Hypersensitivity Reactions

14

I. OVERVIEW

Excessive or inappropriate immune responses sometimes lead to host tissue damage resulting from prolonged or repeated antigen exposure. These reactions, called hypersensitivity reactions, cause tissue injury by the release of chemical substances that attract and activate cells and molecules resulting in **inflammation**. These reactions are classified into four **hypersensitivity types** depending on the mechanism(s) that underlie the tissue damage (Table 14.1); the first three types involve antigen–antibody reactions, whereas the fourth is antibody-independent, involving cell-mediated immune responses only.

- **Type I** (also called **immediate hypersensitivity**) hypersensitivity reactions are rapid, occurring within minutes of exposure to an antigen, and always involve IgE-mediated degranulation of basophils or mast cells.
- **Type II** hypersensitivity reactions are initiated by the binding of antibody to a cell membrane or to the extracellular matrix.

Table 14.1
HYPERSENSITIVITY TYPES

Type	Synonyms	Disorders	Mediated By	Mechanism(s)
I	Atopy, anaphylactic hypersensitivity, allergy	Allergic reactions, anaphylaxis, asthma	IgE antibody, complement not involved	Cross-linking of FcRε-bound IgE antibodies on mast cells cause degranulation and release of vasoactive amines (e.g., histamine) resulting in smooth muscle contraction, vasoconstriction, and vasodilation of capillary endothelium.
II	Cytotoxic	*Erythroblastosis fetalis*, Goodpasture syndrome, autoimmune hemolytic anemia	IgM or IgG ± complement	IgM or IgG antibody binds to epitopes on cells or other tissue components promoting phagocytosis, antibody-dependent cell-mediated cytotoxicity, antibody-mediated function disruption (receptor blocking), or complement-mediated lysis.
III	Immune complex disease	Serum sickness, Arthus reaction, systemic lupus erythematosus	IgG ± complement	Antigen–antibody complexes in tissues or serum activate complement and attract neutrophils that release lytic molecules.
IV	Cell-mediated hypersensitivity	Contact dermatitis, tuberculosis, chronic graft rejection	Cell-mediated antibody-independent	Release of mediators by sensitized $CD4^+$ T cells provoke tissue destruction by mononuclear cells. $CD8^+$ T cells known as cytotoxic T lymphocytes (CTLs) may kill chemically modified host cells and cells that display disparate MHC molecules.

- **Type III** hypersensitivity reactions involve the interaction of antibodies with soluble molecules to make soluble antigen–antibody complexes that become deposited in tissues.
- **Type IV** hypersensitivity reactions are those in which cells of the immune system directly attack host cells in the absence of antibody. These reactions include contact dermatitis (CD, also called contact sensitivity, CS); delayed-type hypersensitivity (DTH); and, occasionally, cytotoxic T-lymphocyte (CTL) responses.

II. TYPE I HYPERSENSITIVITY

Commonly called **allergic** or **immediate hypersensitivity reactions**, type I responses occur within minutes to hours of antigen exposure. Some individuals develop IgE antibodies in response to relatively harmless environmental antigens or **allergens**. IgE molecules readily bind to Fc receptors (FcRε or CD23) on the surfaces of mast cells and basophils (Fig. 14.1). Unlike other FcRs, FcRεs bind antigen-free immunoglobulin (IgE), and the IgE-CD23 complexes function as antigen-specific cell-surface receptors. Cross-linking of surface-bound IgE molecules generates intracellular signals via CD23, leading to mast cell or basophil degranulation and the release of vasoactive amines (e.g., **histamine**) and other inflammatory mediators. Histamine and other inflammatory mediators cause vascular endothelial cell junctions to loosen (**vasodilation**) and increase vascular permeability, resulting in fluid accumulation in the tissues (**edema**). Histamine also induces smooth muscle contraction in arterial and arteriole walls (**vasoconstriction**) to accelerate fluid distribution from the central trunk of the body into peripheral tissues.

A. Localized reactions

Because mast cells accumulate in respiratory passages, intestinal walls, and the skin, type I reactions are often most pronounced in these tissues. Sites affected are typically those where the initiating antigen is most often encountered. Antigens that enter the body by inhalation localize primarily to the nasopharyngeal and bronchial tissues, where smooth muscle contraction and vasodilation increase mucous production and the constriction of respiratory passages (Fig. 14.2). In combination, these responses can produce the severe and potentially fatal disorder known as **asthma**. Allergens that contact other tissues may produce IgE-mediated inflammatory responses, causing rashes, redness, and edema—the classic "wheal and flare" appearance. Food or ingested allergens primarily affect the gastrointestinal tract.

CLINICAL APPLICATION
Asthma

Eighteen months ago, Jenny Q., a 31-year-old female, received a Persian cat (*Felis domesticus*) as a birthday present. Jenny became sensitized to the major cat allergen (the salivary protein Fel d1) and reported persistent symptoms of nasal congestion,

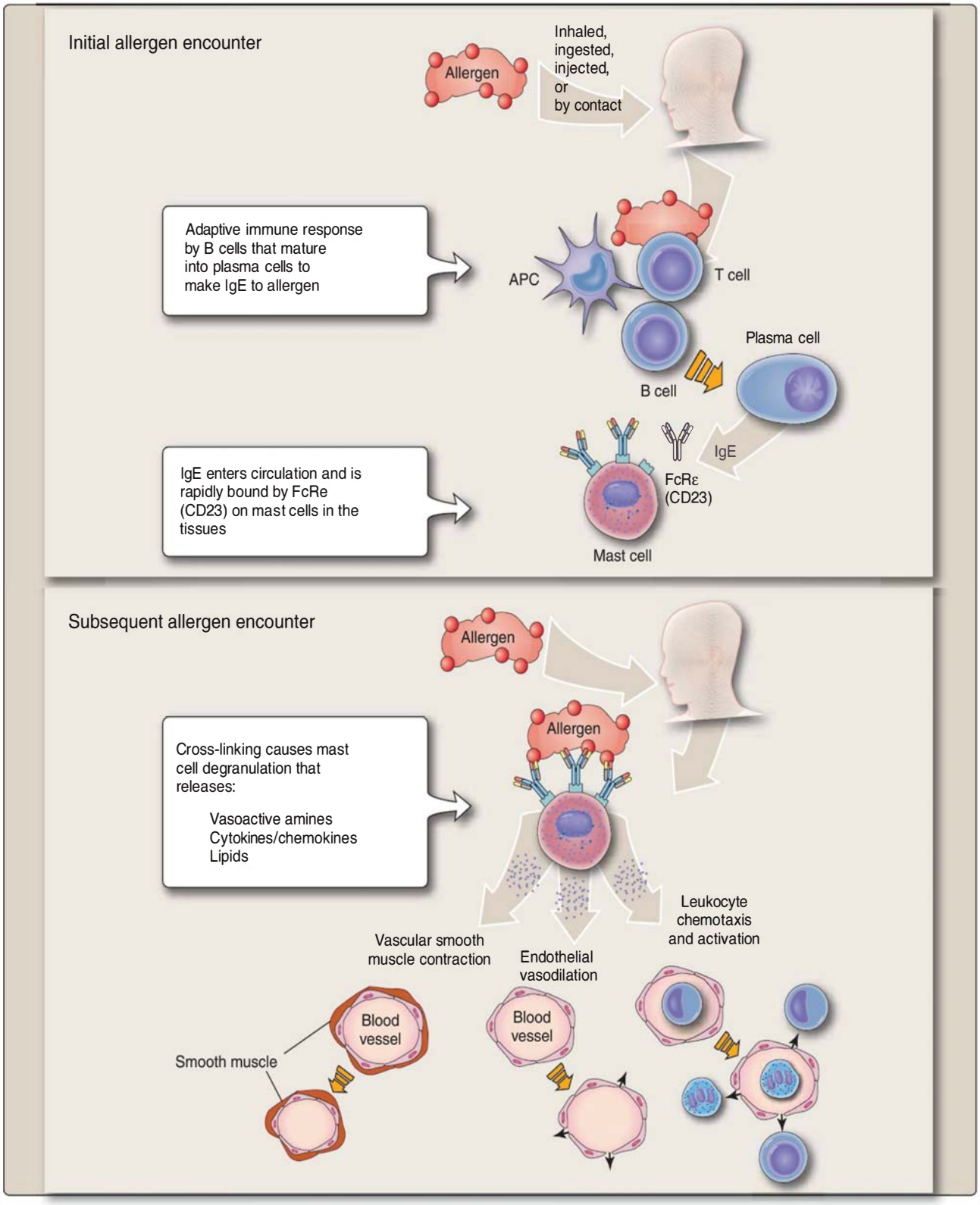

Figure 14.1

Type I reactions. These reactions result from the interaction of surface-bound IgE with antigen. Presentation of antigen (often referred to as allergen) to antigen-specific $CD4^+$ T cells allows them to provide signals to antigen-specific B cells that cause their maturation into IgE secreting plasma cells. IgE enters into the circulation, is rapidly bound by CD23 (FcRε) on tissue mast cells and basophils, and serves as antigen (allergen)-specific receptors on those cells. Subsequent encounter with multivalent (having multiple identical epitopes) allergen cross-links CD23 on mast cells and basophils inducing a signaling cascade, leading to degranulation. The released substances cause contraction of vascular (and other) smooth muscle, dilation of vascular endothelium (vasodilation), leukocyte chemotaxis, and activation.

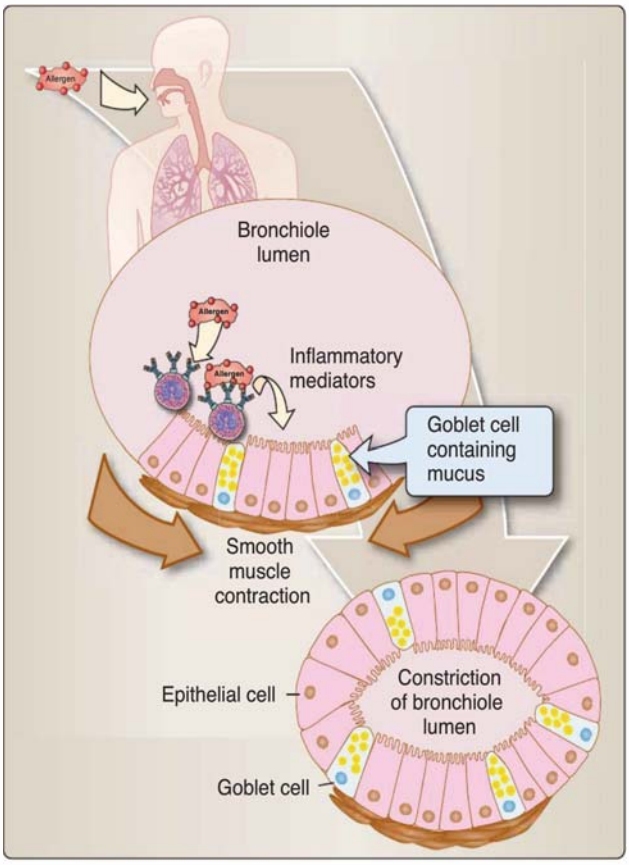

Figure 14.2
Asthma. Asthma is a reversible airway obstruction often caused by the release of inflammatory mediators from mast cells upon encounter with allergen. These inflammatory mediators cause the loosening of tight junctions in the bronchiole epithelium, increased capillary permeability, and spasmatic contraction of smooth muscle surrounding the bronchi. This temporarily decreases the size of the bronchial lumen, resulting in shortness of breath. Bronchospasms triggered by nonimmunologic stimuli such as cold, viral infections, and exercise, also stimulate the same airway inflammation.

rhinorrhea, sneezing, and nasal pruritus (itching). An oral antihistamine was prescribed, and she was advised to limit her exposure to the cat. These measures were effective in alleviating her symptoms for a time. After several months, Jenny presents to the emergency room with breathing difficulty, wheezing, and chest tightness. Physical examination reveals diffuse wheezing during both expiration and inspiration. Spirometry testing in the emergency room reveals reduced peak expiratory flow rate. Jenny mentions that the cat still lives with her and sleeps in her bedroom. Acute asthma associated with cat allergen exposure is diagnosed. This is an example of IgE-mediated Type I hypersensitivity. If the cat is removed from her house or if she limits her exposure to the cat by keeping it out of her bedroom and uses her medications, her prognosis is good.

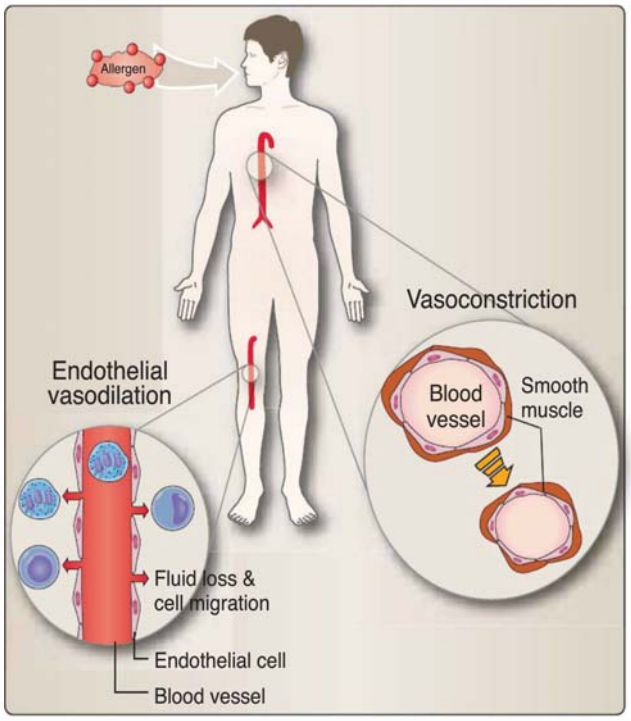

Figure 14.3
Anaphylaxis and shock. Exposure to allergen may cause the rapid release of vasoactive amines from mast cells and basophils as well as a flood of cytokines, resulting in the contraction of smooth muscle in the vasculature and vasodilation of capillary endothelium. Blood pressure decreases, resulting in vascular shock. In addition, the release of mediators increases the contraction of smooth muscles in the bronchi and bronchioles of the respiratory tract, making breathing difficult.

B. Systemic reactions

In some cases, such as injected allergens (e.g., venom or toxins), antigen may be disseminated by the bloodstream, resulting in systemic inflammation. In 1902, at the request and sponsorship of Albert I of Monaco, Charles Richet and Paul Portier investigated jellyfish nematocyst toxin that sometimes induced a life-threatening response. Their experiments were conducted on the Prince of Monaco's yacht (ah, the past glamour of science!). They found that initial injection of dogs with a small amount of toxin had little effect. However, when a second injection of the same amount of the toxin was administered several weeks later, the dogs suffered immediate shock and even death. Termed **anaphylaxis** ("against protection"), this clinical shock syndrome is characterized by vascular smooth muscle constriction (**vasoconstriction**) combined with gap formation between adjacent capillary endothelial cells (**vasodilation**) that results in severe fluid loss and leads to **shock**. This kind of response can also occur in humans when an allergen, to which the individual is highly sensitive, enters the body (Fig. 14.3).

III. TYPE II HYPERSENSITIVITY

Type II hypersensitivity reactions are initiated by the interaction of antibody (IgM or IgG, not IgE) with cell membranes or with the extracellular matrix. Complement may also be involved. The antigens that are recognized may

CLINICAL APPLICATION
Anaphylaxis

Andrew V., an 8-year-old boy, with a history of allergy to walnuts, developed diffuse hives and difficulty breathing after eating a brownie at a school party. The teacher was aware of Andrew's history of walnut allergy and immediately checked the ingredients listed on the brownie package. She noted that the label stated "may contain peanuts and tree nuts." She immediately rushed Andrew to the school nurse's office where the nurse immediately administered a dose of epinephrine using an EpiPen® (Mylan, Inc., Napa, California) and a dose of oral antihistamine. The nurse also called for emergency help to transfer Andrew to the nearest medical facility for further follow-up and therapy.

Andrew's conditions are consistent with anaphylaxis, which is potentially life threatening. Symptoms of anaphylaxis may involve many organ systems including skin, respiratory, gastrointestinal, and cardiovascular. Cardiac arrest can occur. Patients with severe food allergies are educated in avoidance and should carry EpiPen® for immediate treatment in case of inadvertent exposure to the allergen.

be intrinsic to the cell membrane or extracellular matrix, or they may be exogenous molecules, such as a drug metabolite adsorbed onto the cell membrane or extracellular matrix.

A. Interaction of antibody with cells

Cell-surface or extracellular matrix epitope binding by antibodies (usually IgM or IgG) results in a conformational change in the Fc portion of the antibody molecule (Fig. 14.4). The conformational change in the Fc portion of the antibody molecule is recognized by cellular FcRs and by complement; and several immune-mediated destructive mechanisms may then come into play, targeted on the site(s) of antibody binding.

1. **Antibody-dependent cell-mediated cytotoxicity (ADCC):** This is complement independent but requires the cooperation of leukocytes (Fig. 14.5). FcR-bearing cells (e.g., monocytes, neutrophils, eosinophils, and natural killer [NK] cells) bind to cells that have IgG or IgM antibodies bound to surface epitopes on a cell.

2. **Complement:** Complement activated by IgM and IgG antibodies generates active components of the classical pathway, namely, C3b and C4b (discussed previously in Chapter 5). These components are then deposited on the surfaces of antibody-coated cells or extracellular matrix to function as **opsonins**. Phagocytes recognize bound antibody through their FcRs and bound complement components through their complement receptors. In this manner, both complement and antibody function as opsonins to increase phagocytosis and the destruction of microorganisms (Fig. 14.6).

3. **Blood group antibodies:** These exemplify type II hypersensitivity reactions. Hemolytic anemias may result from the binding of IgM

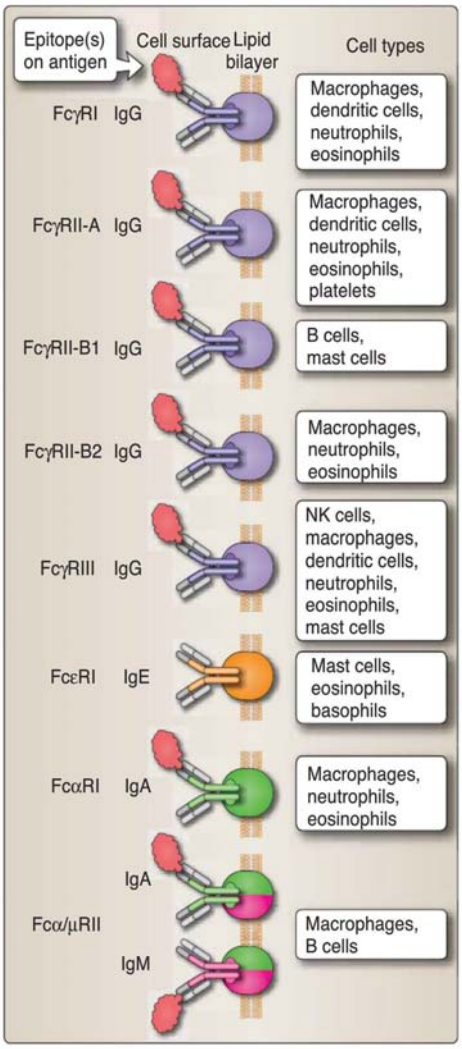

Figure 14.4
Fc receptors. Receptors for Fc portion of immunoglobulin are expressed by various cell types. With the exception of FcRε (CD23), FcRs bind only antigen-bound antibody. IgE readily binds to FcRε (CD23) in the absence of antigen.

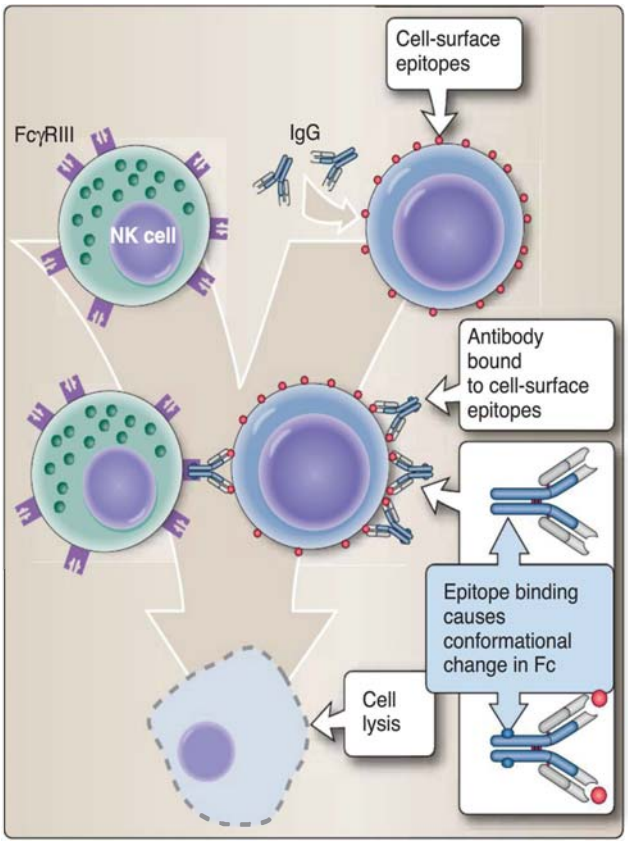

Figure 14.5
Antibody-dependent cell-mediated cytotoxicity. Specific binding of immunoglobulin to cell surface epitopes causes a conformation change in the Fc portion of the antibody molecule. FcγRIII, expressed by natural killer (NK) cells, recognize and bind the altered antibody, causing the NK cell to release perforin granules that cause lysis of the antibody-coated cell.

antibodies to carbohydrate structures on erythrocytes (notably anti-A or anti-B antibodies) resulting in their phagocytosis and in the presence of complement, their rapid lysis (hemolysis) (Fig. 14.7). Antibodies (IgG) to certain protein molecules on erythrocytes (e.g., Rh factor[s]) do not activate complement; erythrocytes are destroyed by phagocytosis (Fig. 14.7).

