately, these antibodies do not convey protection against the virus. Although symptoms are not evident, the infection proceeds on a microbiologic level, including the invasion and selective destruction of $CD4^+$ T cells. The continual decline of $CD4^+$ T cells, which are pivotal cells in the immune response, strips the person with AIDS of protection against common organisms and cancerous cells.

Diagnosis and Classification

Diagnosis. The most accurate and inexpensive method for identifying HIV is the HIV antibody test. The first commercial assays for HIV were introduced in 1985 to screen donated blood. Since then, the use of antibody detection tests has been expanded to include evaluating persons at increased risk for HIV infection. The HIV antibody test procedure consists of screening with an *enzyme immunoassay* (*EIA*), also known as *enzyme-linked immunosorbent assay* (*ELISA*), followed by a confirmatory test, the *Western blot* assay, which is performed if the

EIA is positive.[28] The EIA is based on the reaction of antibodies to HIV in the blood sample with viral proteins in the test material. The Western blot is a more sensitive assay that looks for the presence of antibodies to specific viral antigens.

Polymerase chain reaction (PCR) is a technique for detecting HIV DNA. PCR detects the presence of the virus, rather than the antibody to the virus, which the EIA and Western blot tests detect.[17] PCR is useful in diagnosing HIV infection in infants born to infected mothers because these infants have their mothers' HIV antibody, regardless of whether the children are infected.

Classification. Effective January 1, 1993, the United States Centers for Disease Control implemented a new classification system for HIV infection identifying two categories: one based on laboratory tests and the other on clinical manifestations[29] (Fig. 10-7). The classification system defines three laboratory test categories that correspond to $CD4^+$ cell counts per microliter (µL) of blood: *category 1:* >500 cells/µL, *category 2:* 200 to 499 cells/µL, and *category 3:* <200 cells/µL.

The clinical manifestations are also divided into three categories. *Clinical category A* includes persons who have no symptoms or have persistent generalized lymphadenopathy or symptoms of primary HIV infection (*i.e.,* acute seroconversion illness). *Clinical category B* includes persons with symptoms of immune deficiency not serious enough to be AIDS defining. *Clinical category C* includes AIDS-defining illnesses that are listed in the AIDS surveillance case definition shown in Chart 10-2. Each HIV-infected person has a $CD4^+$ T-cell category and a clinical category. The combination of laboratory and clinical categorizations can guide clinical and therapeutic actions in the management of HIV infection. According to the 1993 case definition, persons in laboratory category 3 or clinical category C are considered to have AIDS.

Clinical Course

The typical course of HIV is defined by three phases, which usually occur during a period of 8 to 12 years. The three stages are the primary infection or the acute clinical syndrome, chronic asymptomatic phase or latency, and overt AIDS[30] (Fig. 10-8).

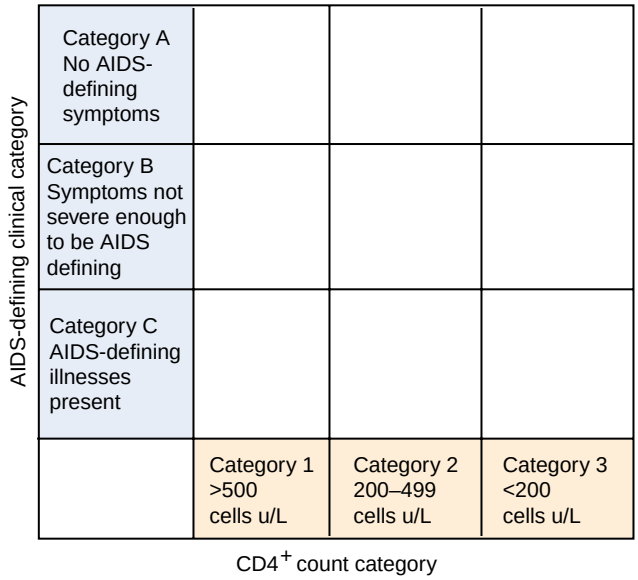
Many persons, when they are initially infected with HIV, have an acute mononucleosis-like syndrome known as primary infection. This acute phase may include fever, fatigue, myalgias, sore throat, night sweats, gastrointestinal problems, lymphadenopathy, maculopapular rash, and headache[30] (Chart 10-3). During this time, there is an increase in viral replication, which leads to very high viral loads, sometime greater than 1,000,000 copies/mL, and a decrease in the $CD4^+$ count. The signs and symptoms of primary HIV infection usually appear 2 to 4 weeks after exposure to HIV and last for a few days to 2 weeks.[30] After several weeks, the immune system acts to control viral replication and reduces it to a lower level, where it remains for several years.