B. Interaction of antibody with the extracellular matrix

Antibodies that bind to extracellular matrix proteins (e.g., basement membrane) may activate the classical pathway of complement, generating anaphylotoxins (e.g., C5a, C4a, C3a, in descending order of potency, not in order of appearance) that recruit neutrophils and monocytes. FcR engagement with the bound antibody results in the release of reactive oxygen intermediates, resulting in inflammation and tissue injury (Fig. 14.8).

C. Antibody-mediated disruption of cellular function

Sometimes antibodies bind to cell surface receptors without activating complement or binding to FcRs. This binding blocks the receptor's ability to interact with its natural ligand (Fig. 14.9). The antibody-receptor interaction may be stimulatory (e.g., Graves disease) or inhibitory (e.g., myasthenia gravis) to the receptor's signaling pathway(s).

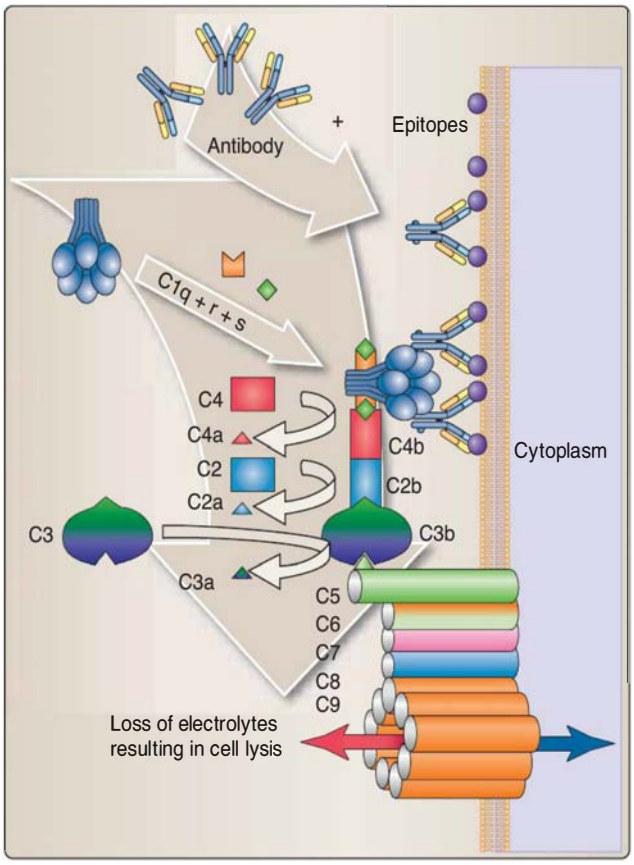

Figure 14.6
Type II hypersensitivity reactions. These reactions may involve complement-mediated lysis. Antibodies that invoke the classical and terminal or lytic pathways of complement activation recognize epitopes on cell membranes and cause formation of the membrane attack complex, transmembrane pore formation, and loss of electrolyte balance, causing lysis.

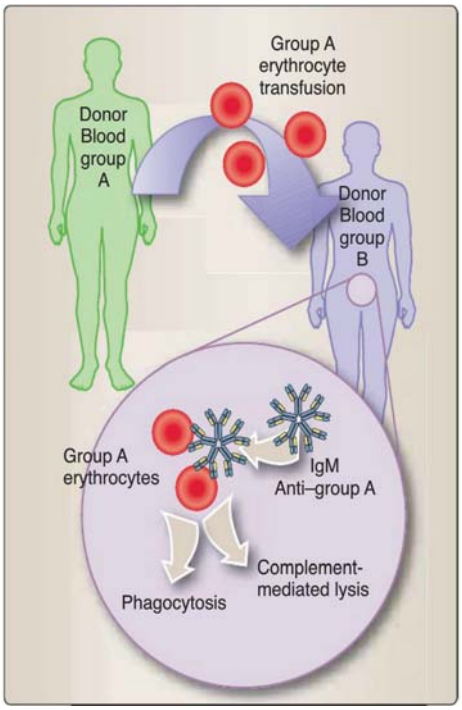

Figure 14.7
"Natural" antibodies against blood group AB antigens. These naturally occurring IgM antibodies bind to erythrocyte membranes, rendering them susceptible to phagocytosis or complement-mediated lysis.

IV. TYPE III HYPERSENSITIVITY

Circulating antigen–antibody complexes may lead to inflammation at their sites of deposition, often resulting in blood vessel inflammation (**vasculitis**). Immune complexes may cause injury resulting from the interaction with exogenous (e.g., microbes, viruses, or chemically modified self-proteins) or endogenous antigens (e.g., serum proteins). Type III reactions may occur locally or systemically.

A. Localized reactions

Localized type III hypersensitivities, also known as **Arthus reactions**, result from acute immune complex vasculitis causing tissue necrosis. These reactions are elicited 4 to 6 hours after the intradermal introduction of a small amount of antigen. Antibody diffuses from the vasculature to form large immune precipitates that activate complement to induce a painful localized edematous inflammatory lesion (Fig. 14.10). Lesions range from necrotizing vasculitis with polymorphonuclear cell infiltration to the formation of a sterile abscess.

B. Systemic reactions

Systemic immune complex disease, in some cases termed **serum sickness**, occurs with the wide dissemination of antigen–antibody

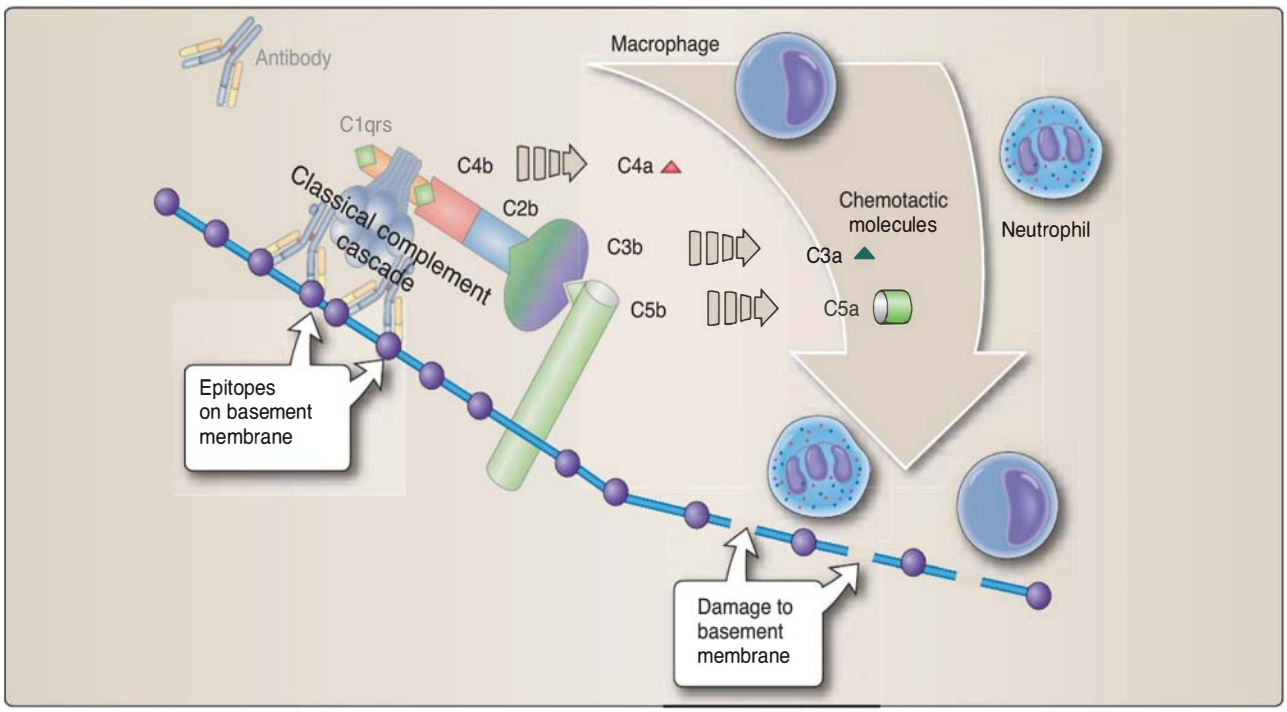

Figure 14.8
Antibodies against matrix proteins. Autoreactive IgG (autoimmune; see Chapter 16) antibodies may react with epitopes on extracellular matrix, such as the basement membrane, and trigger the classical pathway of complement. Sequential activation of complement components C4, C3, and C5 result in the release of C5a, C3a, and C4a (in descending order of potency) activate phagocytes (such as neutrophils and monocytes) to damage the basement membrane.

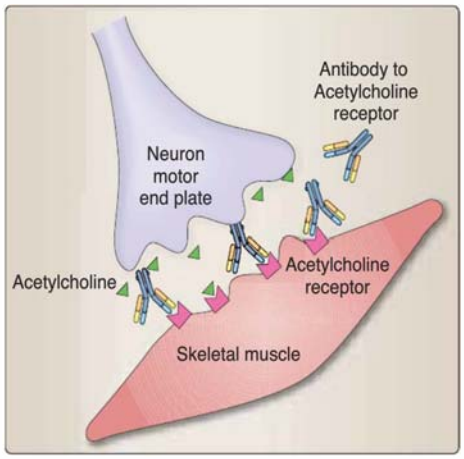

Figure 14.9
Disruption of cellular function by antibody. Autoantibodies (see Chapter 16) may be produced against the acetylcholine receptor (in a condition known as myasthenia gravis), blocking the interaction of the acetylcholine receptor with its obligate ligand (acetylcholine) and leading to increased muscle weakness and death.

complexes throughout the body. Very large immune complexes are rapidly cleared from the body by phagocytic cells and are relatively harmless. Smaller, circulating immune complexes have less chance to be seen by phagocytes and remain in the circulation longer. These complexes have the greatest pathologic consequences.

1. **Exogenous antigens:** Administered either in large amounts or for a prolonged period, these may induce antibody responses. Soluble antigen–antibody complexes immobilized along the endothelium activate complement to cause vascular injury. Complement components (e.g., C5a, C4a, and C3a) attract polymorphonuclear cells to the site, and these cells exacerbate the vascular injury (Fig. 14.11).

Serum sickness used to be solely a consequence of treatment with animal-derived antisera. Before the advent of antibiotics, sera from immunized animals were often administered to human patients to ameliorate infection or the effects of bacterial toxins, such as diphtheria toxin. Horses were commonly immunized with heat-inactivated toxin (called a *toxoid*). Intravenously administered horse antiserum is very efficient at neutralizing the harmful effects of bacterial toxins. Horse serum proteins persist in the patient's circulation and, unfortunately, are very good immunogens in humans. After 7 to 10 days, patients may develop symptoms of immune complex disease, corresponding to the advent of a primary antibody response to horse serum proteins. Serum sickness is a self-limiting disease because the foreign antigen (antiserum) is cleared from the body.

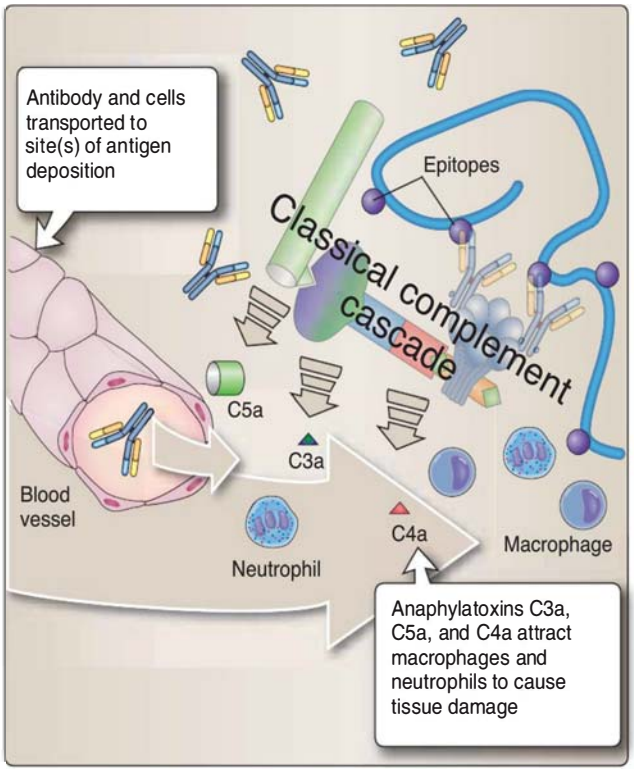

Figure 14.10
Arthus or acute immune complex vasculitis. This localized type III hypersensitivity reaction results from the tissue deposition of antigen–antibody complexes. Circulating antibodies leave the vasculature to interact with antigens introduced into the tissue.

CLINICAL APPLICATION
Drug-induced immune complex disease

An 18-year-old female presents in the emergency room with a 2-day history of fever (39°C), cough, and labored breathing. A diagnosis of lobar pneumonia is made. She is admitted to the hospital, and because a gram-negative organism is suspected, a 10-day course of oral penicillin G is prescribed. Within 48 hours, her temperature is 37.4°C (37°C is normal), and by 96 hours, her respiration has improved and she feels remarkably better. Sputum cultures grow penicillin-sensitive *Streptococcus pneumoniae*, confirming the initial diagnosis. On the 8th day of treatment, she develops edematous eyelids and hives (urticaria) on her abdomen. Penicillin is immediately discontinued, and antihistamine is administered. Nevertheless, she develops tightness in the throat, swollen face, and widespread urticaria. Laboratory tests show an elevated leukocyte count with 67% lymphocytes (30% is normal), plasma cells are present in blood smears, and complement levels are decreased. She has developed a type III hypersensitivity response to penicillin. She is advised by her physician that she must avoid use of penicillin and penicillin derivatives in the future.

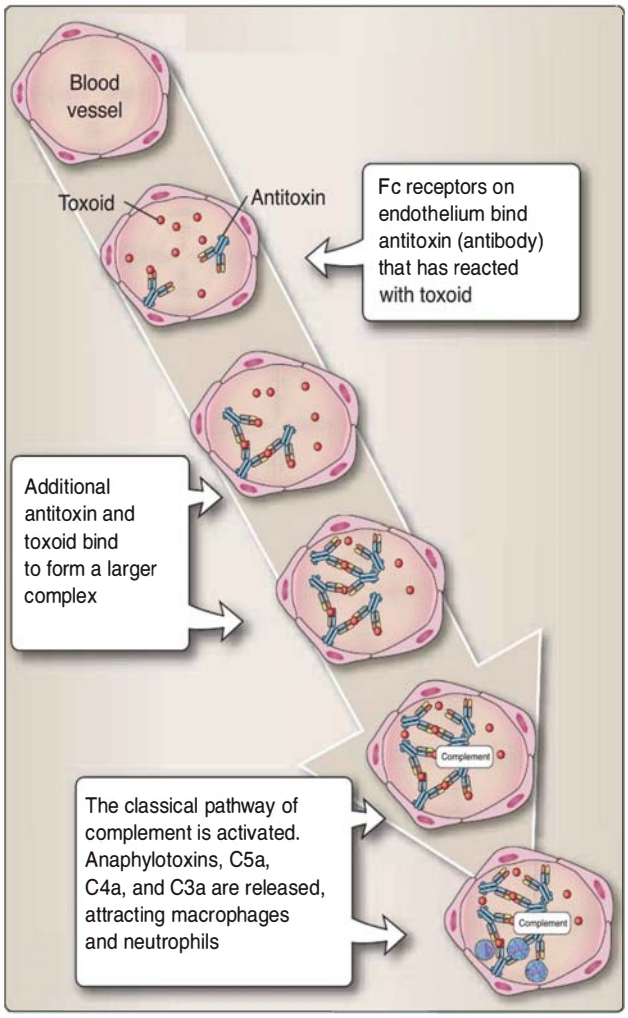

Figure 14.11
Accumulation of immune complexes within the vasculature. Antibodies are produced against circulating antigens. Binding of antigen conformationally changes the Fc portion of antibody, which can then bind to endothelial Fc receptors. More antibody and antigen are bound, forming an immune complex that activates the classical pathway of complement.

2. **Endogenous antigens:** These may also cause immune-complex disease. Unlike exogenous antigens, continually produced endogenous antigens are responsible for chronic antigen exposure, chronic immunization, and prolonged immune-complex disease. Autoimmune diseases are often accompanied by immune-complex disease. Each year, 50 new cases per million of the population of **systemic lupus erythematosus** (**SLE**) are diagnosed. This disease occurs approximately eight times more often in women than in men. SLE is a complex, multifaceted autoimmune disease. Individuals with SLE produce autoantibodies to several different self-antigens. As a consequence, immune complexes are deposited in the vascular beds that activate complement and cause vasculitis.

V. TYPE IV HYPERSENSITIVITY

Type IV hypersensitivity reactions result from the interaction of T cell-initiated inflammation and do not involve antibody. Inflammatory responses result

CLINICAL APPLICATION
Acute rheumatic fever

"Strep" throat is an acute infection of the palatine tonsils often caused by *Streptococcus pyogenes*, making swallowing painful. For most individuals, streptococcal tonsillitis is a self-limiting illness. However, a small number of untreated individuals develop polyarthritis and complications arising from antibody responses to antigen (M protein) expressed in the cell wall of *S. pyogenes*. A minority of these individuals develop antibodies that cross-react with antigens expressed on heart valves, myocardial and smooth muscle sarcolemma, and myosin (anti-M antibodies), a disease known as **acute rheumatic fever** (**ARF**). Because recurrent attacks of *S. pyogenes* result in increased severity of ARF, prophylactic measures are indicated. When *S. pyogenes* infection is confirmed by throat culture, antibiotic therapy (penicillin) is prescribed to help eliminate *S. pyogenes* and to minimize the development of a systemic antibody response.

from the manner in which T cells encounter and respond to antigen. $CD4^+$ T cells may be sensitized and respond to topically applied antigen (**contact dermatitis**, **CD**, also called contact sensitivity) and by antigen-injected antigen (delayed [-type] hypersensitivity, DTH). Alternatively, $CD8^+$ T cells may encounter cell-surface antigen and directly cause the lysis of that cell (CTL).

A. Contact dermatitis

Chemically reactive substances may be absorbed through the epidermis, where they bind to proteins. Potential **contact sensitizers** include synthetic chemicals, plant products, and certain metals (e.g., nickel). Generally, contact sensitizers are, by themselves, too small (<10,000 Da) to be recognized by the immune system. Contact sensitizers interact with self-proteins to form immunogenic **neoepitopes** or **neoantigens** on these proteins. Immunologists often refer to substances that are immunogenic only when bound to another molecule as **haptens**. First acute exposure to a contact sensitizer often occurs without apparent incident but serves to immunize the immune system. After seven or more days, reexposure or chronic exposure elicits a localized inflammation of the dermis. Clinical signs, like those seen for DTH, typically appear 24 to 72 hours after reexposure (Fig. 14.12).

CLINICAL APPLICATION
Poison ivy

Toxicodendron radicans, commonly known as poison ivy, is a woody vine that secretes a toxic oil known as urushiol. *T. diversiloba* (poison oak) and *T. vermix* (poison sumac) also secrete this compound. The name comes from urushi, a Japanese wood lacquer produced from the sap of *T. vernicifluum*. Minute amounts of urushiol (1 ng) are sufficient to elicit contact dermatitis in previously exposed individuals. Over 85% of individuals who had contact with urushiol will develop a type IV hypersensitivity to this compound.

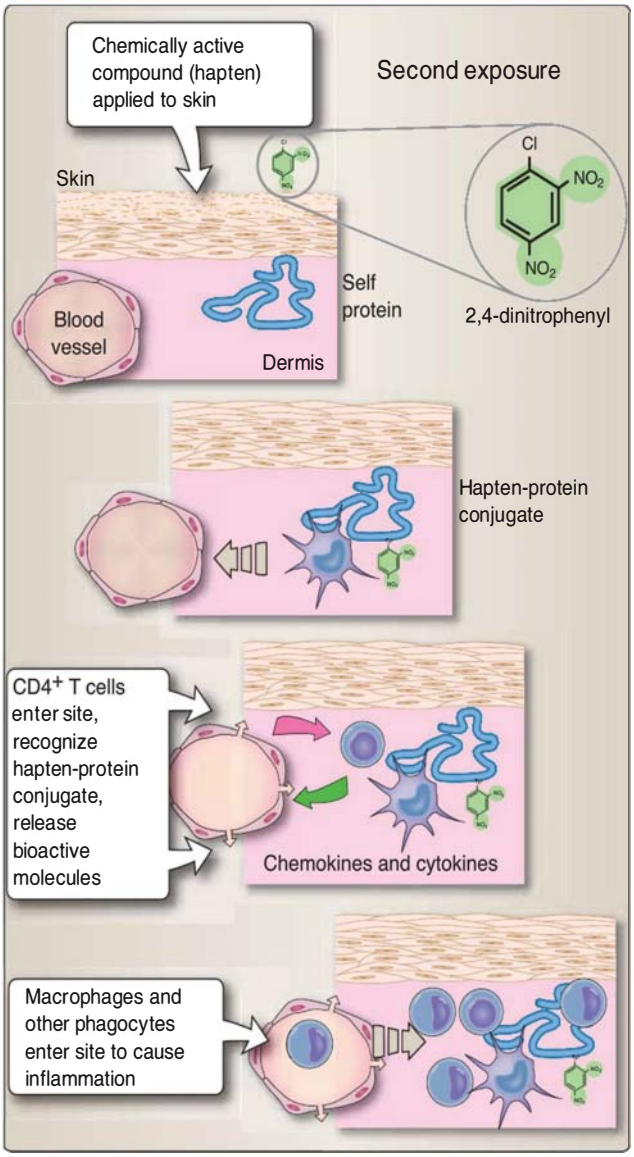

Figure 14.12
Contact dermatitis. Certain chemical compounds (e.g., 2,4-dinitrophenyl or DNP) by themselves do not invoke an immune response (haptens). However, they may penetrate the epidermis and covalently bind to self-proteins (hapten-protein conjugate). Following phagocytosis and presentation by resident dendritic cells in the context of MHC class II, $CD4^+$ T cells entering the site may be activated and release chemokines to attract and cytokines (e.g., IFN-γ) that induce type IV hypersensitivity.

CLINICAL APPLICATION
Canary girls and the munitions factory

As men fought in "the war to end all wars," World War I, Britain found itself with severe shortages of war supplies and labor. The only way to find sufficient labor for production needs was to hire young women to manufacture and load trinitrotoluene (TNT) into explosive shells. TNT is a pale yellow crystalline solid that is readily absorbed through the skin. Munitions workers who handled the chemical

found that their skin turned bright yellow (and red hair turned green) and were nicknamed "canary girls." With time, many developed severe dermatitis, and over 100 workers died from TNT exposure. By themselves, TNT and derivatives of related compounds such as trinitrophenyl, dinitrophenyl, and nitrophenyl cannot stimulate an immune response. These compounds, termed **haptens**, penetrate the epidermis and readily bind to body proteins, where they may induce a hapten-specific type IV immune response. The plight of the canary girls led to increased awareness of industrial and environmental hazards and aided the cause that led to women's suffrage in Britain in 1918.

B. Delayed (-type) hypersensitivity

Delayed (**-type**) **hypersensitivity** (**DTH**) responses occur in sensitized individuals upon nontopical reencounter with antigen. In general, Type IV DTH hypersensitivity responses are stimulated by intracellular parasites such as bacteria (e.g., *Mycobacterium tuberculosis, M. leprae, Leishmania monocytogenes*), fungi (e.g., *Candida albicans*), and some viruses (e.g., mumps virus, a paramyxovirus). DTH responses occur upon reexposure to the stimulating antigen. Reexposure generally must occur more than 1 week after the initial antigenic encounter (Fig. 14.13). Like contact dermatitis responses, DTH responses are delayed, occurring 24 to 72 hours after restimulation. Unlike contact dermatitis responses, DTH responses are not limited to the dermis but can occur at almost any anatomical site in the body.

CLINICAL APPLICATION
Mantoux test

Tuberculosis (**TB**) is a potentially severe contagious disease caused by *Mycobacterium tuberculosis*. TB is spread from person to person through the air. According to the Centers for Disease Control and Prevention and the World Health Organization, one-third of the world's population is infected with TB. More than 2 million people worldwide die from TB each year. Among people older than 5 years of age, TB disease is the leading cause of death due to infectious disease around the world.

The Mantoux skin test is a useful screening test to identify people who have been infected with TB. It involves injection of 5 TU (tuberculin units) of purified protein derivative (tuberculin), usually 0.1 mL, intradermally. Induration (swelling) is assessed at 48 to 72 hours. The induration is caused by cell infiltration and occasionally vesiculation and necrosis. A positive response is an example of type IV hypersensitivity (DTH) and indicates that the subject has had prior exposure to *M. tuberculosis*.

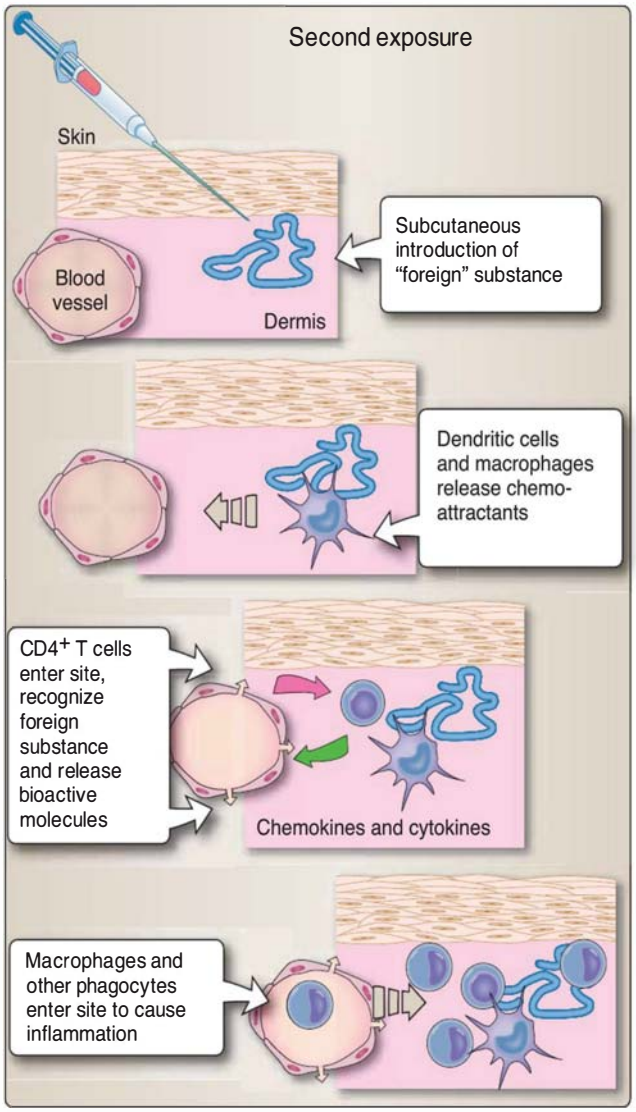

Figure 14.13
Delayed (-type) hypersensitivity. Proteins or intracellular organisms are phagocytosed and presented by resident dendritic cells in the context of MHC class II. $CD4^+$ T cells enter the site, recognize the foreign substance, and release chemokines to attract and cytokines (e.g., IFN-γ) to activate phagocytic cells to cause a type IV hypersensitivity.

CLINICAL APPLICATION
Hypersensitivity pneumonitis

John M., a previously healthy 46-year-old male with no prior history of immune-related illnesses presents with a persistent cough and shortness of breath associated with headache and malaise. Four weeks ago, his physician prescribed an antibiotic for some findings on his lung exam. The antibiotic did not alleviate his symptoms. At that time, his chest radiograph and screening spirometry were normal. For the last 6 months, he has worked in a new location. Others at his workplace began to complain of similar symptoms, and an air quality analysis was performed, revealing fungal spore counts of more than 500 per cubic meter of air

(reference: <200). Radiographs show diffuse patchy lung infiltrate consistent with the diagnosis of hypersensitivity pneumonitis, an example of type IV hypersensitivity mediated by $CD4^+$ T cells. John is prescribed a course of oral corticosteroids, and it is recommended that he find an alternative work location. John follows this advice, and his symptoms resolve quickly. He has remained symptom-free since that time.

C. T cell-mediated cytotoxicity

In some instances, type IV hypersensitivity reactions are caused by $CD8^+$ T lymphocytes. These CTLs respond to reactive chemical agents (haptens) that pass through the cell membrane and bind to cytoplasmic proteins to produce neoantigens (Fig. 14.14). Peptides derived from haptenated cytoplasmic proteins (ubiquitin, proteasome, TAP pathway) are presented by MHC class I molecules to sensitize and elicit a CTL response.

Chapter Summary

- All four hypersensitivity responses occur upon second exposure or chronic exposure to antigen. Only type IV hypersensitivity reactions are antibody independent.
- Hypersensitivity reactions cause tissue injury by the release of chemical substances that attract and activate cells and molecules resulting in **inflammation**.
- Type I hypersensitivity reactions are rapid, occurring within minutes of exposure to an antigen, and always involve IgE-mediated degranulation of basophils or mast cells.
- **Anaphylaxis** ("against protection") is characterized by vascular smooth muscle constriction (**vasoconstriction**) combined with gap formation between adjacent capillary endothelial cells (**vasodilation**) that results in severe fluid loss and leads to **shock**.
- **Type II** hypersensitivity reactions are initiated by the binding of antibody to a cell membrane or to the extracellular matrix. Type II reactions are initiated by the interaction of antibody (IgM or IgG) with cell membranes or with the extracellular matrix. The antigens that are recognized may be intrinsic to the cell membrane or extracellular matrix, or they may be exogenous molecules such as a drug metabolite adsorbed onto the cell membrane or extracellular matrix.
- **Type III** hypersensitivity reactions involve the interaction of antibodies with soluble molecules to make soluble antigen–antibody complexes that become deposited in tissues. Circulating antigen–antibody complexes may lead to inflammation at their sites of deposition, often resulting in blood vessel inflammation (**vasculitis**). Immune complexes may cause injury resulting from the interaction with exogenous antigens (e.g., microbes, viruses, or chemically modified self-proteins) or endogenous antigens (e.g., serum proteins).

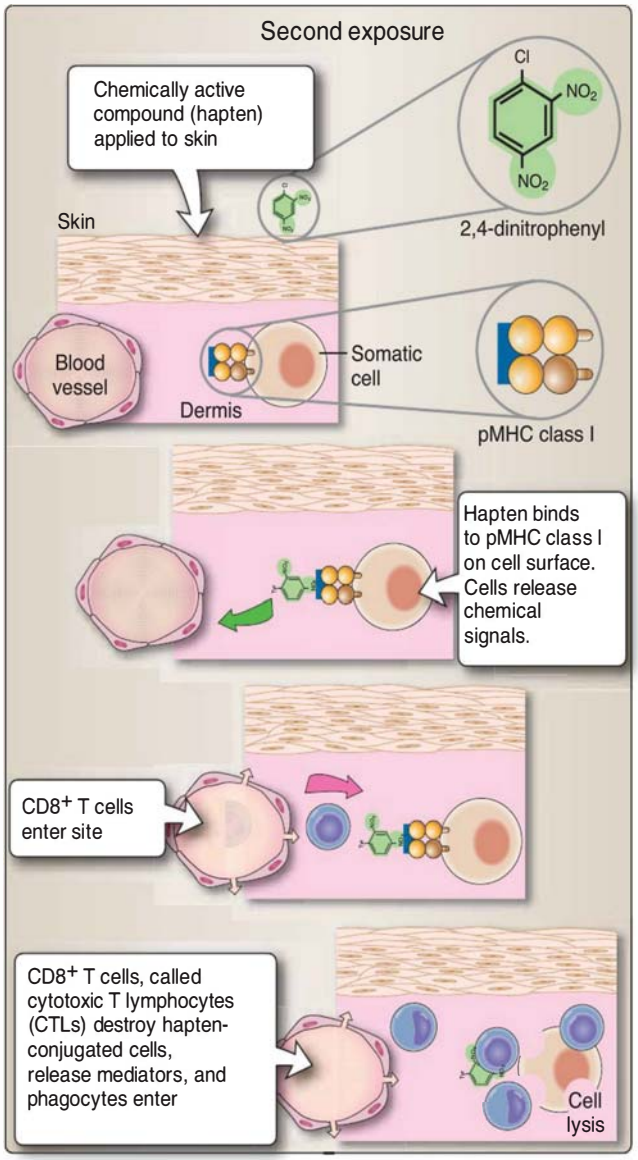

Figure 14.14
Type IV hypersensitivity mediated by cytotoxic $CD8^+$ T lymphocytes. DNP that penetrates the epidermis may covalently bond to self-proteins present on cell surfaces. $CD8^+$ T cells enter the site, where they recognize and kill the hapten-modified cell and release substances that invoke an inflammatory response.

- **Type IV** hypersensitivity reactions involve direct attack of host cells by leukocytes in the absence of antibody. Included are contact dermatitis, delayed (-type) hypersensitivity (DTH), and, sometimes, cytotoxic T-lymphocyte (CTL) responses. Type IV reactions result from T cell-initiated inflammation. Inflammatory responses result from the manner in which T cells encounter and respond to antigen. $CD4^+$ T cells may be sensitized and respond to topically applied antigen (contact dermatitis), or they may be sensitized by injected antigen (DTH), or $CD8^+$ T cells may encounter cell-surface antigen and directly cause cellular lysis (CTL).

Study Questions

14.1. A previously healthy 45-year-old male presents with rhinorrhea, nasal congestion, and persistent respiratory symptoms several months after returning to his home in New Orleans after Hurricane Katrina. He has noticed mold growing along the walls of his house. Skin testing for sensitivity to common mold spores gave positive results to several of them in less than 30 minutes. These findings indicate an example of

A. contact dermatitis.
B. delayed (-type) hypersensitivity.
C. immediate hypersensitivity.
D. serum sickness.
E. type II hypersensitivity.

The correct answer is C. Type I (immediate) hypersensitivity is caused by the cross-linking of FcR (also known as CD23) -bound IgE antibodies on cell surfaces, which triggers the release of vasoreactive amines from mast cell granules. Antigens (allergens) are often airborne and elicit type I reactions that cause respiratory distress. Neither contact dermatitis nor delayed (-type) hypersensitivity reactions involve antibody. Both serum sickness and type II hypersensitivity involve immune complexes.

14.2. A 25-year-old female with a history of penicillin allergy unknown to her physician was given a single injection of penicillin for the treatment of syphilis. Within minutes, she developed diffuse urticaria (hives), tachycardia (rapid heart rate), and hypotension (decrease in blood pressure). This patient has experienced

A. anaphylaxis.
B. anergy.
C. antibody-mediated cytotoxicity.
D. asthma.
E. contact sensitivity.

The correct answer is A. This individual displays the hallmarks of a classical anaphylactic reaction to penicillin. Anergy is the impairment of effector immune responsiveness. Antibody-mediated cytotoxicity is most often localized to tissues bearing epitopes to which the antibody binds. Asthma causes respiratory distress because of the contraction of bronchiole-associated smooth muscle in response to the release of vasoactive mediators from mast cells. Contact sensitivity results from the epicutaneous application of a reactive antigen/hapten; in the present question, the antigen (penicillin) was administered intramuscularly.

14.3. Which of the following is/are initiated by the interaction of host cell membranes with IgM or IgG antibody but never IgE antibody?

A. Arthus reactions
B. Serum sickness
C. Type I hypersensitivity reactions
D. Type II hypersensitivity reactions
E. Type IV hypersensitivity reactions

The correct answer is D. Type II hypersensitivity reactions occur with host cell membranes or with the extracellular matrix. Arthus reactions and serum sickness are type III hypersensitivities that result from the interaction(s) of antibody with soluble antigen(s). IgE is not involved, thus ruling out type I hypersensitivity.

14.4. An 8-year-old female with a known allergy to peanuts inadvertently ingests a cereal containing traces of peanuts. Within 1 hour, she develops diffuse erythema (redness of the skin) and urticaria associated with respiratory symptoms of shortness of breath and diffuse wheezing. These findings suggest which of the following events?

A. Type I hypersensitivity reaction
B. Arthus reaction
C. FcR-bearing cells binding to host cells coated with IgG
D. IgG binding to extracellular matrix of the respiratory passages
E. IgM-mediated interaction with cell membranes of lymphocytes

The correct answer is A. This individual has experienced an immediate or type I hypersensitivity. The clue here is that this reaction occurred within 1 hour of antigen (peanut) ingestion. Her presentation shows hallmarks of IgE-mediated anaphylactic reactions. Arthus reactions and those mediated by IgM and IgG neither cause mast cell degranulation nor do they cause rapid respiratory distress.

14.5. The 8-year-old patient recovered from the event described in Study Question 14.4. The next day, she went to play with a friend who had recently returned from a family trip to Asia. The friend gave her a Japanese lacquered box as a gift. Two days later, she developed itchiness in her hands, and her mother noticed that they were bright red. Her mother also noticed clear fluid vesicles on her right forearm. These findings suggest which type of hypersensitivity?

A. Type I, mediated by $CD4^+$ T cells
B. Type I, mediated by $CD8^+$ T cells
C. Type II, mediated by $CD8^+$ T cells
D. Type III, mediated by $CD4^+$ T cells
E. Type IV, mediated by $CD4^+$ T cells

The correct answer is E. Urushiol, common to poison ivy and poison oak, is a component of Japanese lacquer. The urticaria (itchiness) and fluid vesicles on her forearm are hallmarks of contact dermatitis, a type IV hypersensitivity mediated by $CD4^+$ T cells. Type I and type II hypersensitivities are mediated by antibodies; type IV is not.

14.6. A 45-year-old female with a history of hepatitis C viral infection presents with decreased renal function, hypertension (increased blood pressure), and anemia. Laboratory findings reveal decreased serum C3. Her urine sediment contains leukocytes, erythrocytes, and red blood cell casts (a proteinaceous mold of the renal tubules that includes erythrocytes). Her renal biopsy is consistent with glomerulonephritis. These findings suggest which type of hypersensitivity?

A. Type I, mediated by $CD4^+$ T cells
B. Type II, mediated by IgM antibodies
C. Type III, mediated by IgG antibodies
D. Type IV, mediated by $CD4^+$ T cells
E. Type IV, mediated by IgG (and sometimes IgM) antibodies

The correct answer is C. Glomerulonephritis is often associated with immune complex deposition, a type III hypersensitivity. Red blood cell casts are indicative of glomerulonephritis, and reduced C3 levels indicate a high level of cleavage and activation of C3. Type I hypersensitivity is mediated by IgE, not by $CD4^+$ T cells. Type II hypersensitivity responses usually involve IgG. Type IV hypersensitivities do not involve antibodies.

14.7. A 35-year-old male presents with headache, fatigue, light-headedness, dyspnea (difficulty in breathing), and tachycardia (rapid heart rate). Laboratory findings reveal decreased hemoglobin and a positive direct Coombs test (presence of antibodies on erythrocyte surfaces). The patient is currently taking an antibiotic for symptoms of upper respiratory infection. These findings suggest which type of hypersensitivity?

A. Type I, mediated by IgG antibodies
B. Type II, mediated by IgG antibodies
C. Type III, mediated by IgG antibodies
D. Type III, mediated by IgG or IgM antibodies
E. Type IV, mediated by $CD4^+$ T cells

The correct answer is B. Type II reactions involve antibodies directed against self-cells (such as erythrocytes) or membranes. Certain drugs react with erythrocytes to form neoantigens. Type I responses are against foreign antigens (e.g., allergens), cause IgE responses, and do not invoke a Coombs reaction. Type III reactions involve soluble antigen–antibody complexes, and type IV reactions do not involve antibody.

15 Immune Deficiency

I. OVERVIEW

Sometimes it seems as if the immune system is so complicated that it cannot possibly work. Failure seems almost assured, and indeed, small deficits in the generation of T- and B-cell receptors are common (see Chapter 8). Because redundancy is built in, failure in one component of the immune system may sometimes be covered by another component with a similar or overlapping function. In other cases, failures in immune function become overt and may have a severe clinical impact.

Overt failures of the immune system leave the affected individual with a reduced ability to resist infection. **Immune deficiencies** or **immunodeficiencies** caused by defects in various components of the immune system are infrequent, although not insignificant, and occur in two different ways. **Primary immune deficiencies** are those caused by intrinsic or congenital defects. These deficiencies usually are genetic in nature, but they may sometimes appear as the result of randomly occurring errors in development. Over 100 primary immune deficiency diseases have been identified in humans, and for many of these diseases, the specific defective genes have been identified.

Primary immunodeficiency diseases were once considered rare, but many are actually more common than was previously thought. Selective IgA deficiency has a frequency of about 2 individuals per thousand, compared with numerous others that occur with frequencies of 1 to 10 per hundred thousand. However, because there are so many different primary immunodeficiency diseases, they become a significant health problem when considered collectively. Most primary immune deficiencies become apparent at about 6 months of age, when the maternally derived antibodies that entered the fetal circulation in utero begin to disappear and the infant becomes dependent on his or her own immune system.

Secondary immune deficiencies are caused by environmental causes such as infection, therapeutic treatments, cancer, and malnutrition. These deficiencies may occur at any time of life, depending on when the exposure to the causative factor(s) occurs. As with primary immune deficiencies, affected individuals are more susceptible to infection.

Immune deficiencies are characterized by several features. Some features occur in most forms of immunodeficiency, and some occur with a more limited set of deficiencies. Still others are associated only with specific diseases. These disease-specific features are often useful in diagnosis of a particular individual's disease.

Characteristics seen in many immune deficiency diseases include the following:

- Recurrent or chronic infections
- Inability to clear infectious agents after standard antibiotic therapy
- Unusual infectious agents

Characteristics seen in a limited set of immune deficiency diseases include the following:

- Failure of infants to gain weight normally, known as *failure to thrive* (severe combined immune deficiency disease [SCID], interferon-γ receptor deficiency, bare lymphocyte syndrome)
- Hepatosplenomegaly (common variable immune deficiency [CVID], interferon-γ receptor deficiency, Chediak–Higashi syndrome)
- Skin rashes (SCID, Wiskott–Aldrich syndrome [WAS], X-linked agammaglobulinemia)
- Diarrhea (associated with gastrointestinal infection) (CVID, WAS, X-linked agammaglobulinemia, bare lymphocyte syndrome, SCID, chronic granulomatous disease [CGD])
- Recurrent abscesses (CGD, leukocyte adhesion molecule defects)

Nonimmunologic characteristics that occur in specific immune deficiency diseases include the following:

- Platelet deficiency (thrombocytopenia) (Wiskott–Aldrich syndrome)
- Loss of balance (ataxia) and widened blood capillaries (telangiectasia) (immunodeficiency with ataxia telangiectasia)
- Partial or complete albinism (Chediak–Higashi syndrome)

II. PRIMARY (CONGENITAL) IMMUNE DEFICIENCIES

Defects causing primary immune deficiencies may occur in different cell lineages: the combined lymphoid cell lineage, T- or B-cell lineages separately, lineages producing phagocytic cells and natural killer (NK) cells, and even cells producing complement components. Additionally, defects in cells of one lineage may affect the development of other lineages that are intrinsically normal. For example, abnormalities in T cells may prevent the activation of B cells that are otherwise normal. And the interactions between cells from different lineages may result in a single defect inhibiting multiple types of immune responses.

Autosomal gene defects (whether recessive or dominant) affect both sexes equally. However, defective X-linked genes (usually recessive) affect males far more frequently than females. Unlike females, males cannot compensate for a defective X-linked gene with a normal counterpart of that gene on the other X chromosome.