The primary phase is followed by a latent period during which the person has no signs or symptoms of illness. The median time of the latent period is 10 years. During this time, the $CD4^+$ count falls gradually from the normal range (800 to 1000 cells/µL) to 200 cells/µL or lower.[30] Lymphadenopathy

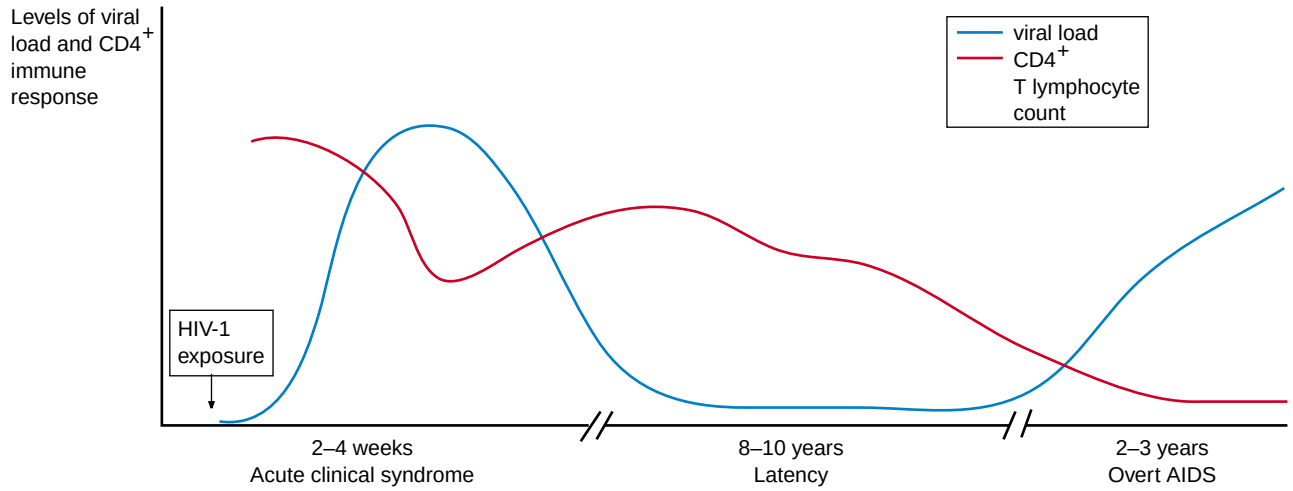
CHART 10-2 Conditions Included in the 1993 AIDS Surveillance Case Definition

Candidiasis of bronchi, trachea, or lungs
Candidiasis, esophageal
Cervical cancer, invasive*
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month's duration)
Cytomegalovirus disease (other than liver, spleen, or nodes)
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy, HIV-related
Herpes simplex: chronic ulcer(s) (>1 month's duration) or bronchitis, pneumonitis, or esophagitis
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month's duration)
Kaposi's sarcoma
Lymphoma, Burkitt's (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium-intracellulare complex or *M. kansasii,* disseminated or extrapulmonary
Mycobacterium tuberculosis, any site (pulmonary* or extrapulmonary)
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis carinii pneumonia
Pneumonia, recurrent*
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain
Wasting syndrome due to HIV

*Added to the 1993 expansion of the AIDS surveillance case definition.
(Centers for Disease Control and Prevention. [1992]. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *Morbidity and Mortality Weekly Report* 41 [RR-17], 19)



■ **FIGURE 10-7** ■ $CD4^+$ category and clinical category.



■ **FIGURE 10-8** ■ Viral load and CD4⁺ count during the phases of HIV.

develops in some persons with HIV infection during this phase. Persistent generalized lymphadenopathy usually is defined as lymph nodes that are chronically swollen for more than 3 months in at least two locations, not including the groin. The lymph nodes may be sore or visible externally.