A. Defects in stem cells

The **pluripotent stem cells** that ultimately generate the granulocytic, erythrocytic, monocytic, thrombocytic, and lymphocytic lineages of the hematopoietic system are initially found in the aorta-gonad-mesonephros of the developing embryo. These cells undergo two

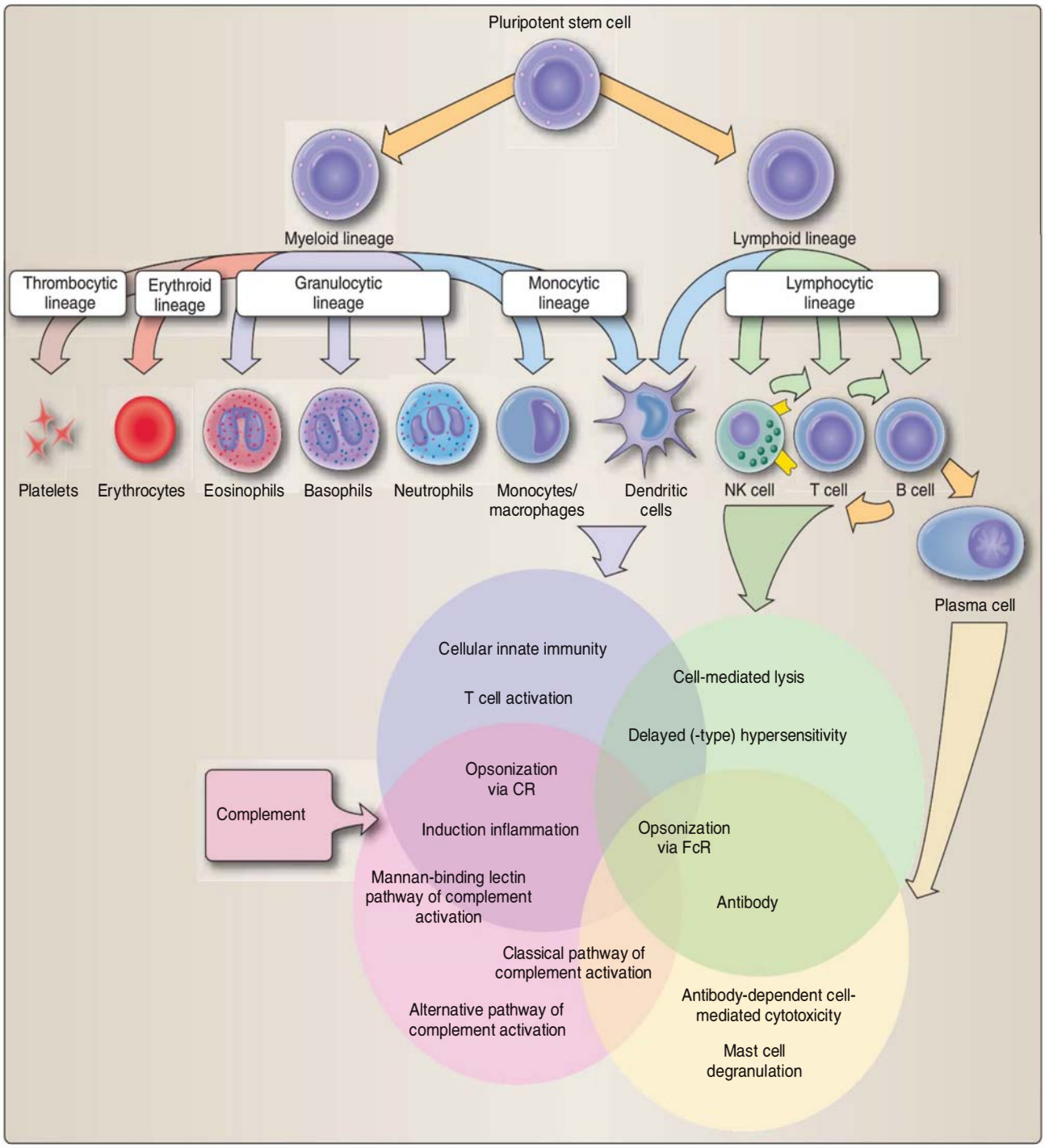

Figure 15.1
Hematopoietic stem cells and lineages. Pluripotent stem cells in the bone marrow give rise to all five hematopoietic cell lineages: lymphocytes, thrombocytes, monocytes, granulocytes, and erythrocytes. Note that both the lymphocytic and monocytic lineages produce dendritic cells.

migrations. During embryonic and fetal development, they migrate to the fetal liver. Later, before birth, they migrate again, this time to the bone marrow, where they remain for life. Some of the pluripotent stem cells differentiate into slightly differentiated stem cells that give rise to each of the five hematopoietic lineages (Fig. 15.1). Lymphoid stem cells generate both B cells (B-1 and B-2) and T cells ($\alpha\beta$ and $\gamma\delta$). Recall from Chapter 7 that the B-2 cell lineage remains within the

bone marrow for development, the B-1 lineage relocates to and self-replicates in the peritoneal/pleural tissues, and the T-cell lineage migrates to the thymus.

Defects in lymphoid stem cells giving rise to both the T- and B-cell lineages result in defective function of both cell types (Fig. 15.2). Individual defects may result in abnormal T- and B-cell numbers or

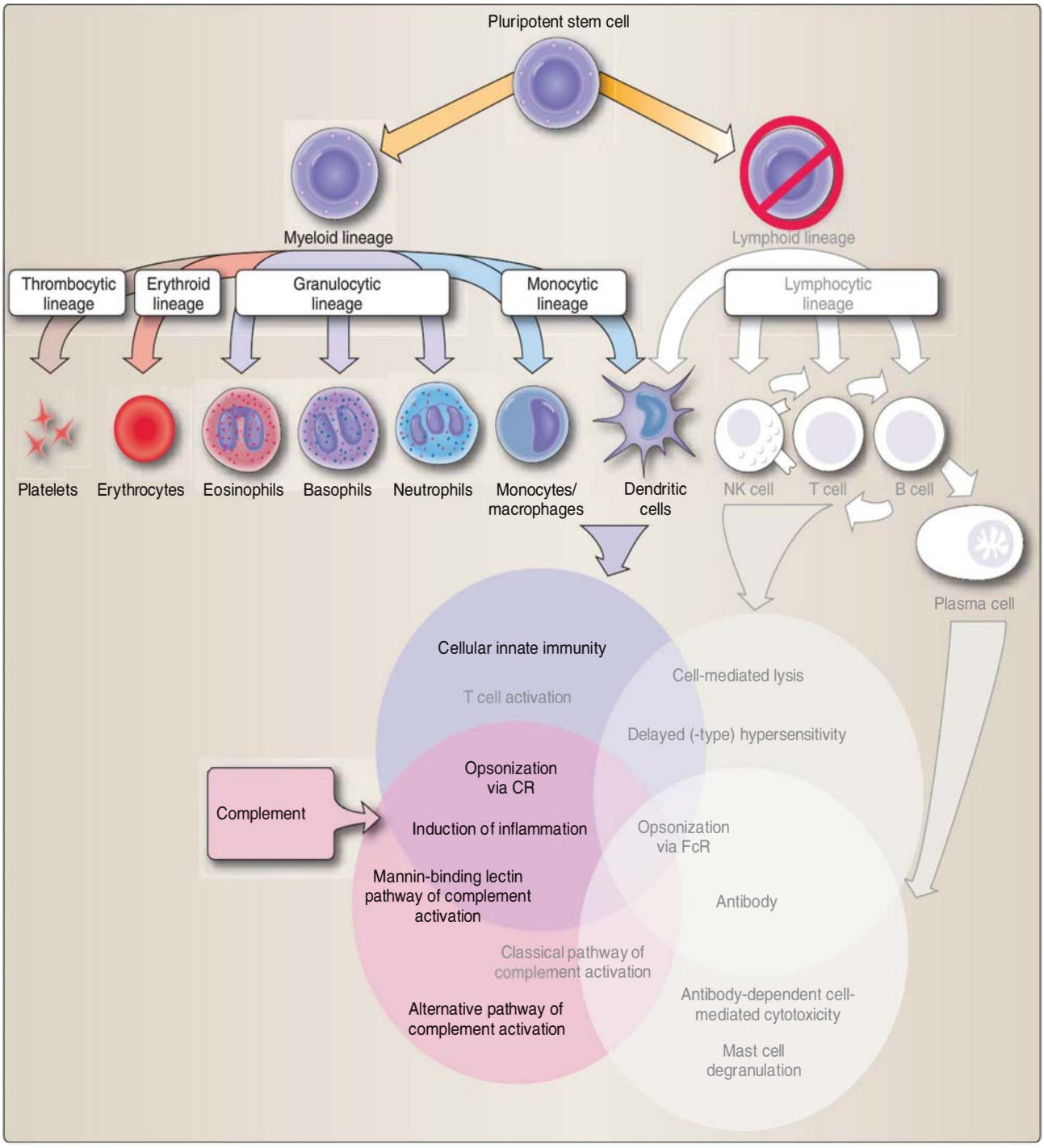

Figure 15.2
Effects of lymphoid cell lineage deficiencies. Defects in the lineage producing both T and B lymphocytes impair the development and/or functionality of both types of lymphocytes.

functions or both. Cell-mediated responses (e.g., cell-mediated lysis and delayed type hypersensitivity) are usually reduced, as is immunoglobulin production. The relative impacts of individual defects, however, are not always equal in T and B cells, nor do they always have equally severe consequences among affected individuals.

Severe combined immunodeficiency (**SCID**) is the classic example of defects in the combined lymphocyte lineage. SCID is not a single disease; it is a group of diseases caused by different defects in individual genes that have similar functional consequences (Table 15.1). SCID-related defects may occur in the genes that encode enzymes

Table 15.1
PRIMARY IMMUNE DEFICIENCY DISEASES ATTRIBUTABLE TO STEM CELL DEFECTS

Disease	Inheritance	Gene	Chromosome	Consequences
Adenosine deaminase (ADA) deficiency	Autosomal-recessive	*ADA* (adenosine deaminase)	20	Very susceptible to infection; impaired purine metabolism; T- and B-cell numbers and functions decreased because of toxic metabolites; immunoglobulin levels decreased
Immunodeficiency with ataxia telangiectasia	Autosomal-recessive	*ATM* (ataxia telangiectasia mutated)	11	Increased susceptibility to infection; frequent sinopulmonary infections; DNA repair affected and variable signs, including ataxia and telangiectasia (problems with balance and widened small capillaries); occurs at varying ages and in varying functions; T-cell numbers and functions and immunoglobulin levels (especially IgG, IgA, and IgE) may decrease; B-cell numbers may be normal; autoantibodies and chromosomal abnormalities are frequently found
Purine nucleoside phosphorylase deficiency	Autosomal-recessive	*NP* (nucleoside phosphorylase)	14	Increased susceptibility to infection; impaired purine metabolism; declining T-cell numbers over time (more susceptible than B cells to accumulated toxic metabolites); declining immunoglobulin levels because of decreased T-cell help
Severe combined immune deficiency (SCID)	Autosomal-recessive	*RAG1* and/or *RAG2* (recombination-activating genes)	11	Increased susceptibility to infection; unable to rearrange DNA to form variable regions of immunoglobulins and T-cell receptors; T- and B-lymphocyte numbers/functions reduced or absent; immunoglobulin levels reduced or absent
	X-linked recessive	*IL2RG* (common cytokine receptor γ chain, a component of the receptor complexes for IL-2, IL-4, IL-7, IL-9, and IL-15)	X	Multiple effects because common γ chain is a component of receptors for several cytokines; increased susceptibility to infection; T-cell numbers and immunoglobulin levels decreased; B-cell numbers normal or increased
	Autosomal-recessive	*JAK3* (Janus kinase 3)	19	Increased susceptibility to infection; defective intracellular signaling; T-cell numbers and immunoglobulin levels decreased; B-cell numbers normal or increased
Wiskott–Aldrich syndrome	X-linked recessive	WAS (Wiskott–Aldrich syndrome)	X	Increased susceptibility to infection, especially by *Staphylococcus aureus*, develops during infancy and early childhood; T- and B-cell numbers and functions reduced, as are immunoglobulin levels; platelets abnormal and reduced in number

CLINICAL APPLICATION
X-linked SCID

Luca D., a 4-month-old male, presents with severe diarrhea and failure to thrive. Over the past 2 months, he has had two episodes of ear infections requiring antibiotic therapy. Examination reveals a poorly nourished child with minimal tonsillar tissue and the presence of oral thrush. Blood tests reveal lymphocyte counts significantly below normal with an absence of T cells ($CD3^+$) and NK cells ($CD16^+$, $CD56^+$) and significantly reduced numbers of B cells ($CD19^+$). A further workup by an immunology consultant indicates a diagnosis of X-linked SCID. The hematology/immunology transplant team is notified, and the patient receives a bone marrow transplant.

(RAG-1, RAG-2) responsible for the rearrangements of DNA that produce the variable regions of immunoglobulins and T-cell receptors. Other examples include defects in cytokine receptors and in molecules involved in cell-to-cell interaction for the activation of lymphocytes. Defective production of **purine nucleoside phosphorylase** provides an example of a genetic defect that affects both T and B cells but with differing intensity. The accumulated toxic metabolites resulting from this defect impair the functions of T cells far more severely than those of B cells.

B. Defects in T cells

Primary immune deficiencies intrinsic to T cells result in abnormal T-cell numbers and/or functions. However, because T-cell "help" is critical to the activation of naive and memory B cells, many T-cell defects also cause abnormalities in B-cell numbers and immunoglobulin production (Fig. 15.3). Several representative diseases resulting from T-cell defects are given in Table 15.2. Some are common to both $CD4^+$ and $CD8^+$ T cells; some affect only one T-cell type or the other. Because the delayed-type hypersensitivity response is largely responsible for clearance of fungi, frequent or recurrent fungal infections are suggestive of defects in T-cell function.

A second category of T-cell defects comprises those in which the responsible mutation(s) are not limited to T cells but may occur in cells that are critical to the development or activation of T cells. Some T-cell defects arise from mutations in other cells that influence the development or activation of T cells. For example, **TAP-2 deficiency** (also known as **bare lymphocyte syndrome I**) is caused by defects in the transporter associated with the antigen presentation (TAP; either TAP1 or TAP2) system. These defects ultimately impair the loading of peptide fragments into nascent MHC class I molecules in all nucleated cells and reduce the number of MHC class I molecules that successfully reach the cell surface. This reduced MHC I expression decreases the number of functional $CD8^+$ T cells and can also affect the functions of NK cells monitoring MHC class I expression on body cells (although the NK cells appear not to attack uninfected host

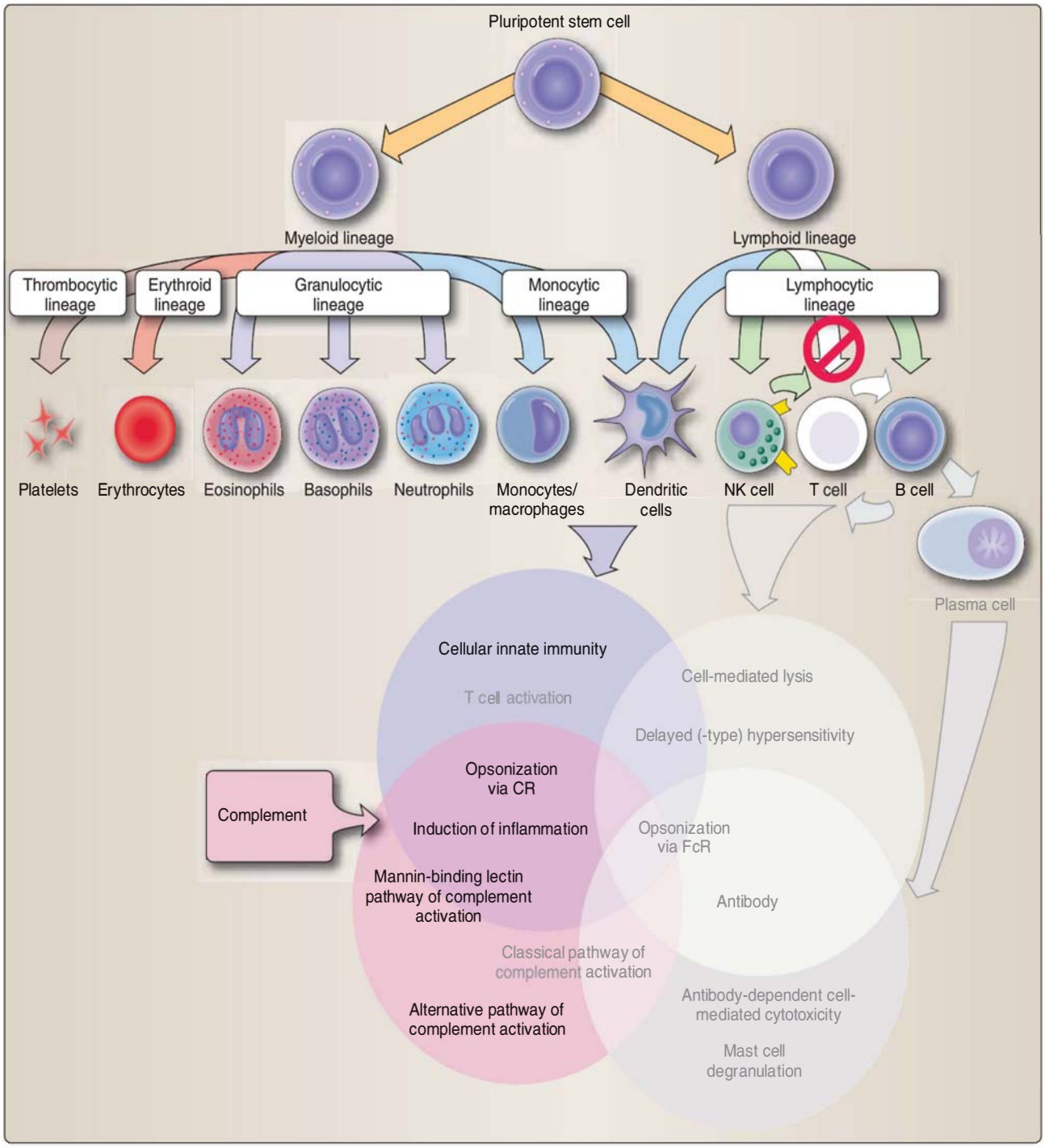

Figure 15.3
Effects of T-lymphocyte deficiencies. Defective T cells not only reduce cell-mediated immune responsiveness, but also often reduce B-cell functions because of the regulatory role for T cells in B-cell activation.

cells). Likewise, defects inhibiting expression of MHC class II molecules reduce the number of functional $CD4^+$ T cells. An additional example is **DiGeorge syndrome** (see Table 15.2) in which defects in thymic development arising from abnormal embryonic changes in the third and fourth pharyngeal pouches may inhibit or prevent development and thymic education of T cells. The severity of effects of DiGeorge syndrome is variable. In addition to abnormal development

Table 15.2
PRIMARY IMMUNE DEFICIENCY DISEASES ATTRIBUTABLE TO T-CELL DEFECTS

Disease	Inheritance	Gene	Chromosome	Consequences
CD3 deficiency	Autosomal-recessive	*CD3G* or *CD3E*	11	Increased susceptibility to infection; defects in CD3γ (CD3G) or CD3ε (CD3E) proteins; variable effects on T-cell functions
DiGeorge syndrome	Autosomal-dominant or spontaneous	Unknown defects in embryonic thymic development	22 (when genetic)	Increased susceptibility to infections; T-cell numbers and functions intrinsically normal but reduced and variable owing to abnormal development of thymus from third and fourth branchial arches; variable immunoglobulin levels; deletions in chromosome 22 frequently seen; often accompanied by other defects (e.g., facial features, palate, aorta, and parathyroid glands and calcium metabolism)
MHC class II deficiencies (bare lymphocyte syndrome)	Autosomal-recessive	*CIITA* or *RFX5*	16 or 1	Increased susceptibility to infection; defective intracellular signaling; $CD4^+$ T cell numbers reduced; immunoglobulin levels decreased owing to defective T-cell help
Purine nucleoside phosphorylase deficiency	Autosomal-recessive	NP (nucleoside phosphorylase)	14	Increased susceptibility to infection; impaired purine metabolism; T-cell numbers decline over time (more susceptible than B cells to accumulated toxic metabolites); immunoglobulin levels decline because of decreased T-cell help
Transporter associated with antigen presentation (TAP) -1 or -2 deficiency	Autosomal-recessive	*TAP1* or *TAP2*	6	Increased susceptibility to viral infections and to some intracellular bacteria; decreased MHC I expression and antigen presentation; $CD8^+$ T cell numbers and functions decreased
ZAP-70 deficiency	Autosomal-recessive	*ZAP70* (ζ chain-associated protein kinase)	2	Recurrent severe infections; defective signaling from TCR; $CD8^+$ T cells absent; $CD4^+$ T cells present in normal numbers but nonfunctional

of the pharyngeal pouches, the syndrome may include malformations of the aorta, the face and jaw, and the parathyroid glands. Most individuals with DiGeorge syndrome carry small deletions in chromosome 22, although the relevant gene or genes and their functions are still unidentified. These associated features allow early detection and treatment of DiGeorge syndrome at birth.

C. Defects in B cells

Several inherited genetic defects are intrinsic to B cells (Fig. 15.4). These B-cell defects are responsible for the majority (more than 80%) of human immunodeficiency diseases (Table 15.3). Immunoglobulin levels are typically affected, but not necessarily B-cell numbers. Some B-cell deficiencies are characterized by abnormal production of all immunoglobulin isotypes, whereas others affect only one or a few. T-cell numbers and functions are typically normal. The following examples illustrate the range of effects seen.

X-linked (Bruton) agammaglobulinemia, a recessive X-linked disorder, is one of the best known B-cell immunodeficiencies, resulting from a defect in the gene (*BTK*) that encodes Bruton tyrosine kinase, an enzyme that is crucial to the early development of B cells. Consequently,

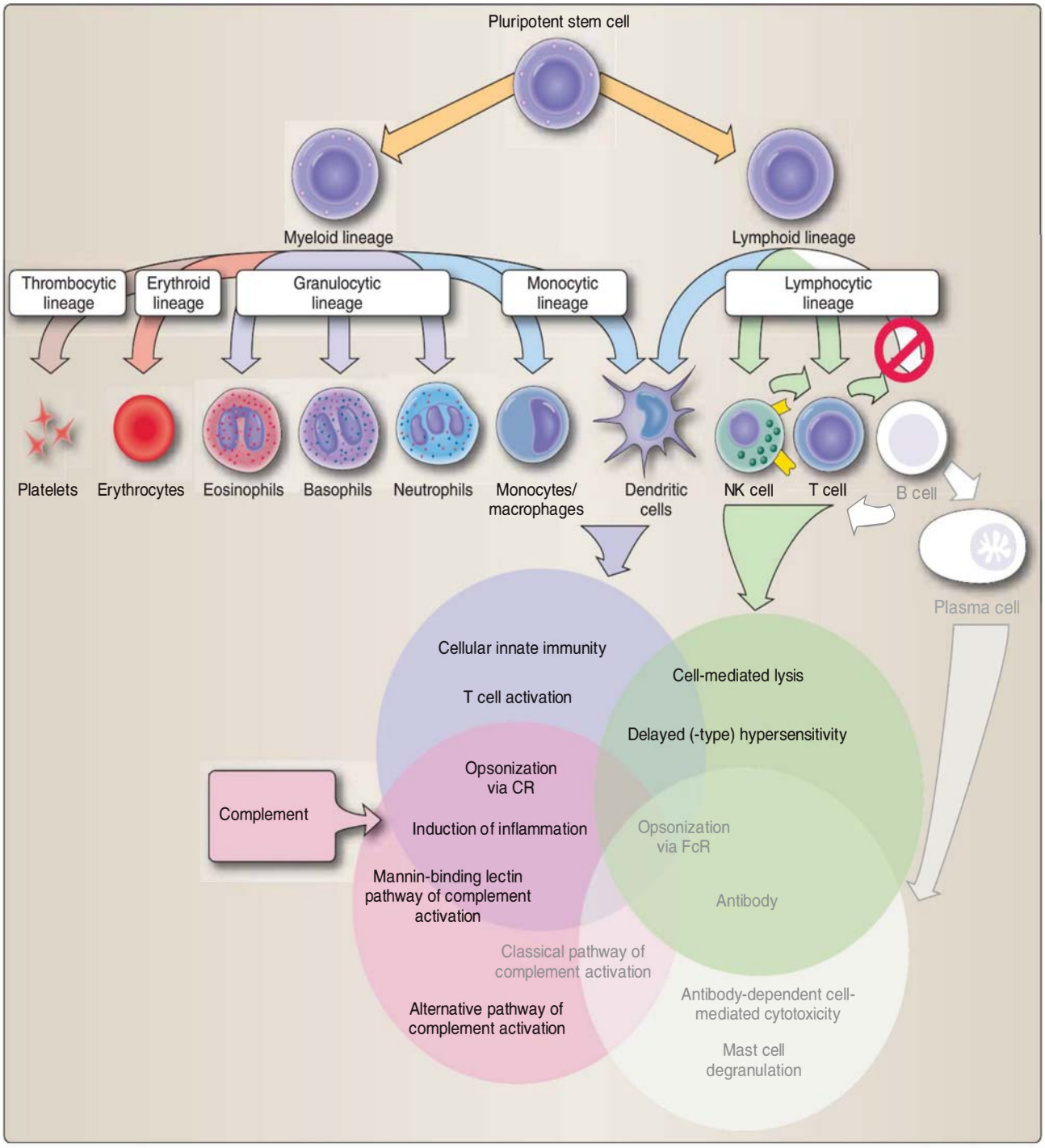

Figure 15.4
Effects of B-lymphocyte deficiencies. Defective B cells affect humoral responses by altering B-cell numbers and/or functions, including immunoglobulin production. T cell functions are usually unaffected.

Table 15.3
PRIMARY IMMUNE DEFICIENCY DISEASES ATTRIBUTABLE TO DEFECTS IN B CELLS AND IMMUNOGLOBULINS

Disease	Inheritance	Gene Locus	Chromosome	Consequences
Autosomal-recessive agammaglobulinemia	Autosomal-recessive	Various genes involved in early differentiation	Various	Increased susceptibility to infection; failure in early differentiation of B cells
X-linked (Bruton) agammaglobulinemia	X-linked recessive	*BTK* (Bruton agammaglobulinemia tyrosine kinase)	X	Increased susceptibility to infection; increased susceptibility to encapsulated bacteria (e.g., *Haemophilus influenzae*, *staphylococci*, and *streptococci*); drastic decrease in B-cell numbers and immunoglobulin levels
Common variable immunodeficiency (CVI or CVID)	Multiple forms	Unknown	?	Increased susceptibility to pyogenic infection; variable symptoms; varying isotypes (or combinations of isotypes) reduced or absent
Immunodeficiency with hyper-IgM	X-linked recessive Autosomal-recessive	*CD40LG* (CD40 ligand, CD154)	X	Increased susceptibility to pyogenic infection; inability of B cells to undergo isotype switching or somatic hypermutation; elevated IgM with decreased/absent IgG, IgA, and IgE; 70% of cases because of X-linked defect
Ig heavy chain gene deletions	Autosomal-recessive	Heavy chain constant genes	14	Increased susceptibility to infection (patients with IgG1 deficiency have increased susceptibility to pyogenic infections, whereas those with IgG2 or IgG3 are susceptible to encapsulated bacteria); various immunoglobulin isotypes absent (dependent on the affected heavy chain gene); IgG most frequently affected; B-cell numbers frequently reduced
Kappa chain deficiency	Autosomal-recessive	κ chain genes	2	Decreased or absent immunoglobulin containing κ chains; little or no effect on susceptibility to infection
Selective IgA deficiency	Multiple forms	Multiple genes	Various	Although patients with this deficiency display no increase in infections, an increased susceptibility to infections may be seen in some, especially recurrent pyogenic bacterial infections in patients also deficient in IgG2; IgA-expressing B cells decreased or absent; serum IgA reduced and often accompanied by IgG subclass deficiency; frequent allergic or autoimmune disorders; frequency of one to two per thousand individuals makes it one of the most common immune deficiency diseases

CLINICAL APPLICATION
X-linked (Bruton) agammaglobulinemia

X-linked (Bruton) agammaglobulinemia was named after an American pediatrician, Dr. Ogden Carr Bruton. In 1952, Dr. Bruton described the clinical case of an 8-year-boy who had recurrent bacterial infections, including many episodes of pneumococcal sepsis. Dr. Bruton vaccinated the boy, but the patient did not produce any antibodies to *Pneumococcus*. In fact, the boy did not produce antibodies to any antigen and had undetectable levels of serum immunoglobulins. Dr. Bruton treated this patient with monthly injections of exogenous gamma globulin. The boy did not have any occurrences of sepsis over the 14 months during which he received injections. Because this condition was observed only in male patients, it was determined to be X-linked.

CLINICAL APPLICATION
Common variable immunodeficiency

Martha D., a 40-year-old woman, presents with recurrent sinusitis requiring antibiotic treatment. She has had two hospitalizations within the past 2 or 3 years for bacterial pneumonia. She also reports symptoms of chronic diarrhea, abdominal pain, weight loss, and fatigue. Laboratory tests reveal evidence of malabsorption because of infection with *Giardia lamblia*. Serum immunoglobulin assessments reveal a significantly decreased level of IgG and a mildly decreased level of IgA, consistent with common variable immunoglobulin deficiency. She is treated with passive immunoglobulin therapy, and her IgG level increases to within normal range. She continues to receive immunoglobulin therapy and remains free of significant infection or diarrhea for several years thereafter.

in this disorder, B cells are few in number, and all immunoglobulin isotypes are diminished. Defects in several autosomal genes also lead to aberrant B-cell development and similar agammaglobulinemias.

Selective IgA deficiency is the single most common immune deficiency disease, with a frequency estimated at one to two per thousand individuals. Multiple gene defects produce it, and there is evidence that some forms of the disease may involve defective isotype switch signaling from T cells. Individuals with selective IgA deficiency have normal levels of other isotypes and often display additional immunologic disorders (e.g., allergy or autoimmunity).

B-cell activation is dependent in part on interaction with helper $CD4^+$ T cells. Some of this interaction involves the binding of CD40 on T cells to CD154 (CD40-ligand) on B cells. **Immune deficiency with hyper-IgM** results from a defect in the gene encoding the CD40 ligand. As a result, the isotype switch does not occur normally, and individuals with this defect produce high levels of IgM but are deficient in B cells that produce IgG, IgA, or IgE.

D. Defects in phagocytes and natural killer cells

Immune deficiency may also result from defects in nonlymphocytic cells such as phagocytes, neutrophils, and NK cells (Fig. 15.5, Table 15.4). Defects in phagocytic cells are significant because of their key roles in both innate and adaptive immune responses. The defects affect two major functions of these cells: their ability to kill microbes and their interactions with other cell types.

Several defects can interfere with the phagocyte's microbe-killing function. Defects in the genes associated with **chronic granulomatous disease** (**CGD**) result in defective enzymes and other microcidal molecules (e.g., toxic oxygen metabolites) involved in destruction and degradation of ingested microbes. In contrast, individuals with **Chediak–Higashi syndrome** have normal levels of these enzymes and microcidal molecules, but a defect in organelle membranes inhibits the normal fusion of lysosomes (carrying the enzymes and

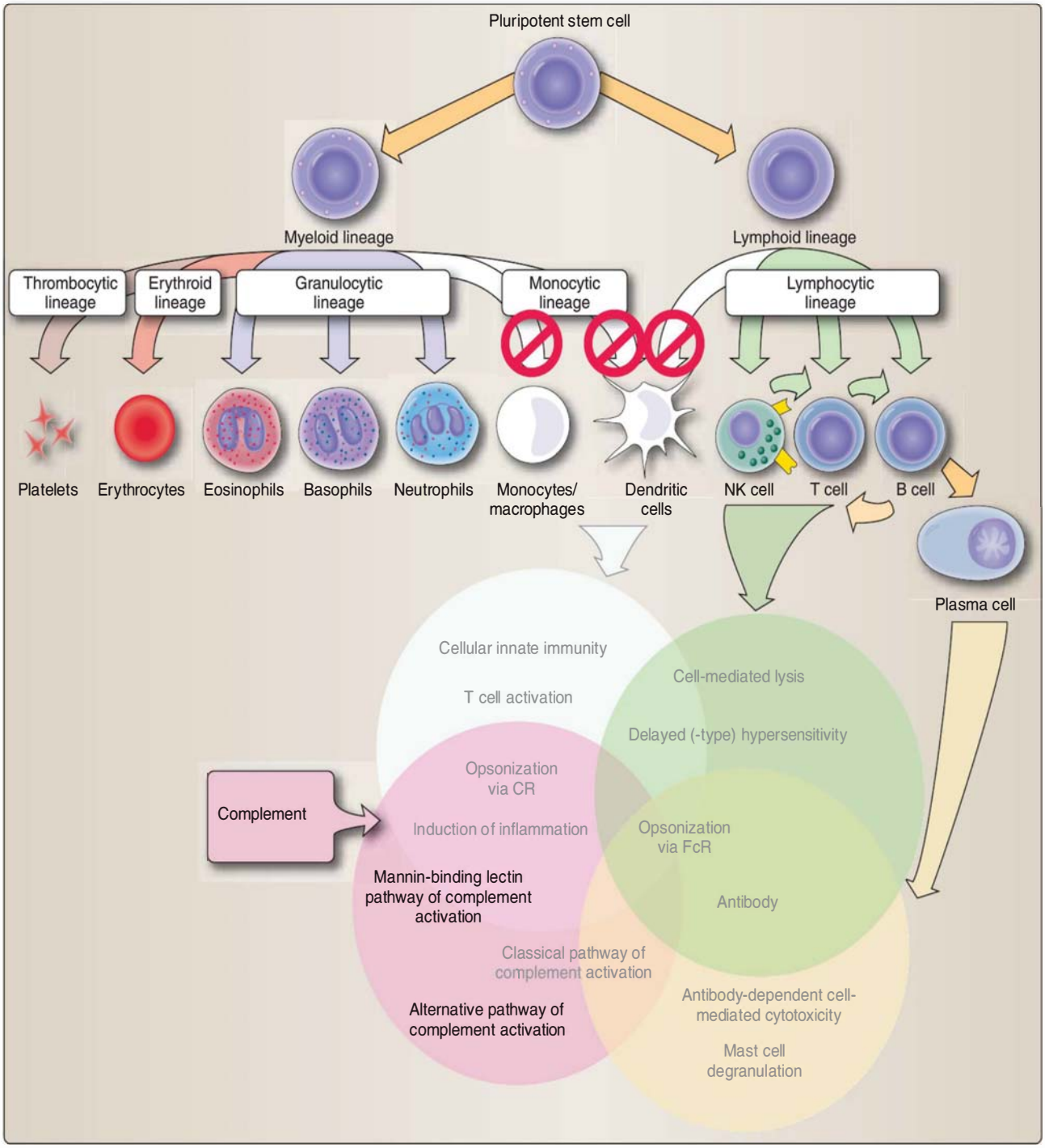

Figure 15.5

Effects of phagocytic cell and natural killer cell deficiencies. Defects in phagocytic cells reduce the ability to ingest and degrade microbes and to engage in antigen presentation to T cells. Defective NK cells have reduced ability to kill virally infected cells and participate in development of Th1 immune responses.

Table 15.4
PRIMARY IMMUNE DEFICIENCY DISEASES ATTRIBUTABLE TO DEFECTS IN ACCESSORY CELLS

Disease	Inheritance	Gene Locus	Chromosome	Consequences
Chediak–Higashi syndrome	Autosomal-recessive	*LYST* (lysosomal trafficking regulator; also called CHS1)	1	Increased susceptibility to infection by pyogenic bacteria; defective fusion of lysosomes and phagosomes because of defect in organelle membranes; reduced ability to kill ingested microbes; decreased NK and T-cell functions; frequent albinism of eyes and skin and other defects of organelle membranes; giant granules in neutrophils and other cells
Chronic granulomatous disease (CGD)	X-linked recessive	*CYBB* (β chain of cytochrome b; also called gp91phox)	X	Increased susceptibility to infection, especially *Staphylococcus aureus, Salmonella enteric, S. typhimurium, Serratia marcescens*; macrophages and neutrophils affected; unable to produce superoxide metabolites
	Autosomal-recessive	*NCF1* (p47phox)	7	Increased susceptibility to infection; unable to produce superoxide metabolites for killing of ingested microbes; macrophages and neutrophils affected; NCF1 and NCF2 encode components of the NADPH oxidase complex; CYBA encodes the α chain of cytochrome b
		NCF2 (p67phox)	1	
		CYBA (p22phox)	16	
IFN-γ receptor deficiency	Autosomal-recessive	*IFNGR1* (IFN-γ receptor)	6	High susceptibility to mycobacterial infections; macrophages, neutrophils, NK cells, and Th1 cells are affected
Leukocyte adhesion defect 1 (LAD-1)	Autosomal-recessive	*ITGB2* (also known as CD18)	21	Increased susceptibility to recurrent infection by bacteria; frequent nonresolving abscesses; defective chemotaxis and adherence to endothelial surfaces by macrophages, neutrophils, and NK cells
Leukocyte adhesion defect 2 (LAD-2)	Autosomal-recessive	*GDP-fucose transporter 1*	11	Increased susceptibility to recurrent infection by bacteria and nonresolving abscesses; impaired synthesis of CD15s, a carbohydrate adhesion molecule; defects in ability of leukocytes to adhere to endothelial surfaces; reduced ability of leukocytes to move from vasculature into tissues; also causes Bombay blood group phenotype

microcidal molecules) with phagosomes (containing the ingested microbes). Consequently, the phagocytes fail to destroy ingested microbes. Defects in receptors (e.g., pattern recognition receptors, IFN-γ receptors) used by phagocytic cells to respond to external activation signals can also leave the affected individuals susceptible to bacterial infections.

A second group of defects (e.g., **leukocyte adhesion defect 1** [**LAD-1**] and **LAD-2** deficiencies) inhibit accessory cell function, including the ability of these cells to migrate and interact with other types of cells. For example, some leukocytes must interact with vascular endothelium to move from the vasculature into the tissues. Leukocytes of affected individuals may be unable to migrate to the organs in which lymphocyte activation occurs and to sites of infections, where they are needed to destroy and clear the infectious agents.

E. Defects in the complement system

Deficiencies in the complement system can affect both innate and adaptive immune responses (Fig. 15.6, Table 15.5). Numerous gene defects involving complement components and regulatory molecules increase susceptibility to infection and sometimes to the risk of autoimmune disorders as well. In general, defects in

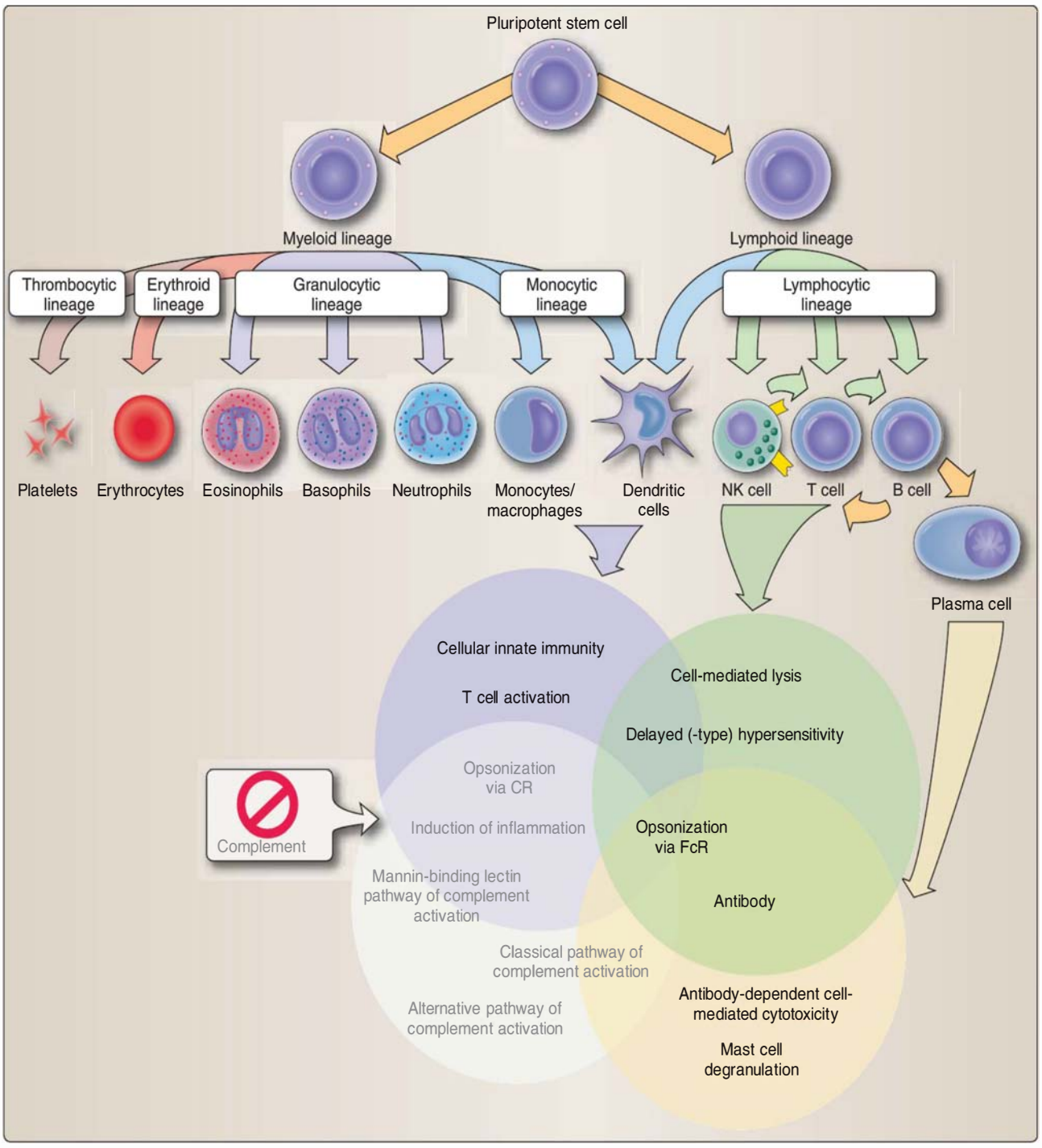

Figure 15.6
Effects of complement system deficiencies. Defective complement components can impair opsonization, lytic killing of microbes (via the membrane attack complex), and the ability to induce inflammation. Defects in regulatory components can lead to uncontrolled episodes of inflammation.