The third phase, overt AIDS, occurs when a person has a CD4⁺ count of less than 200 cells/μL or an AIDS-defining illness. Without antiretroviral therapy, this phase leads to death within 2 to 3 years. The risk of death and opportunistic infection increases significantly when the CD4⁺ count reaches this level.[30]

The clinical course of HIV varies from person to person. Most (60% to 70%) of those infected with HIV acquire AIDS 10 to 11 years after infection. These people are the *typical progressors.*[30] Another 10% to 20% of those infected experience more rapid progression. They acquire AIDS in less than 5 years and are called *rapid progressors.*The final 5% to 15% are *slow progressors,* who do not experience progression to AIDS for more than 15 years. There is a subset of slow progressors, called *long-term nonprogressors,* who account for 1% of all HIV infections. These people have been infected for at least 8 years, are antiretroviral naive, have high CD4⁺ counts, and usually have very low viral loads.[30]

CHART 10-3 Signs and Symptoms of Acute HIV Infection

- Fever
- Fatigue
- Rash
- Headache
- Lymphadenopathy
- Pharyngitis
- Arthralgia
- Myalgia
- Night sweats
- Gastrointestinal problems
- Aseptic meningitis
- Oral or genital ulcers

Opportunistic Infections

When the immune system becomes severely compromised, an opportunistic infection or malignancy may occur. The number of CD4⁺ T cells directly correlates with the risk of developing opportunistic infections. The risk of opportunistic infections increases greatly once the CD4⁺ count drops to less than 200 cells/μL.[31] Opportunistic infections involve common organisms that normally do not produce infection unless there is impaired immune function. Although a person with AIDS may live for many years after the first serious illness, as the immune system fails, these opportunistic illnesses become progressively more severe and difficult to treat.

In the United States, the most common opportunistic infections are *Pneumocystis carinii* pneumonia (PCP), oropharyngeal or esophageal candidiasis (thrush), cytomegalovirus (CMV), and respiratory infections caused by *Mycobacterium avium-intracellulare complex* (MAC).[31]

Respiratory Infections. The most common causes of respiratory disease in persons with HIV infection are PCP and pulmonary tuberculosis (TB). Other organisms that cause opportunistic pulmonary infections in persons with AIDS include CMV, MAC, *Toxoplasma gondii,* and *Cryptococcus neoformans.* Pneumonia also may occur because of more common pulmonary pathogens, including *Streptococcus pneumoniae, Haemophilus influenzae,* and *Legionella pneumophila.* Some persons may be infected with multiple organisms. Kaposi's sarcoma (KS) also can occur in the lungs.

P. carinii pneumonia was the most common presenting manifestation of AIDS during the first decade of the epidemic. Since highly active antiretroviral therapy (HAART) and prophylaxis for PCP were instituted, the incidence has decreased.[32] PCP still is common in people who do not know their HIV status, those who choose not to treat their HIV, and in those with poor access to health care. The best predictor of PCP is a CD4⁺ T-cell count of less than 200 cells/μL, and it is at this point that prophylaxis with trimethoprim-sulfamethoxazole

is started. PCP is caused by *P. carinii*, an organism that is common in soil, houses, and many other places in the environment. Although *P. carinii* does not cause infection in persons with healthy immune systems, it can multiply quickly in the lungs of persons with AIDS and cause pneumonia. The symptoms of PCP may be acute or gradually progressive. The person may present with mild cough, fever, shortness of breath, and weight loss. Physical examination may demonstrate only fever and tachypnea, and breath sounds may be normal. As the disease progresses, the alveoli become filled with foamy protein-rich fluid, causing impairment of gas exchange (Fig. 10-9). Diagnosis of PCP is made on recognition of the organism in pulmonary secretions. This can be done through examination of induced sputum, bronchoalveolar lavage, occasionally bronchoscopy, and rarely, lung biopsy.

Tuberculosis is the leading cause of death for people with HIV worldwide. There are more than 80,000 people coinfected with HIV and TB in North America and another 5 million in the rest of the world.[33]

Although the lungs are the most common site of *M. tuberculosis* infection, extrapulmonary infections of the kidney, bone marrow, and other organs also occur in people with HIV. Whether a person has pulmonary or extrapulmonary TB, most patients present with fever, night sweats, cough, and weight loss.[33] Persons infected with *M. tuberculosis* (*i.e.*, those with positive tuberculin skin tests) are more likely to have reactivated TB develop if they become infected with HIV; if they are coinfected, they are more likely to have a rapidly progressive form of TB.[33] Equally important, HIV-infected persons with TB coinfection usually have an increase in viral load, which decreases the success of TB therapy. They also have an increased number of other opportunistic infections and an increased mortality rate.[33]

Since the late 1960s, most persons with TB have experienced good response to therapy. However, in 1991, there were outbreaks of multidrug-resistant (MDR) TB. Many cases of drug-resistant TB occur in HIV-infected persons.

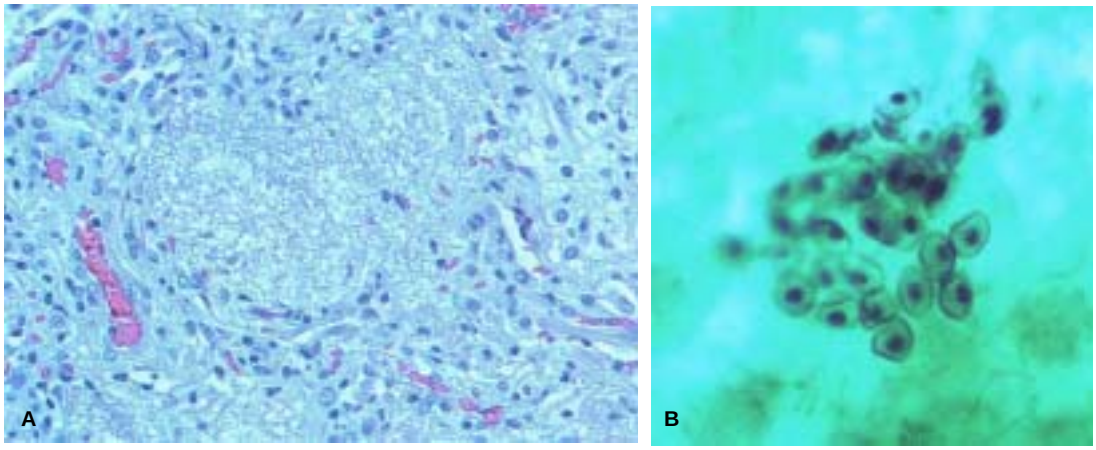
Gastrointestinal Infections. Infections of the gastrointestinal tract are some of the most common complications of HIV and AIDS. Esophageal candidiasis (thrush), CMV infection, and herpes simplex virus infection are common opportunistic infections that cause esophagitis in people with HIV. Persons experiencing these infections usually report painful swallowing or retrosternal pain. The clinical presentation can range from no symptoms to a complete inability to swallow and dehydration.

Diarrhea or gastroenteritis is common in persons with HIV. The most common protozoal infection that causes diarrhea is *Cryptosporidium parvum*. The clinical features of cryptosporidiosis can range from mild diarrhea to severe, watery diarrhea with a loss of as much as several liters of water per day. The most severe form usually occurs in persons with a $CD4^+$ count of less than 50 cells/μL, and also can include malabsorption, electrolyte disturbances, dehydration, and weight loss.[34] Other organisms that cause gastroenteritis and diarrhea are *Salmonella*, CMV, *Clostridium difficile*, *Escherichia coli*, *Shigella*, *Giardia*, and Microsporida.

Nervous System Manifestations. HIV infection, particularly in its late stages of severe immunocompromise, leaves the nervous system vulnerable to an array of neurologic disorders, including AIDS dementia complex (ADC), toxoplasmosis, and progressive multifocal leukoencephalopathy (PML). These disorders can affect the peripheral (PNS) or central nervous system (CNS) and contribute to the morbidity and mortality of persons with HIV.[35]

AIDS dementia complex is a syndrome of cognitive and motor dysfunction. ADC is caused by HIV itself, rather than an opportunistic infection, and usually is a late complication of HIV. The clinical features of ADC are impairment of attention and concentration, slowing of mental speed and agility, slowing of motor speed, and apathetic behavior. The diagnosis of ADC can be based on these clinical findings.