Table 15.5
PRIMARY IMMUNE DEFICIENCY DISEASES ATTRIBUTABLE TO DEFECTS IN THE COMPLEMENT SYSTEM

Disease	Inheritance	Gene Locus	Chromosome	Consequences
C1q, C1r deficiency	Autosomal-recessive	*C1QA*, *C1QB*, *C1QC* (A, B, and C chains of C1q)	1	Increased incidence of infections; systemic lupus erythematosus (SLE) -like syndromes (type III hypersensitivities; see Chapter 8); impaired removal of immune complexes
		C1R or *C1S* (C1r and C1s)	12	
C2 deficiency	Autosomal-recessive	*C2*	6	SLE-like syndromes; vasculitis; impaired removal of immune complexes
C3 deficiency	Autosomal-recessive	*C3*	19	Recurrent pyogenic infections; impaired opsonization
C4 deficiency	Autosomal-recessive	*C4*	6	Increased incidence of infections; SLE-like syndromes; impaired removal of immune complexes
C5, C6, C7 deficiency	Autosomal-recessive	*C5*, *C6*, or *C7*	9, 5, or 5	Increased susceptibility to *Neisseria*; unable to form membrane attack complex; SLE-like syndromes
C8 deficiency	Autosomal-recessive	*C8A* or *C8B* (α, β, CD8 chains)	2	Increased susceptibility to *Neisseria*; unable to form membrane attack complex; SLE-like syndromes
C9 deficiency	Autosomal-recessive	*C9*	5	Increased susceptibility to *Neisseria*; unable to form membrane attack complex
Factor H deficiency	Autosomal-recessive	*CFH* (*Factor H gene*)	1	Recurrent pyogenic infections; increased activation of alternative pathway
Factor P (Properdin) deficiency	X-linked recessive	*PFC* (properdin factor, complement)	X	Increased susceptibility to infection, particularly by *Neisseria* spp.; impaired alternative pathway; reduced stability of C3bBb convertase on microbial surfaces
Hereditary angioedema	Autosomal-dominant	*SERPING1* (C1 inhibitor)	11	Excessive spontaneous activation of classical complement pathway (especially C2) causing local inflammation; swelling of tracheal and bronchial passages that can be life threatening
Paroxysmal nocturnal hemoglobinuria	X-linked recessive	*PIGA* (phosphatidylinositol glycan)	X	Impaired synthesis of phosphatidylinositol glycan (PIG); absence of PIG prevents fixation of DAF and CD59 to the host cell membrane; unable to break down complement complexes on the host cell; excessive lysis of erythrocytes

the alternative pathway and mannan-binding lectin (MBL) pathways lead to increased susceptibility to infection. Defects in the classical pathway (except for C3) are not associated with significantly increased susceptibility to infection except for those caused by encapsulated bacteria. In these infections, antibodies, complement, and neutrophils are all required simultaneously to opsonize and kill these bacteria. **C3 deficiency** results in severe problems with recurrent infection and with immune complex-mediated disease because of the central position of C3 in all three of the complement activation pathways.

The MBL and alternative pathways are able to generate sufficient complement-mediated protection against infection, even in the absence of the classical pathway. Deficiencies in the components of the alternative pathway (e.g., C3, B, D) are associated with increased

susceptibility to infection. Deficiencies in C1, C2, and C4 can lead to inefficient clearance of immune complexes, increasing the risk of type III hypersensitivity diseases and injury to kidneys, joints, skin, and blood vessels (see Chapter 14).

Deficiencies in regulatory complement components can also cause disease. The most common is **hereditary angioedema** (or **hereditary angioneurotic edema**), in which reduced levels of C1 inhibitor reduce the ability to control activation of the classical pathway. As a result, uncontrolled inflammatory episodes occur that can become serious when the vascular system, respiratory tract, and GI tract are affected. Deficiencies in **decay accelerating factor** (**DAF**) or **CD59** allow accumulation of complement complexes, including the membrane attack complex, on host cell membranes with ensuing cell injury.

III. SECONDARY (ACQUIRED) IMMUNE DEFICIENCIES

Some immunodeficiency diseases arise not from genetic or developmental causes but from environmental exposures. These diseases are called **secondary immune deficiencies**. They may occur at any time of life, depending on when exposure occurs (Table 15.6). Among the environmental factors that can induce immune deficiencies are therapeutic treatments, infections, malignancy, and general health.

A. Physiologic sequelae

Many factors that affect the overall health of the body can impair immune function. Stress, for example, has been associated not only with reduced general health, but also with impaired immune function. Among the most investigated of these environmental factors is nutrition. Malnutrition has been shown to diminish the immune system's ability to protect against infection. In some cases, reduced levels of specific dietary components have been shown to play a role in immunodeficiency. The amino acid glutamine, for example, is critical for normal levels of energy metabolism, and shortages of certain minerals and vitamins have been implicated in reduced immune function. Various reports indicate that reduced levels of iron, zinc, selenium, and vitamins A, B6, C, and E are also associated with impaired immune function.

B. Therapeutic treatment

A normal individual's immune system may become suppressed, either intentionally or as a side effect of medical treatment (see Chapter 18). Transplant recipients usually undergo treatment to inhibit their immune responsiveness, at least for a period of time (see Table 15.6), to heighten the chances of survival for the grafted tissue. During this treatment (and sometimes afterward), transplant recipients have a heightened susceptibility to **opportunistic infection** and must be monitored and treated to avoid the onset of overwhelming infection.

Table 15.6
SOURCES OF SECONDARY IMMUNE DEFICIENCY

Cause	Examples	Mechanisms
Physiologic sequelae	General malnutrition	High impact on functions with high energy requirements
	Energy metabolism	Deficiencies of amino acids crucial for energy metabolism
	Trace metal deficiencies	Deficiencies of critical cofactors
	Vitamin deficiencies	Deficiencies of critical cofactors
Therapeutic treatment	Ionizing radiation	Damages replicating cells; induces oxidative stress
	Cytotoxic drugs (including many used for cancer treatment)	Damage/kill replicating cells
	Anti-inflammatory drugs (e.g., corticosteroids)	Interfere with production of some cytokines
	Immunosuppressive drugs (e.g., cyclosporine, tacrolimus, rapamycin)	Interfere with production of some cytokines
Infection	Human immunodeficiency virus (HIV)	Kills $CD4^+$ T cells, monocytes, and even $CD8^+$ T cells; the viral *nef* gene product also redirects pMHC I molecules from the cell surface and into lysosomes where they are degraded
	Epstein-Barr virus	Produces analog of interleukin-10
	Schistosoma	Secretes enzymes capable of cleaving immunoglobulins
	Herpesvirus	Inhibits MHC class I maturation within the endoplasmic reticulum
	Human cytomegalovirus (HCMV)	Interferes with transport of peptides into ER through TAP; redirects MHC class I molecules into cytoplasm rather than to cell surface
	Chlamydia	Interferes with phagocytic function by preventing fusion of phagosomes and lysosomes
	Staphylococcus	Produces toxin that kills phagocytic cells; produces protein that interferes with FcR-driven opsonization
	Yersinia	Produces toxin that kills phagocytes
	Streptococcus	Produces toxin that kills phagocytes
	Mycobacterium	Produces toxin that kills phagocytes; inhibits acidification within phagosomes by preventing fusion with lysosomes; inhibits oxidative degradation within phagosomes
	Salmonella	Inhibits oxidative degradation within phagosomes
	Leishmania	Inhibits oxidative degradation within phagosomes
Cancer	Multiple myeloma	Increasingly oligoclonal immune response
	Burkitt lymphoma	Epstein-Barr virus (causative agent) produces an analog of IL-10
	Waldenström macroglobulinemia	Excessive production of immunoglobulins; increased blood viscosity
	Chronic lymphocytic leukemia (CLL)	Reduced production of immunoglobulins
	Small lymphocytic lymphoma (SLL)	Reduced production of immunoglobulins

Similarly, individuals with autoimmune diseases (see Chapters 16 and 18) may be treated with agents that diminish the immune responses that are causing their problems, but again, such treatment often leaves them more susceptible to opportunistic infection. Treatments aimed at other medical problems, such as cancer therapy, also injure the immune system as they are directed at cells undergoing rapid division.

C. Infection

As was discussed in Chapter 13, many infectious organisms circumvent or evade immune responses generated against them. In

many cases, these evasive tactics leave the host more susceptible to other infectious agents as well. For example, some bacteria secrete enzymes that destroy local immunoglobulins and complement components. Some bacteria and viruses protect themselves after ingestion by phagocytes by inhibition of several key phagocyte activities: fusion of phagosomes with lysosomes, synthesis and release of microcidal molecules, and presentation of peptides by MHC class I (pMHC I) molecules. Yet other microbes (e.g., *Plasmodium*) evade the immune system by living within cells such as erythrocytes that express neither MHC class I nor II molecules on their surfaces. As a result, T cells cannot detect whether such cells are infected or not. Finally, some infectious organisms influence the entry of naive T cells into either the Th1 or Th2 pathways, whichever is least effective for clearance of those particular microbes.

HIV (**human immunodeficiency virus**) destroys $CD4^+$ T cells, leading to **acquired immune deficiency syndrome** (**AIDS**). HIV can also infect and kill monocytes and even $CD8^+$ T cells as the infection progresses. Because $CD4^+$ T cells are so central to the development of numerous immune responses, their progressive loss produces a gradual decline in humoral and cellular responses and an increasing susceptibility to opportunistic infection that eventually becomes fatal.

In 2009, an estimated 33.3 million people were living with HIV/AIDS worldwide, most in sub-Saharan Africa. According to the Joint United Nations Programme on HIV/AIDS 2009 report, some 60 million people worldwide have been infected with HIV, and 25 million have died of HIV-related causes since the epidemic began. Since the early 1990s, however, the number of new cases of AIDS- and HIV-related deaths has decreased significantly owing to effective antiviral therapies. These decreases have been most evident in the United States and Europe thus far (Fig. 15.7). The availability of antiviral therapy in other parts of the world has begun to improve, and there is hope that it will eventually provide similar benefit.

CLINICAL APPLICATION
HIV infection and AIDS

AIDS (acquired immune deficiency syndrome) is caused by HIV (human immunodeficiency virus). HIV is a retrovirus that damages the cells of the body's immune system. People with HIV may develop opportunistic infections and various forms of cancer. The Centers for Disease Control and Prevention CDC) defines AIDS as laboratory confirmation of HIV infection and $CD4^+$ T cell count of 200 cell/mL; or $CD4^+$ T cell percentage of <14; or documentation of an AIDS-defining condition (with laboratory confirmation of HIV infection). Among the AIDS-defining conditions are candidiasis of the esophagus, cryptococcosis (extrapulmonary), histoplasmosis (disseminated or extrapulmonary), *Pneumocystis jirovecii* pneumonia, and *Mycobacterium tuberculosis* infection of any site.

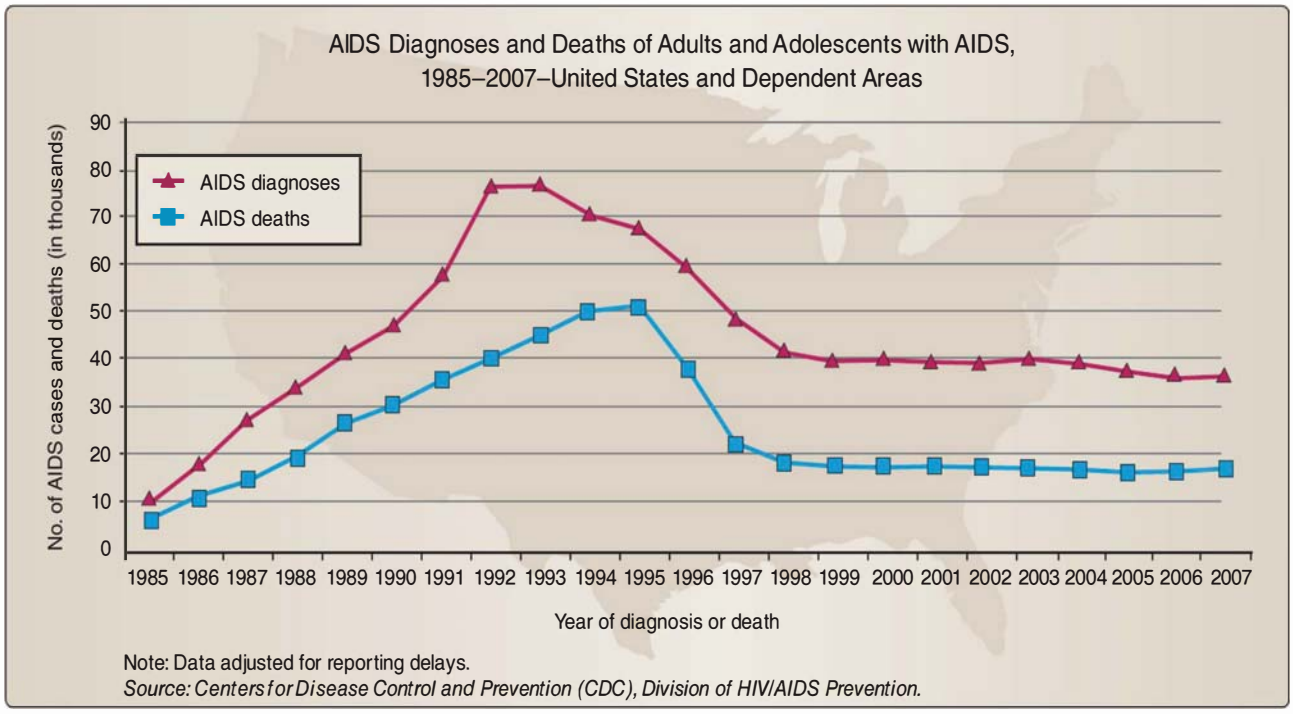

Figure 15.7
Impact of HIV/AIDS in the USA. Although the number of persons with HIV/AIDS has continued to increase in the USA, the availability of antiviral treatment is associated with deceases in the number of new cases and the numbers of deaths.

The CD4 molecule expressed on subsets of human T cells, dendritic cells, and macrophages is the major means by which HIV binds and enters cells. However, it also uses two chemokine receptor molecules as coreceptors for the two types of cells that are preferentially infected: CCR5 on macrophages and dendritic cells and CXCR4 on lymphocytes (Fig. 15.8). In the absence of these coreceptors, HIV is unable to successfully enter the cells. A small percentage of individuals of Caucasian descent fail to express CCR5 and are protected from infection by HIV. Infection of $CD4^+$ $CCR5^+$ dendritic cells appears to be the primary route of initial infections; infection of $CD4^+$ $CXCR4^+$ T cells occurs later in the disease process.

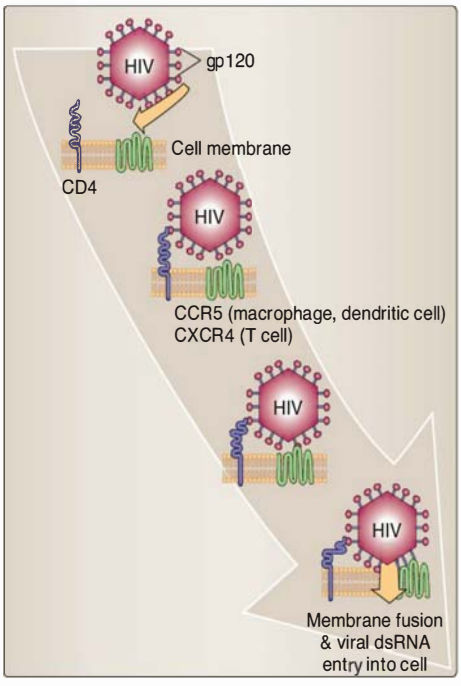

Figure 15.8
Coreceptors for cell infection by HIV. In addition to the CD4 molecule, HIV requires either CCR5 or CXCR4 to successfully enter and infect a cell.

D. Cancer

Cancerous lymphocytes reduce the immune system's ability to respond to different antigens by overgrowing the rest of the lymphocyte population. As a result, the immune repertoire becomes limited as it is dominated by fewer and fewer clones of lymphocytes. Lymphocytes and other monocytes that become malignant (**lymphomas** and **leukemias**) can begin to crowd out the ability of normal hematopoietic cells to maintain proper levels. They often also begin to display aberrant surface molecules and alter their normal production of cytokines, antibodies, and other molecules. As a result, they can induce immune deficiencies by abnormal interactions with other parts of the immune system. In one interesting example, individuals with **Waldenström macroglobulinemia** secrete such excessive amounts of immunoglobulins that the viscosity of the blood is increased.

IV. TREATMENT OF IMMUNE DEFICIENCIES

Several methods have been used to attempt restoration of deficient immune functions or to alleviate their consequences. Some provide only temporary benefits and must be regularly repeated, whereas other approaches carry the potential for permanent cure.

A. Passive supplementation

The passive administration or supplementation of deficient components can often be beneficial, although the benefits are usually temporary. Injection of **intravenous immunoglobulin**, for example, provides exogenous antibodies that boost insufficient intrinsic immunoglobulin levels. Cytokines or even enzymes (e.g., in patients with adenosine deaminase deficiency) can also be administered passively. Passive therapies must be repeated at regular intervals, however, because the injected cells or molecules have finite half-lives. In some cases, even cells can be passively transferred for temporary effect.

B. Bone marrow transplantation

For long-term or permanent deficiencies, passive administration may be effective but requires constant repetition. In some cases, there may also be a risk of serum sickness. Replacement by engineered stem cells may provide a means to a permanent cure. A bone marrow transplant from a suitable donor currently offers the most effective means of replacing a damaged immune system. The requisite stem cells for lymphocytes, phagocytes, neutrophils, eosinophils, mast cells, and basophils are all present in the transferred bone marrow. Except for conditions in which immune deficiencies arise from sources outside of the hematopoietic system (e.g., DiGeorge syndrome), replacement of an immunodeficient patient's bone marrow with marrow from a normal donor should provide a permanent source of normal immune components.

Because bone marrow transplantation involves placement of immunocompetent tissues into immunoincompetent recipients, it is possible for the transplanted tissue to react against the recipient. Mature, immunocompetent T cells present in the transplanted marrow might view the recipient as nonself and attack the host cells (**graft-versus-host disease**) unless they are carefully removed prior to the transfer (see Chapter 17). Bone marrow transplantation has become increasingly effective as the techniques involved have been refined.

C. Genetic engineering

Advances in genetic engineering have permitted replacement of defective cells with "repaired" cells. An individual's defective cells are removed, engineered in vitro to replace defective genes with functional ones, and inserted into back into the patient. However, numerous procedural difficulties have limited the use of this technique. First, unless the repaired cells are stem cells, the procedure constitutes passive therapy and will have to be repeated as the injected cells die. Second, once injected, the engineered cells must be able to migrate properly

to the sites where they can grow and develop normally. Third, the "repaired" genes must be appropriately regulated and expressed, and the engineered cells must respond appropriately to signals affecting the expression and secretion of the new gene products. Finally, one must consider the risk that the engineering might lead to a malignant transformation or some other aberrant behavior in the engineered cell population.

Several successful attempts to treat immune deficiencies have been performed at the National Institutes of Health involving patients suffering from ADA deficiency, and in some cases, the engineering involved stem cells. Although many of these patients have received considerable benefit, full functional replacement of sufficient numbers of stem cells has not yet been achieved, and the patients continue to receive periodic passive administration of engineered cells. It is hoped that continued research will improve the efficacy of these procedures.

Chapter Summary

- **Primary immune deficiencies** are caused by intrinsic genetic or congenital defects. More than 100 primary immunodeficiency diseases are known in humans, and the specific defective genes are known for many of them. Defects causing primary immune deficiencies occur in various cell lineages, affecting different sets of cells/molecules.
- **Secondary immune deficiencies** are caused by environmental factors such as infection, therapeutic treatments, cancer, and malnutrition. They may occur at any time of life, depending on when the exposure to the causative factor(s) occurs.
- **Severe combined immunodeficiency** (**SCID**) is caused by defects in the combined lymphocyte lineage that impair T- and B-cell functions. SCID is actually a group of diseases caused by different individual genetic defects (autosomal and X-linked) that have similar functional consequences.
- **TAP deficiency** is a condition in which defects in the transporter associated with the antigen presentation (TAP) system impair the loading of peptide fragments into nascent MHC class I molecules in all nucleated cells. As a result, the number of MHC class I molecules that successfully reach the cell surface is reduced.
- **DiGeorge syndrome** results from defects in thymic development that prevents normal development and thymic education of T cells. DiGeorge syndrome varies in the severity of effects and may be accompanied by abnormalities caused by abnormal development of embryologically related tissues: the aorta, the face and jaw, and the parathyroid glands.
- **X-linked (Bruton) agammaglobulinemia** is a recessive X-linked disorder resulting from a defective gene (*BTK*) that encodes Bruton tyrosine kinase, an enzyme crucial to the early development of B cells. B cells are reduced in number or absent.

- **Selective IgA deficiency** is the single most common immune deficiency disease, with a frequency estimated at one to two per thousand individuals.
- **Immune deficiency with hyper-IgM** results from a defect in the gene encoding the CD40 ligand (CD154). As a result, the isotype switch does not occur normally, and individuals with this defect produce high levels of IgM but are deficient in B cells that produce IgG, IgA, or IgE.
- Defects in several different genes causing **chronic granulomatous disease** (**CGD**) encode defective enzymes and other microcidal molecules (e.g., toxic oxygen metabolites) involved in destruction and degradation of ingested microbes.
- **Chediak–Higashi syndrome** results from an inability to fuse lysosomes (carrying enzymes and microcidal molecules) with phagosomes (containing ingested microbes).
- Some immunodeficiencies (e.g., **leukocyte adhesion defect 1** [**LAD-1**] and **LAD-2** deficiencies) arise from defects in molecules needed for leukocytes to migrate and interact with each other or other cell types.
- **Hereditary angioedema**, caused by reduced levels of C1 inhibitor, reduces the ability to control activation of the classical pathway.
- **HIV** (**human immunodeficiency virus**) destroys $CD4^+$ T cells, leading to **acquired immune deficiency syndrome** (**AIDS**).
- Injection of **intravenous immunoglobulin** provides exogenous antibodies that boost insufficient intrinsic immunoglobulin levels.
- For long-term or permanent deficiencies, replacement of an immunodeficient patient's bone marrow with marrow from a normal donor may provide a permanent restoration of immune function. The requisite stem cells for lymphocytes, phagocytes, neutrophils, eosinophils, mast cells, and basophils are all present in the donated bone marrow.