Toxoplasmosis is a common opportunistic infection in persons with AIDS. The organism responsible, *T. gondii*, is a parasite that most often affects the CNS. Toxoplasmosis usually is a reactivation of a latent *T. gondii* infection that has been dormant in the CNS.[36] The typical presentation includes fever, headaches, and neurologic dysfunction, including confusion



■ **FIGURE 10-9** ■ *Pneumocystis carinii* pneumonia. (**A**) The alveoli are filled with a foamy exudate, and the interstitium is thickened and contains a chronic inflammatory infiltrate. (**B**) A centrifuged bronchoalveolar lavage specimen impregnated with silver shows a cluster of *Pneumocystis carinii* cysts. (From Rubin E., Farber J.L. [1994]. *Pathology* [2nd ed.]. Philadelphia: J.B. Lippincott)

and lethargy, visual disturbances, and seizures. Computed tomography scans or magnetic resonance imaging (MRI) should be performed immediately to detect the presence of neurologic lesions. Prophylactic treatment with trimethoprim-sulfamethoxazole is effective against *T. gondii* when the $CD4^+$ T-cell count decreases to less than 200 cells/μL.

Progressive multifocal leukoencephalopathy is a demyelinating disease of the white matter of the brain caused by the JC virus, a DNA papovavirus that attacks the oligodendrocytes. PML advances slowly, and it can be weeks to months before the person seeks medical care.[37] It is characterized by progressive limb weakness, sensory loss, difficulty controlling the digits, visual disturbances, subtle alterations in mental status, hemiparesis, ataxia, diplopia, and seizures. Diagnosis is based on clinical findings and an MRI, and confirmed by the presence of the JC virus. The mortality rate is high, and the average survival time is 2 to 4 months.[37]

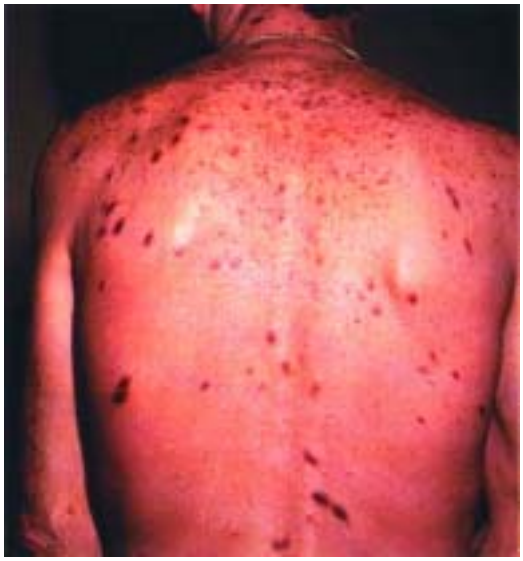
Cancers and Malignancies

Persons with AIDS have a high incidence of certain malignancies, especially Kaposi's sarcoma (KS), non-Hodgkin's lymphoma, and noninvasive cervical carcinoma. The increased incidence of malignancies probably is a function of impaired cell-mediated immunity. Non-Hodgkin's lymphoma develops in 3% to 4% of people with HIV infection (see Chapter 11). Women with HIV infection experience a higher incidence of *cervical dysplasia* than do women without HIV infection.[38] Cervical dysplasia, which usually results from infection with a human papillomavirus, is a slowly developing precursor to cervical carcinoma (see Chapter 34). In women with HIV infection this progression is much more rapid.[38]

Kaposi's Sarcoma. Kaposi's sarcoma is a malignancy of endothelial cells that line small blood vessels. An opportunistic cancer, KS occurs in immunosuppressed persons (e.g., transplant recipients or persons with AIDS). KS was one of the first opportunistic cancers associated with AIDS and still is the malignancy most frequently related to HIV.[39]

The lesions of KS can be found on the skin and in the oral cavity, gastrointestinal tract, and lungs. More than 50% of people with skin lesions also have gastrointestinal lesions. The disease usually begins as one or more macules, papules, or violet skin lesions that enlarge and become darker (Fig. 10-10). They may enlarge to form raised plaques or tumors. These irregularly shaped tumors can be from one eighth of an inch to silver dollar size. Tumor nodules frequently are located on the head, neck, and trunk. They usually are painless in the early stages, but discomfort may develop as the tumor ages. Invasion to the internal organs, including the lungs, gastrointestinal tract, and lymphatic system, commonly occurs. Gastrointestinal tract KS often is asymptomatic but can cause pain, bleeding, or obstruction. Pulmonary KS usually is a late development of the disease. Pulmonary KS causes dyspnea, cough, and hemoptysis. The progression of KS may be slow or rapid.

A presumptive diagnosis of KS usually is made based on visual identification of red or violet skin or oral lesions. Biopsy of at least one lesion must be done to establish the diagnosis and to distinguish the KS from other skin lesions that may resemble it. Effective HAART, local therapy with liquid nitrogen or vinblastine, chemotherapy, radiation, and interferon injections are the most common therapies. These therapies are largely palliative and are not a cure.



■ **FIGURE 10-10** ■ Disseminated Kaposi's sarcoma. Multiple red to brown papules distributed along the skin lines in a man with AIDS. (Hall J.C. [2000] *Sauer's manual of skin* [p.197]. Philadelphia: Lippincott Williams & Wilkins.)

There is recent evidence linking KS to a herpesvirus (herpesvirus 8, also called KS-associated herpesvirus [KSHV]).[40] More than 95% of KS lesions, regardless of the source or clinical subtype, have reportedly been found to be infected with KSHV. The virus is readily transmitted through homosexual and heterosexual activities. Maternal–infant transmission also occurs. The virus has been detected in saliva from infected persons, and other modes of transmission are suspected.

Wasting Syndrome

In 1997, wasting became an AIDS-defining illness. The syndrome is common in persons with HIV infection or AIDS. Wasting is characterized by involuntary weight loss of at least 10% of baseline body weight in the presence of diarrhea, more than two stools per day, or chronic weakness and a fever. This diagnosis is made when no other opportunistic infections or neoplasms can be identified as causing these symptoms. Factors that contribute to wasting are anorexia, metabolic abnormalities, endocrine dysfunction, malabsorption, and cytokine dysregulation. Treatment for wasting includes nutritional interventions such as oral supplements, or enteral or parenteral nutrition. There also are numerous pharmacologic agents used to treat wasting, including appetite stimulants, cannabinoids, and megestrol acetate.[41]

Metabolic Disorders

A wide range of metabolic disorders is associated with HIV infection, including lipodystrophy and mitochondrial disorders.

Lipodystrophy. A metabolic disorder called *lipodystrophy* is one of the newest group of problems for those infected with HIV. The symptoms of HIV-associated lipodystrophy fall into two categories: changes in body appearance and metabolic changes. The alterations in body appearance include an increase in abdominal girth, abnormal distribution of fat in the supraclavicular area (*i.e., buffalo hump*), wasting of fat from the face and

extremities, and breast enlargement in men and women. The metabolic changes include elevated serum cholesterol and triglyceride levels and insulin resistance. Originally attributed to the use of protease inhibitors, the pathogenesis of lipodystrophy still is not understood. It may be caused by protease inhibitor therapy or nucleoside reverse transcriptase inhibitor therapy, or may arise simply because people are living longer with HIV.

The diagnosis of lipodystrophy is based on appearance changes, elevated serum levels of triglycerides and cholesterol, and observed changes in body shape (measured changes in waist and hip girth).[42] The management of lipodystrophy is a matter of controversy because the etiology is unknown. Some authorities recommend switching to a nonprotease inhibitor-based HAART regimen. The problem with this approach is that, although serum levels of triglycerides and cholesterol decrease and there may be some resolution of the fat redistribution, the viral load often increases and becomes detectable.[43]

Mitochondrial Disorders. Mitochondrial disorders are metabolic disorders caused by antiretroviral therapy, in particular, the nucleoside reverse transcriptase inhibitors.[42] The mitochondria control many of the oxidative chemical reactions that release energy from glucose and other organic molecules. In the absence of normal mitochondrial function, cells revert to anaerobic metabolism with generation of lactic acid. Patients often present with nonspecific gastrointestinal symptoms, including nausea, vomiting, and abdominal pain. On examination, they can have hepatomegaly with normal liver function tests. The only laboratory abnormality may be lactic acidosis.[42] Mitochondrial dysfunction is the most feared complication of antiretroviral therapy. This fear is caused by the condition's unpredictability, its fatality in half the presenting patients, the nonspecific presenting symptoms, and the prevalence of elevated lactate levels in 8% to 22% of patients who have no symptoms.[42]

Treatment

There is no cure for AIDS. Although many companies are working on a vaccine to prevent HIV infection, none has been approved. There currently are three different types of HIV antiretroviral medications: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors.[44] Each type of agent attempts to interrupt viral replication at a different point.