Study Questions

15.1. A 2-month-old male infant presents with persistent diarrhea, signs and symptoms of *Pneumocystis carinii* pneumonia, and an oral fungal infection with *Candida albicans*. His weight is in the 10th percentile. Test results for HIV are negative by polymerase chain reaction. The most likely cause of these findings is

A. grossly reduced levels of B cells.
B. an X-linked inheritance of HLA genes.
C. defective isotype switching.
D. defective T-cell function.
E. selective IgA deficiency.

The correct answer is D. The fungal infection is highly suggestive of a T-cell defect. Choices A, C, and E do not of themselves imply a deficiency in T-cell function. HLA genes are autosomal, not X-linked.

15.2. A 5-year-old girl has a small deletion in chromosome 22. She has impaired thymus development with a significant deficiency in the number of functional T cells. The most likely etiology for these findings is

A. adenosine deaminase (ADA) deficiency.
B. Chediak–Higashi syndrome.
C. DiGeorge syndrome.
D. hereditary angioedema.
E. severe combined immunodeficiency (SCID).

The correct answer is C. Impaired thymic development leading to T-cell dysfunction and small deletions in chromosome 22 are characteristic of DiGeorge syndrome. Thymic development is normal in all of the other choices.

15.3. A 3-year-old boy with an X-linked defect in the Bruton tyrosine kinase (BTK) gene is impaired in which of the following mechanisms?

A. Antibody-mediated bacterial clearance
B. Formation of the membrane attack complex
C. Delayed (-type) hypersensitivity (DTH) responses
D. IFN-γ secretion by $CD4^+$ T cells
E. T-cell precursor migration to the thymus

The correct answer is A. Bruton agammaglobulinemia results in a near or total absence of B cells and immunoglobulins; hence antibody-mediated responses to microbes are severely impaired. Even in the absence of antibodies and the classical pathway of complement activation, the membrane attack complex can be generated through the MBL and alternative pathways. Antibodies are not involved in the other choices.

15.4. A 6-month-old male infant has diarrhea, extensive fungal infections, and skin rashes and has failed to gain weight. He is deficient in both T- and B-cell function. The thymus is of normal size. The most likely prospect for permanent restoration of normal immunity for this patient would be

A. an antibiotic "cocktail" given at regular intervals.
B. bone marrow transplantation.
C. exogenous immunoglobulins administered periodically.
D. isolation to an antiseptic environment.
E. thymic hormones given throughout his life.

The correct answer is B. The signs suggest a defect in the lymphocytic lineage. This could potentially be permanently alleviated by replacement of defective stem cells through bone marrow transplantation. Isolation is beneficial but is a severe imposition on the quality of life and constitutes protection rather than restoration of function. The remaining choices require constant repetitive application but not permanent restoration of function.

15.5. A female neonate has a malformed jaw, cardiac abnormalities, and hypocalcemia, in addition to diminished cell-mediated and B-cell responses. Which of the following immune deficiencies should be included in the differential diagnosis of this patient?

A. Adenosine deaminase (ADA) deficiency
B. DiGeorge syndrome
C. Hereditary angioedema
D. Severe combine immunodeficiency disease (SCID)
E. Wiskott–Aldrich syndrome

The correct answer is B. The defects in jaw and cardiac structure and the defective calcium metabolism (because of abnormal parathyroid development) point to aberrant development of structures derived from the third and fourth pharyngeal pouches. None of the other diseases given are associated with these accompanying features. This individual is likely to also include the thymus, and this patient is likely to have an underdeveloped thymus, which is a hallmark of DiGeorge syndrome.

15.6. A 21-year-old woman has a history since childhood of recurrent episodes of swelling of the submucosal and subcutaneous tissue of the gastrointestinal and respiratory tracts. Her C1 inhibitor level is less than 5% of the reference value. These findings support a diagnosis of

A. DiGeorge syndrome.
B. hereditary angioedema.
C. nutrition-based immune deficiency.
D. paroxysmal nocturnal hemoglobinuria.
E. Wiskott–Aldrich syndrome.

The correct answer is B. Hereditary angioedema is caused by deficient levels of C1 inhibitor. DiGeorge syndrome is caused by aberrant development of the thymus. Nutrition-based immunodeficiencies are not characteristically identified by severely reduced levels of specific cell types or related molecules. Paroxysmal nocturnal hemoglobinuria is caused by a deficiency of CD59, and Wiskott–Aldrich syndrome is caused by a deficiency of the Wiskott–Aldrich syndrome protein.

15.7. A 3-month-old male infant has recurrent infections and is found to have an impaired ability to kill microbes by the nitroblue tetrazolium test (which evaluates effectiveness of degradative enzymes). Which of the following conditions is most likely responsible for the findings in this patient?

A. Chediak–Higashi syndrome
B. Chronic granulomatous disease
C. Hereditary angioedema
D. HIV/AIDS
E. Waldenström macroglobulinemia

The correct answer is B. Chronic granulomatous disease is caused by defects in various degradative enzymes or other molecules involved in the oxidative burst. Chediak–Higashi syndrome is caused by an inability to fuse lysosomes with phagosomes. HIV/AIDS results from progressive destruction of $CD4^+$ T cells. Although HIV can infect macrophages and dendritic cells, they remain capable of normal phagolysosome function. Hereditary angioedema results from a deficiency in C1 inhibitor, and Waldenström macroglobulinemia is caused by excessive production of IgM.

15.8. A 24-year-old male presents with fever, cough, and night sweats. Examination reveals an elevated temperature, increased respiratory rate, oral thrush (fungal infection), and decreased breath sounds in the right midlung field. Laboratory testing reveals a CD4 count of 60/mL (reference range: 400/mL). On the basis of these findings, the most likely underlying process is

A. autoimmune disease with pneumonia.
B. bacterial pneumonia.
C. HIV/AIDS with possible mycobacterium tuberculosis.
D. hypersensitivity pneumonitis.
E. *Mycobacterium tuberculosis* infection only.

The correct answer is C. The key feature is the extreme deficiency of $CD4^+$ T cells that is characteristic of HIV/AIDS. None of the other choices would be associated with this finding. Respiratory difficulties caused by *Mycobacterium tuberculosis* infection are frequently seen in HIV/AIDS patients.

16 Autoimmunity

I. OVERVIEW

The innate immune system relies on a set of "hard-wired" genetically encoded receptors that have evolved to distinguish self from nonself. The adaptive immune system faces a much greater challenge in making such distinctions. The B-cell receptors (BCRs) and T-cell receptors (TCRs) of the adaptive immune system are randomly generated within each individual, without prior knowledge of the epitopes that may be encountered. As a result, some BCRs and TCRs recognize nonself and others recognize self. Several mechanisms are used to identify and control or eliminate cells that are potentially self-reactive. The failure of these mechanisms to inactivate or eliminate self-reactive cells leads to **autoimmunity**.

Rheumatoid arthritis, type 1 diabetes mellitus, multiple sclerosis, psoriasis, and systemic lupus erythematosus (SLE), to name only a few, are autoimmune diseases. Autoimmunity is complex. It may arise by different mechanisms, and its risk is affected by various environmental and genetic factors, many of which are as yet unidentified. Together, however, these various influences contribute to a breakdown in self-tolerance, that is, the ability of the immune system to effectively distinguish self from nonself and to refrain from attacking self.

II. SELF-TOLERANCE

Tolerance is the failure of the immune system to respond to an epitope in an aggressive way. Most **self-tolerance** results from the deliberate inactivation or destruction of lymphocytes bearing BCRs or TCRs that recognize and bind self-epitopes. Inactivation or destruction may occur during early development (central tolerance) or may be imposed on lymphocytes in the periphery (peripheral tolerance). An understanding of how the immune system naturally imposes self-tolerance can provide critical clues for the development of therapeutic strategies for autoimmune diseases caused by the loss of self-tolerance.

A. Central tolerance

Central tolerance occurs during the early differentiation of B cells in the bone marrow and T cells in the thymus. Normally, both B and T cells that bind self-epitopes at distinct early stages of development meet an apoptotic death, thus eliminating large numbers of potentially self-reactive cells before they enter the circulation (see Chapter 9).

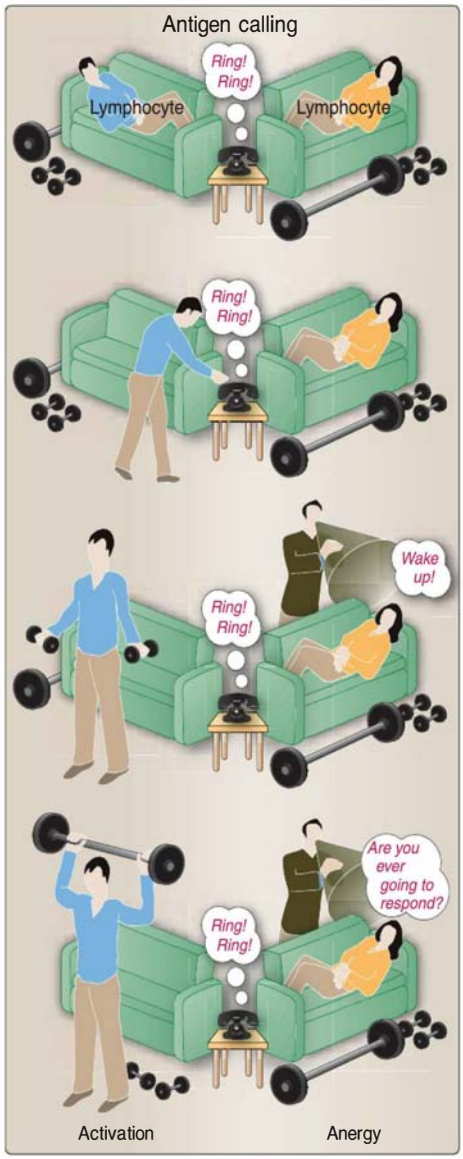

Figure 16.1
Anergy. Binding of antigen (for B cells) or pMHC (for T cells) can initiate either activation or anergy in lymphocytes.

B cells express surface IgM as their BCRs. Epitope recognition by BCRs of developing B cells within the bone marrow triggers their apoptotic death, a process known as **negative selection**. Likewise, the binding of peptide-MHC complex (pMHC I or pMHC II) by TCRs of single positive ($CD4^+CD8^-$ or $CD4^-CD8^+$) thymocytes causes them to undergo apoptotic death. This process removes many potentially autoreactive B and T cells before they enter the periphery (see Fig. 9.1). A major caveat imposed on central tolerance is that not all self-epitopes are to be found in the primary lymphoid organs, especially those self-epitopes that arise after lymphogenesis, such as those that arise during puberty. Other means are needed to prevent the autoreactive cells among them from inflicting damage on the body.

B. Peripheral tolerance

Several additional mechanisms, collectively called **peripheral tolerance**, control or eliminate autoreactive B and T cells after they exit the bone marrow or thymus. One such mechanism is the induction of **anergy**, a state of nonresponsiveness in lymphocytes after their receptors bind antigen (B cell) or pMHC (T cell) (Fig. 16.1 provides a whimsical view of anergy). Another mechanism is **suppression**, whereby regulatory cells inhibit the activity of other cells.

1. **Anergy:** Binding of TCRs to an appropriate pMHC I or pMHC II on the surface of antigen-presenting cells (APCs) provides the first signal for activation of T cells, but T cells must also receive second signals from the APCs (cytokines, etc.) for activation to proceed (see Chapter 10). Naive $CD8^+$ T cells may recognize and bind to self-pMHC I on non-APCs as well as on APCs. In binding to non-APCs, engagement of their TCRs with pMHC I provides the first signal, but no second signals. Receipt of the first signal in the absence of second signals causes naive T cells to enter a state of inactivity known as **anergy** (Fig. 16.2). So profound is this state that anergized $CD8^+$ T cells usually cannot be activated by subsequent encounters with both first and second signals. There are, however, circumstances in which anergy can be broken and self-reactive $CD8^+$ T cells can become activated, resulting in some autoimmune diseases. It is unclear whether $CD4^+$ T cells can or cannot be anergized by comparable mechanisms because almost all binding by TCRs of $CD4^+$ T cells occurs with pMHC II complexes on APCs.

   B cells can also undergo anergy. Some naive autoreactive B cells leave the bone marrow. Their subsequent activation in the lymph nodes requires interaction with T cells, providing the necessary soluble signals and surface ligands. Like naive $CD8^+$ T cells, naive B cells can be anergized if their surface immunoglobulins bind to self-antigens in the absence of the additional necessary T-cell signals.

2. **Suppression:** Tolerance to self-epitopes can also be induced by regulatory cells (Fig. 16.3). The molecular bases for these regulatory actions are still unclear, but in most cases, the regulatory cells are T cells (see Chapter 12). Examples include the following:
   - $CD4^+CD25^+$ T cells diminish the activity of T cells stimulated by various epitopes. They have been shown to have important roles

in preventing development of inflammatory diseases (e.g., inflammatory bowel disease).

- Some $CD8^+$ T cells are able to inhibit the activation and proliferation of $CD4^+$ T cells, including some that mediate autoreactive type IV hypersensitivity (DTH) responses.
- $CD8^+$ and $CD4^+$ T cell subpopulations have been demonstrated, in various models, to inhibit antibody production.

Autoimmune responses vary in the pathologies they induce, and this sometimes depends on the **Th1/Th2** balance in the responses (see Chapter 5) to a particular self-antigen. For example, a Th2 response to a particular self-epitope may produce little or no pathology, but a Th1 response may produce an injurious cell-mediated inflammatory response such as DTH. As a result, the overt autoimmune disease may be determined by the relative balance in Th1 and Th2 responses generated against the epitope, and factors that influence that balance may alter the risk. Such a situation exists in the intestinal mucosal immune system of the gut-associated lymphoid tissues (see Chapter 13). Here, intestinal epithelial cells and some intraepithelial lymphocytes produce anti-inflammatory Th2 cytokines (IL-4, IL-10, and TGF-β) that create a microenvironment promoting production of IgA antibodies and inhibiting inflammatory cellular responses. Changes that favor development of Th1-like cell-mediated inflammatory responses, perhaps triggered by pathogenic bacteria, may be the basis for autoimmune **inflammatory bowel diseases** such as **Crohn disease** and **ulcerative colitis**.

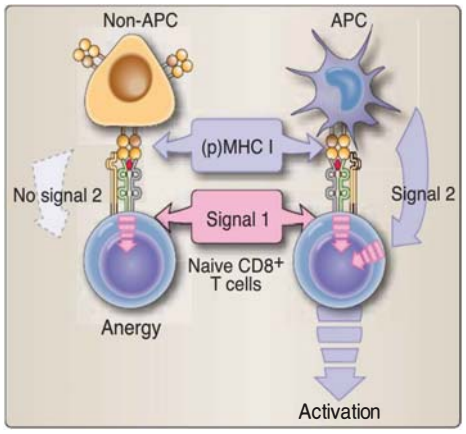

Figure 16.2
Induction of T-cell anergy by binding to non-APCs. Engagement of TCRs on naive $CD8^+$ T cells by binding to pMHC I on non-APCs provides the first signal for activation. T cells receiving signal 1 in the absence of signal 2 are anergized.

III. LOSS OF SELF-TOLERANCE

Despite the various mechanisms that are in place to prevent responses to self-epitopes, autoimmunity still occurs occasionally. How does this happen? What types of situations provide opportunities for self-reactive immune cells to escape the traps set for them and become free to attack the body's cells and tissues? There are, in fact, several different situations that make this possible.

A. Molecular mimicry

Infection is frequently associated with development of autoimmunity. Experimental evidence in vitro has shown that under certain circumstances, the addition of high levels of exogenous cytokines can cause the activation of naive T cells in the absence of interactions with APCs, and in some cases, even anergized T cells can be activated. Inflammation at sites of infection, originating with activated phagocytes responding to the presence of infectious agents, can generate elevated levels of proinflammatory cytokines that may mimic the effects seen in vitro. Within this setting, T cells recognizing self-epitopes may receive sufficient stimulation to become activated, even if they are not directly interacting with APCs (Fig. 16.4). Although this mechanism has yet to be definitively demonstrated in vivo, the tendency for the development of autoimmune diseases to follow episodes of infection is suggestive.

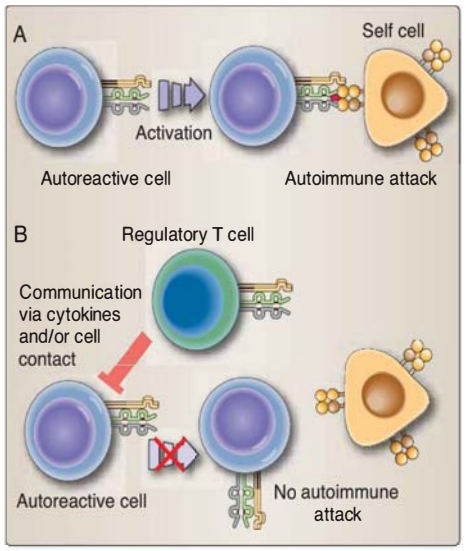

Figure 16.3
Regulatory cell inhibition. Regulatory cells (usually T cells) can prevent some responses by other lymphocytes. **A.** Autoreactive T cells that become activated can bind and attack host cells. **B.** Regulatory cells inhibit the activation of autoreactive cells and sometimes even of activated ones.

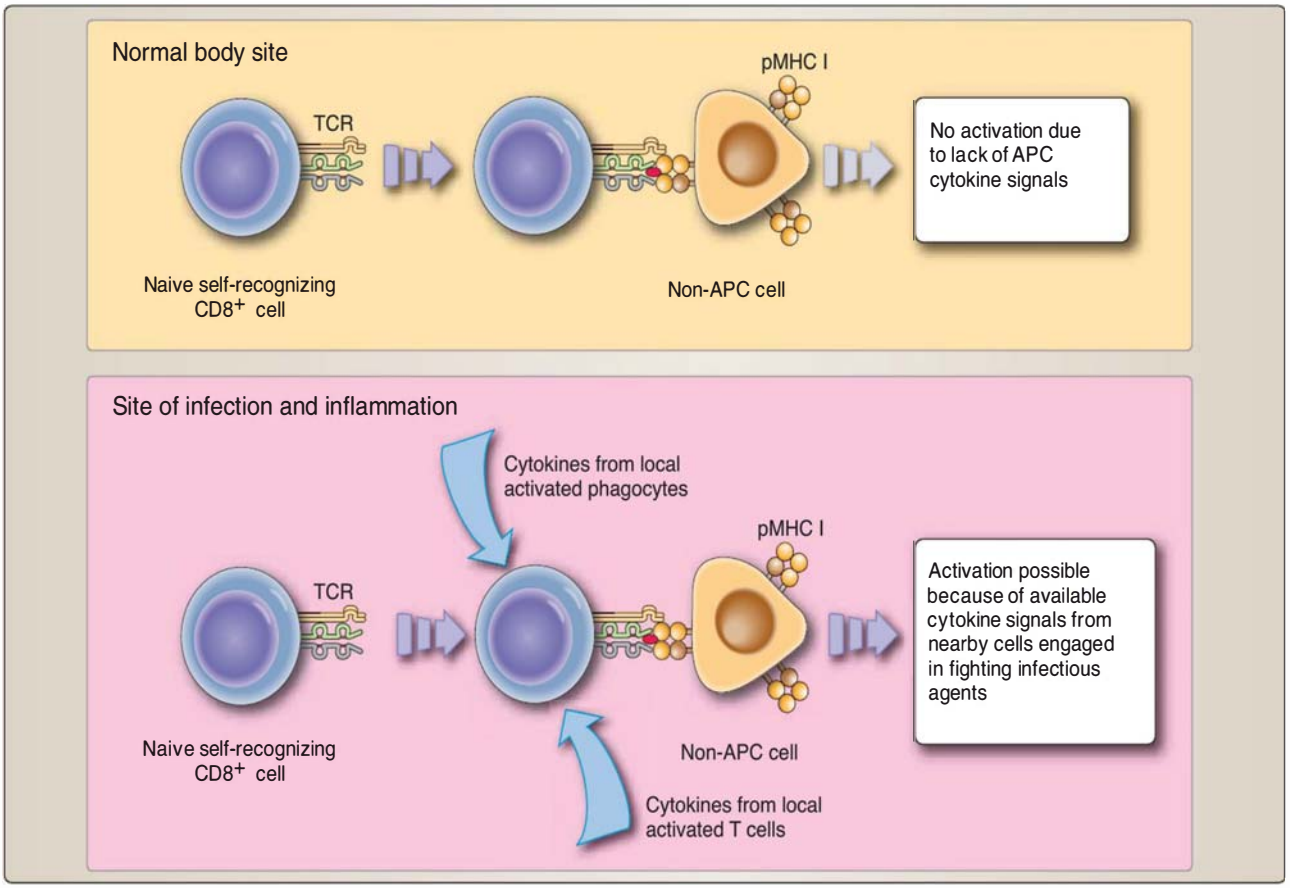

Figure 16.4
Inflammation and autoimmunity. Under normal circumstances, autoreactive cells in the body are not activated by contact with self-molecules. Unless they are interacting with APCs, they are not also receiving cytokine signals necessary for activation. However, in inflammatory sites, local cytokine levels may be sufficient to activate autoreactive T cells when they are binding to self-epitopes on non-APCs.