Reverse transcriptase inhibitors inhibit HIV replication by acting on the enzyme reverse transcriptase. There are two types of HIV medications that work on this enzyme: nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors. *Nucleoside reverse transcriptase inhibitors* act by blocking the elongation of the DNA chain by stopping more nucleosides from being added. *Non-nucleoside reverse transcriptase inhibitors* work by binding to the reverse transcriptase enzyme so it cannot copy the virus's RNA into DNA. *Protease inhibitors* bind to the protease enzyme and inhibit its action. This inhibition prevents the cleavage of the polyprotein chain into individual proteins, which would be used to construct the new virus. Because the information inside the nucleus is not put together properly, the new viruses that are released into the body are immature and noninfectious.

The treatment of HIV is one of the most rapidly evolving fields in medicine. Optimal treatment of HIV includes a combination of drugs because different drugs act on different stages of the replication cycle. The goal of HAART, using a combination of antiviral drugs, is a sustained suppression of HIV replication, resulting in an undetectable viral load and an increasing $CD4^+$ count. In general, antiviral therapies are prescribed to improve the overall survival time of persons with HIV infection and to slow the progression to AIDS.

Drugs and vaccines commonly are used for the prevention and treatment of opportunistic infections and conditions, including PCP, toxoplasmosis, MAC, candidiasis, CMV infection, influenza, hepatitis B, and *S. pneumoniae* infections. Prophylactic medications are used once an individual's $CD4^+$ count has dropped below a certain level that indicates his or her immune system is no longer able to fight off the opportunistic infections.

Persons with HIV should be advised to avoid infections as much as possible and seek evaluation promptly when they occur. Immunization is important because persons infected with HIV are at risk for contracting many infectious diseases. Some of these diseases can be avoided by vaccination while the immune system's responsiveness is relatively intact.

Infection in Pregnancy and in Infants and Children

Early in the epidemic, children who contracted HIV could have become infected through blood products or perinatally. Now, almost all of the children who become infected with HIV at a young age in the United States get HIV perinatally. Infected women may transmit the virus to their offspring in utero, during labor and delivery, or through breast milk.[45] The risk of transmission is increased if the mother has advanced HIV disease as evidenced by low $CD4^+$ counts, high levels of HIV in the blood (high viral load); if the time from the rupture of membranes to delivery is prolonged; if there is increased exposure of the fetus to maternal blood; or if the mother breast-feeds the child.[25]

Diagnosis of HIV infection in children born to HIV-infected mothers is complicated by the presence of maternal HIV IgG antibody, which crosses the placenta to the fetus. Consequently, infants born to HIV-infected women can be HIV antibody positive by ELISA for as long as 18 months, even though they are not HIV infected.[25] PCR testing for HIV DNA is used most often to diagnose HIV in infants younger than 18 months. Two positive PCR tests for HIV DNA are needed to diagnose HIV in a child. Children born to mothers with HIV infection are considered uninfected if they become HIV antibody negative after 6 months of age, have no other laboratory evidence of HIV infection, and have not met the surveillance case definition criteria for AIDS in children.[25]

Perinatal transmission can be lowered by approximately two thirds by administering zidovudine to the mother during pregnancy and labor and delivery and to the infant when it is born.[45] Thus, the U.S. Public Health Service recommends that HIV counseling and testing should be offered to all pregnant women and women of childbearing age in the United States.[45] The recommendations also stress that women who test positive for HIV antibodies should be informed of the perinatal prevention benefits of zidovudine therapy and offered treatment that includes zidovudine alone, or HAART therapy. The benefits of voluntary testing for mothers and newborns include re-

duced morbidity because of intensive treatment and supportive health care, the opportunity for early antiviral therapy for mother and child, and information regarding the risk of transmission from breast milk.[45]

Because pregnant women in less developed countries do not always have access to zidovudine, studies are being conducted in Africa to determine if any other simple and less expensive antiretroviral regimen can be used to decrease the transmission from mother to infant.

Children have a very different pattern of HIV infection than do adults. Failure to thrive, CNS abnormalities, and developmental delays are the most prominent primary manifestations of HIV infection in children.[28] Children born infected with HIV usually weigh less and are shorter than noninfected infants. A major cause of early mortality for HIV-infected children is PCP. As opposed to adults, in whom PCP occurs in the late stages, children experience PCP early, with the peak age of onset at 3 to 6 months. For this reason, prophylaxis with trimethoprim-sulfamethoxazole is started by 4 to 6 weeks for all infants born to HIV-infected mothers, regardless of their $CD4^+$ count or infection status.[46]

In summary, an immunodeficiency is defined as an absolute or partial loss of the normal immune response, which places a person in a state of compromise and increases the risk for development of infections or malignant complications. Any components of the immune response, including antibody or humoral (B-cell) immunity or cellular or T-cell immunity, may contribute to immunodeficiencies. The variety of defects known to involve the immune response can be classified as primary (*i.e.,* endogenous or inherited) or secondary (*i.e.,* caused by exogenous factors such as drugs or infection).

Most primary immunodeficiency states are inherited and are either present at birth or become apparent shortly after birth. Primary immunodeficiencies can be categorized into three types: humoral (B-cell) immunodeficiencies, cellular (T-cell) immunodeficiencies, and combined (B-cell and T-cell) immunodeficiencies. B-cell immunodeficiencies can selectively affect a single type of immunoglobulin (*e.g.,* IgA immunodeficiency) or all of the immunoglobulins. Defects in B-cell function increase the risk of recurrent pyogenic infections, including those caused by *Streptococcus pneumoniae, Haemophilus influenzae,* and *Staphylococcus aureus,* and by gram-negative organisms such as *Pseudomonas* species. There are few primary forms of T-cell immunodeficiency, probably because persons with defects in this branch of the immune response rarely survive beyond infancy or childhood. Combined immunodeficiency disorders involve both B-cell and T-cell dysfunction and include a spectrum of inherited (autosomal recessive and X-linked) conditions. The spectrum of disease resulting from combined immunodeficiency ranges from mild to severe to ultimately fatal forms.

AIDS is the most common type of secondary immunodeficiency. AIDS is an infectious disease of the immune system caused by the retrovirus HIV. The disease is prevalent worldwide and is one of the leading causes of death among young adults in the United States. HIV is transmitted from one person to another through sexual contact, through blood exchange, or perinatally. HIV is a retrovirus that infects the body's $CD4^+$ T cells and macrophages. The destruction of $CD4^+$ T cells by HIV constitutes an attack on the entire immune system because this subset of lymphocytes exerts critical regulatory and effector functions that involve both humoral and cellular immunity.

Manifestations of infection, such as acute mononucleosis-like symptoms, may occur shortly after infection, and this is followed by a latent phase that may last for many years. The end of the latent period is characterized by the marked decrease in $CD4^+$ T cells and the development of opportunistic infections, cancers, and other disorders as the person moves toward an AIDS diagnosis. The complications of these infections, manifested throughout the respiratory, gastrointestinal, and nervous systems, include pneumonia, esophagitis, diarrhea, gastroenteritis, tumors, wasting syndrome, altered mental status, seizures, motor deficits, and metabolic disorders. There is no cure for AIDS. Treatment largely involves the use of drugs that interrupt the replication of the HIV virus and prevention or treatment of complications such as opportunistic infections.

Infected women may transmit the virus to their offspring in utero, during labor and delivery, or through breast milk. Diagnosis of HIV infection in children born to HIV-infected mothers is complicated by the presence of maternal HIV antibody, which crosses the placenta to the fetus. This antibody usually disappears within 18 months in uninfected children. The administration of zidovudine to the mother during pregnancy and labor and delivery and to the infant after birth can decrease perinatal transmission.

REVIEW QUESTIONS

- Describe the immune mechanisms involved in a type I, type II, type III, and type IV hypersensitivity reaction and use these mechanisms to describe the pathogenesis of allergic rhinitis, food allergy, serum sickness, contact dermatitis, and hypersensitivity pneumonitis.
- Compare the immune mechanisms involved in host-versus-graft and graft-versus-host transplant rejection.
- Relate the mechanisms of self-tolerance to the possible explanations for development of autoimmune disease.
- Describe three or more postulated mechanisms underlying autoimmune disease.
- Compare and contrast immunodeficiency disorders caused by B-cell, T-cell, and combined B- and T-cell disorders.
- Explain why the attack by the HIV virus on the $CD4^+$ cell is so devastating in terms of the function of the immune system.
- Explain why it is not possible to state with certainty that a person with a positive ELISA antibody test for HIV does in fact have the disease and needs to be retested using the Western blot test.
- Relate the altered immune function in persons with HIV infection and AIDS to the development of opportunistic infections.
- Discuss the vertical transmission of HIV from mother to child and explain why the HIV test might be positive even the infant does not have the virus.

connection

Visit the Connection site at connection.lww.com/go/porth for links to chapter-related resources on the Internet.

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