Molecular mimicry is a process in which infection by particular microbes is associated with the subsequent development of specific autoimmune diseases. The antigenic molecules on some infectious agents are similar enough to some host self-molecules that B- and T-cell responses generated against the microbial antigens can result in damage to host cells bearing similar molecules (Fig. 16.5). The best understood example of this process is the cardiac damage resulting from rheumatic fever after infection by *Streptococcus pyogenes* ("strep," the causative agent of strep throat) (Fig. 16.6). Group A β-hemolytic strains of *S. pyogenes* express high levels of an antigen known as the M protein, a molecule that shares some structural similarities with molecules found on the valves and membranes of the heart. If the levels of IgM and IgG generated against the M protein during infection reach sufficient levels, there may be sufficient binding to host cells to induce damage and reduced cardiac function. In addition to cardiac sites, antibodies against the M protein can also cross-react to some degree with molecules on host cells in the joints and kidneys. The accumulated damage to cardiac and other tissues may be fatal. It is therefore important that patients who present with sore throats be tested to determine whether strep is present and, if so, to

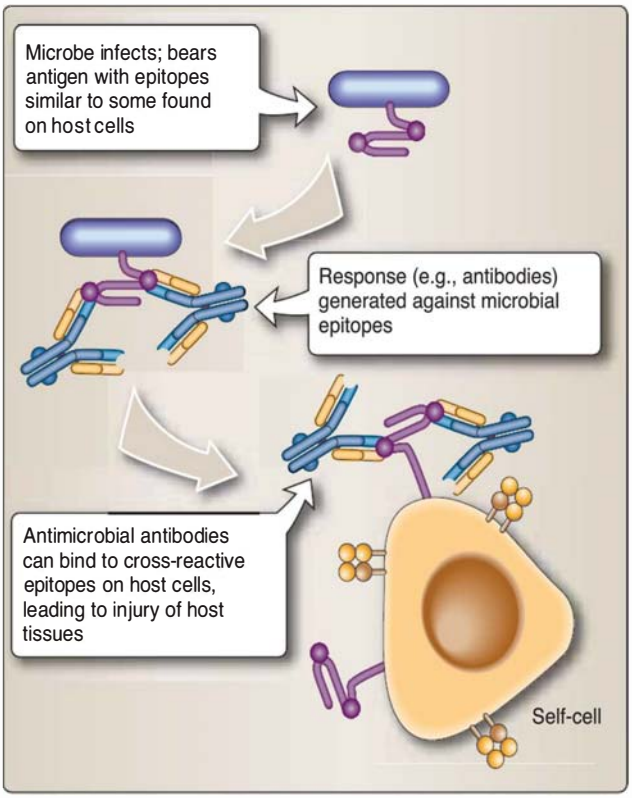

Figure 16.5
Molecular mimicry. Some microbial antigens bear epitopes that are similar to or identical to some epitopes on host molecules. Strong responses against the microbial epitopes can result in sufficient binding of host epitopes to produce immune-mediated injury.

begin antibiotic therapy to clear the infection before vigorous antibody responses against strep antigens can develop.

Molecular mimicry appears to be involved in several autoimmune diseases, including diabetes. Certain peptide fragments from Coxsackie virus and cytomegalovirus cross-react with glutamate decarboxylase, a major target of autoreactive T cells found in patients with type 1 diabetes. In addition, peptides from other several viruses (e.g., cytomegalovirus, measles, hepatitis C virus) are cross-reactive with phosphatase IA-2, an enzyme produced by the pancreatic β cells, and may provide the basis for some cases of diabetes.

An association with infectious organisms has been demonstrated for several autoimmune diseases. A group of inflammatory arthritic diseases known as **reactive arthritis** occur more frequently in individuals who have had food poisoning. Two of these diseases, **ankylosing spondylitis** (usually involving the lower spine) and **Reiter disease** (affecting the joints of the lower limbs and the gastrointestinal/genital/urinary tracts), have increased frequencies in individuals who carry the HLA-B27 gene and have been infected by *Klebsiella*. In fact, some structural similarities have been noted between the HLA-B27 molecule itself and certain proteins expressed by *Klebsiella*, suggesting a possible role for molecular mimicry. In addition, the acetylcholine

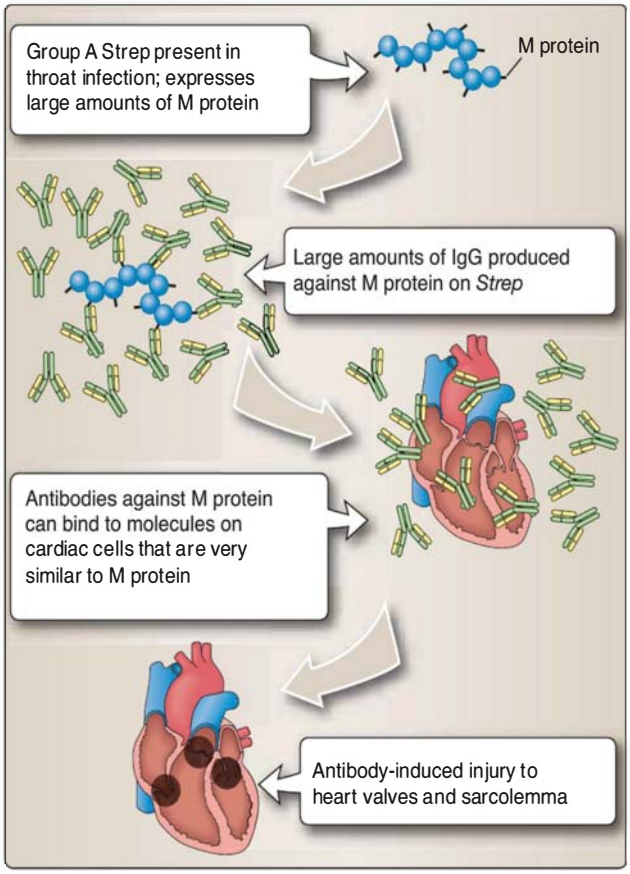

Figure 16.6
Association of cardiac damage and rheumatic fever. Rheumatic fever results from infection (usually of the throat) by Group A strep. High levels of antibodies can be generated against the bacterial M protein. IgG against M protein can cross-react with molecules on cardiac tissues that are highly cross-reactive with M protein. As a result, antibody-induced injury, especially to the valves and sarcolemma, can produce serious cardiac disease. Other tissues may also be affected.

receptor, the self-molecule that is targeted in autoimmune **myasthenia gravis**, shares some structural similarities with certain poliovirus proteins. As a whole, these data suggest that molecular mimicry could be an important factor in the generation of some autoimmune diseases.

B. Epitope spreading

Another phenomenon that may contribute to the influence of infectious organisms on autoimmunity is **epitope spreading**. The epitope that initiates a response leading to autoimmunity might not be the epitope that is targeted by immune responses that develop later during the pathogenesis of the disease. For example, initial responses against an infectious agent may result in damage that exposes self-epitopes in ways that subsequently trigger true autoimmune responses. In some animal models of human multiple sclerosis, responses to particular viral epitopes regularly precede the development of responses to specific epitopes associated with the myelin sheath that protects neuronal axons.

Additionally, the dominant self-epitope targeted by an autoimmune response does not necessarily remain constant over the course of the disease. In some experimental models of autoimmune diseases, in which a relapsing-remitting course of clinical signs may occur, these patterns may actually result from a series of independent responses generated against different self-epitopes rather than from alternating increased and decreased responses to a single epitope (Fig. 16.7). The possibility that the epitopes that initiate an autoimmune disease are different from those involved in the pathogenesis complicates attempts to devise therapies. Epitope spreading is suspected to play a role in several autoimmune diseases, including systemic lupus erythematosus, inflammatory bowel disease (Crohn disease and ulcerative colitis), multiple sclerosis, pemphigus vulgaris, and type 1 diabetes.

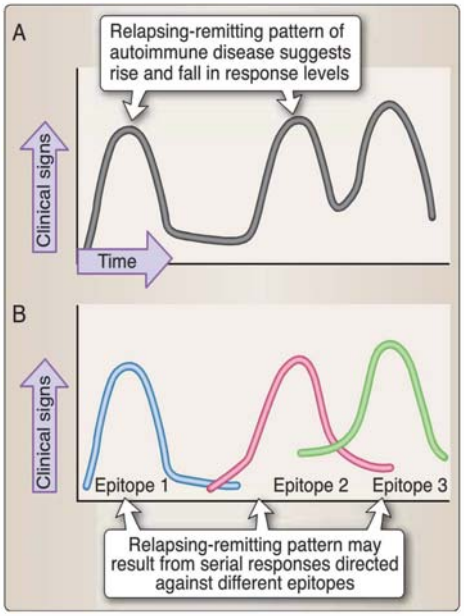

Figure 16.7
Association of autoimmune diseases with serial responses to different epitopes. **A.** Some autoimmune diseases have alternating periods of exacerbation and remission of clinical signs (relapsing-remitting pattern). **B.** In some models of human autoimmune disease, the relapsing phases of exacerbation have been shown to be caused by a series of newly generated responses to different epitopes.

C. Loss of suppression

Suppressor cells of various types serve to maintain peripheral tolerance. Evidence suggests that the numbers of these suppressor cells decline with age, increasing the risk that previously suppressed autoreactive lymphocytes can become active. A pattern of increasing risk with increasing age is indeed seen in some autoimmune diseases, such as **systemic lupus erythematosus** (**SLE**). It can be difficult, however, to differentiate between an increase in risk because of changes that result from aging and the simple fact that increased age provides more opportunity for a disease to occur.

D. Sequestered antigens

Some self-molecules are "sequestered" and are normally never exposed to the immune system for various reasons. As a result, if they do become exposed, as a result of injury for example, the immune system may view them as foreign and attack them. Among the best understood examples of sequestered antigens are those associated with spermatogonia and developing sperm within the lumen of testicular tubules. The tubules are sealed off early in embryonic development, prior to development of the immune system, by enclosure within a sheath of tightly joined Sertoli cells. Immune cells do not penetrate the barrier presented by the Sertoli cells and therefore are never exposed to self-molecules that are unique to the testicular tubule lumen. If these are exposed by injury (or by procedures such as surgery or vasectomy), immune responses may occur against the self (but seemingly foreign) molecules. It is believed that some cases of male sterility are caused by this mechanism.

Collectively, sites in the body that are associated with some degree of isolation from the immune system are called **immunologically privileged sites**. In addition to the lumen of the testicular tubule, these sites include the cornea and the anterior chamber of the eye, the brain, and the uterine environment during pregnancy. The reduced vasculature of the cornea and the fluid-filled chamber of the anterior chamber of the eye, together with other immunosuppressive mechanisms, may help to protect the delicate structures of the eye from the damage and permanent injury that could follow strong inflammatory responses. For example, the fluid in the anterior chamber of the eye contains many anti-inflammatory molecules.

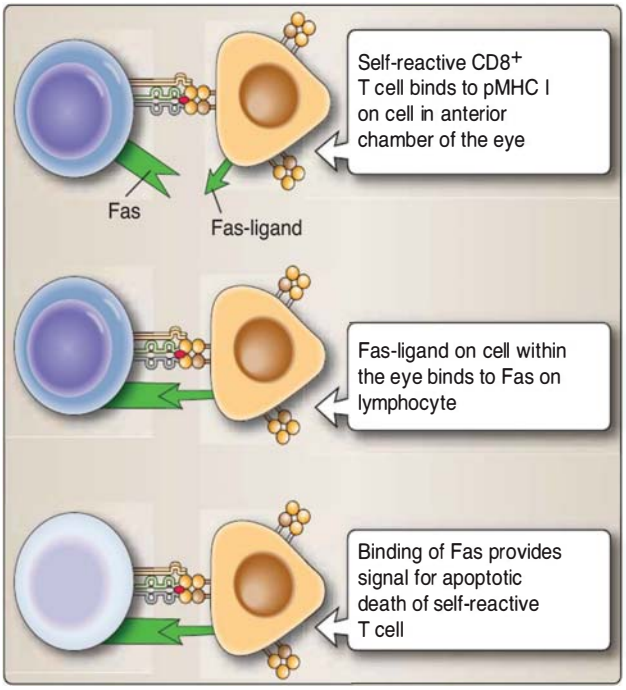

Figure 16.8
Role of Fas-ligand in protection of cells within immunologically privileged sites. Fas-ligand is widely expressed on cells in the anterior chamber of the eye. When autoimmune T cells attempt to bind to cells of the anterior chamber, Fas-ligand binds to Fas molecules expressed by T cells. This binding induces apoptotic death of the Fas-bearing cell (in this case, the T cell) and immune-mediated damage to the cells of the anterior chamber is avoided.

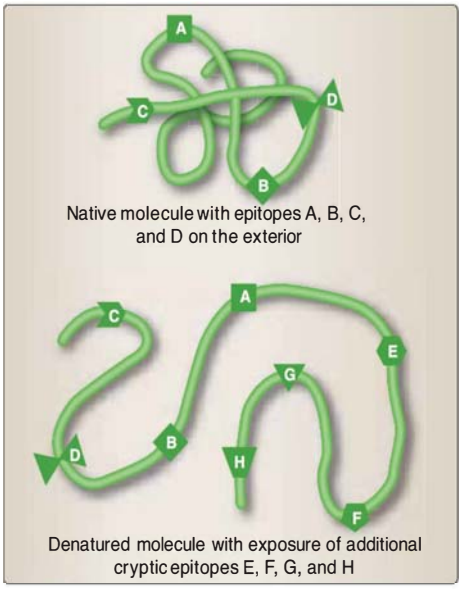

Figure 16.9
Cryptic epitopes. Some epitopes may not be readily available to the immune system because they are protected within the three-dimensional structure of a molecule. A structural change in the molecule, such as cleavage or denaturation, may make these cryptic epitopes more accessible to antibodies.

In addition, cells in the anterior of the eye widely express the **Fas-ligand** molecule (CD178) on their surface. When Fas-ligand binds to **Fas** (CD95) on activated T cells, those T cells undergo an apoptotic death (Fig. 16.8). Thus, cells in the anterior chamber can protect themselves by killing autoreactive T cells that bind to them. Another mechanism helps to protect the brain. The **blood–brain barrier** consists of dense, tightly packed vascular endothelium that limits the flow of cells and large molecules from the vasculature into the brain, thus decreasing the ability of the immune system to infiltrate the brain. Again, the blood–brain barrier is thought to be beneficial because strong inflammatory responses could easily inflict irreparable damage on the brain.

Molecules may also sometimes possess a type of immunologically privileged site. The three-dimensional configurations of some molecules may shelter epitopes in the interior from contact with the immune system. If the molecule is altered by denaturation or cleavage, however, the "hidden" internal epitopes may become exposed and available for recognition and binding by antibodies (Fig.16.9). These are termed **cryptic epitopes**. The presence of rheumatoid factor, associated with inflammatory rheumatoid diseases, provides an example of this phenomenon (Fig. 16.10). The binding of IgG molecules trigger conformational changes in their Fc regions that expose "hidden" sites, some of which facilitate the binding of complement or Fc receptors and some

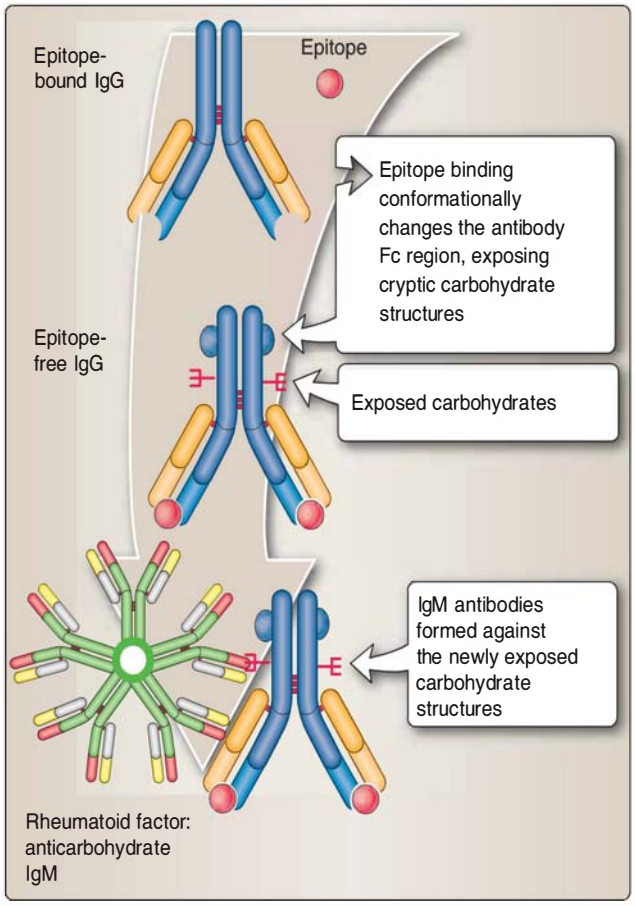

Figure 16.10
Rheumatoid factor. Rheumatoid factor (IgM produced against IgG) results from recognition of cryptic epitopes. Binding of antibodies, including IgG, to their epitopes produce a conformational change in the Fc region, exposing sites that become available for the binding of complement and recognition by cellular Fc receptors. The exposed sites include previously cryptic carbohydrate structures that, once available, can be recognized and bound by IgM molecules. (IgM and IgG molecules are not drawn to scale.)

of which expose cryptic carbohydrate structures that can be recognized and bound by IgM antibodies. IgM antibodies directed at the cryptic carbohydrate structures on antigen-bound IgG molecules are called **rheumatoid factors**. The binding of IgM to IgG augments the formation of immune complexes and the activation of complement (see Chapter 14). The presence of rheumatoid factor is associated with several inflammatory autoimmune diseases.

E. Neoantigens

Responses to neoantigens may mimic autoimmune responses. **Neoantigens** are self-antigens that have been modified by some extrinsic factor (e.g., binding of a reactive chemical) so that they appear foreign to the immune system. Thus, they are not true autoantigens, and the reactions against them are not truly autoimmune. However, the effects of responses to neoantigens can be nearly identical to those against autoantigens. Some responses that are currently classified as autoimmune may in fact be caused by neoantigens created by some unknown environmental agent. One feature that distinguishes responses against neoantigens from true autoimmune responses is that responses to neoantigens should cease if the agent responsible for creation of the neoantigens is removed. True autoantigens, by contrast, persist for the individual's lifetime and continue to stimulate autoimmune responses unless they are destroyed and eliminated.

IV. AUTOIMMUNE DISEASES

Table 16.1 lists several human autoimmune diseases. These diseases involve numerous different molecules, cells, and tissues that are targeted by the autoimmune responses. Some autoimmune diseases are systemic or diffuse, because of the distribution of the target antigens. For example, SLE and rheumatoid arthritis affect various joints and other body tissues. Other diseases affect specific organs and tissues. Some autoimmune diseases, including SLE, Sjögren syndrome, and rheumatoid arthritis, occur more frequently in females than in males. Examples of autoimmune diseases include the following:

- Crohn disease (intestine)
- Goodpasture disease (kidney and lung)
- Hashimoto thyroiditis (thyroid gland)
- Insulin-dependent diabetes mellitus type 1 (β cells of the pancreas)

Table 16.1
AUTOIMMUNE DISEASES

Affected Tissue	Disease	Target Antigen
Anterior parts of the eye	Uveitis (anterior)	Beta B1-crystallin, other proteins of the ciliary body epithelium
Connective tissue	Scleroderma	Scl-70, PM-Scl antigens
Erythrocytes	Autoimmune hemolytic anemia	Erythrocyte surface molecules
Heart valves and sarcolemmal membranes	Rheumatic fever	Streptococcal M protein, cardiac muscle antigens
Joints of lower extremities; sometimes eyes and genital, urinary, or GI systems	Reiter disease (reactive arthritis)	Possible association with infectious agents
Kidneys, lungs	Goodpasture syndrome	Type IV collagen of basement membranes
Large intestine	Ulcerative colitis	Unknown
Lower spine	Ankylosing spondylitis	Unknown
Myelin of the central nervous system	Multiple sclerosis	Myelin proteins (several)
Pancreatic islet β cells	Type 1 insulin-dependent diabetes mellitus (IDDM)	Glutamate decarboxylase, preproinsulin, other β cell products
Platelets	Thrombocytic purpura	Platelet integrin molecules
Skeletal muscle	Myasthenia gravis	Acetylcholine receptor
Skeletal muscle	Polymyositis	Jo-1, PM-Scl antigens
Skin	Pemphigus vulgaris	Desmoglein-3
Skin	Psoriasis	Unknown, but there is some association with streptococcal infections
Skin, vasculature, muscle, joints, kidney	Systemic lupus erythematosus (SLE)	Nucleic acids, chromosomal proteins
Small intestine	Crohn disease	Unknown
Spermatogonia, sperm	Male sterility (some forms)	Unknown
Synovial membranes, joints	Rheumatoid arthritis	Unknown
Tear ducts	Sjögren syndrome	Ro/SS-A antigens
Thyroid gland	Graves disease	TSH receptor
Thyroid gland	Hashimoto thyroiditis	Thyroglobulin

CLINICAL APPLICATION
Multiple sclerosis

Mavis N., a 40-year-old woman, with a 3-year-history of progressive right leg weakness, presents with difficulty walking. Recently, she also has experienced intermittent blurred vision of her left eye.

She has no other neurological symptoms or medical problems. The physical examination is remarkable for weakness and difficulty walking, mainly with her right leg. She requires a cane to walk.

Laboratory examination reveals positive results for oligoclonal bands in the cerebrospinal fluid (CSF). The brain and spine magnetic resonance imaging shows lesions that are consistent with multiple sclerosis (MS).

Multiple sclerosis is an inflammatory demyelinating disease of the central nervous system. Clinical symptoms can include optic neuritis, which is an inflammation of the optic nerve that may cause a unilateral visual loss, and spastic weakness of the limbs. Oligoclonal bands are bands of IgG that are seen in the CSF of approximately 85% of patients with MS.

Medical treatment options for MS are listed in Table 18.1.

- Multiple sclerosis (white matter of the brain and spinal cord)
- Sjögren syndrome (tear ducts)

Autoimmune diseases can result from damage inflicted on cells and tissues by humoral responses, cell-mediated immune responses, or both. It should be noted that the assignment of humoral or cell-mediated damage is sometimes based on data from experimental models.

A. Humoral-associated autoimmune diseases

Some autoimmune diseases result from the binding of self-reactive antibodies, leading to type II and type III hypersensitivity responses. The antibodies responsible for initiating the diseases are usually of the IgG isotype, although IgM antibodies can contribute as well. The activation of complement and the opsonization of injured cells promote inflammatory responses that increase the damage inflicted on the targeted cells and tissues. Autoreactive T cells are typically present as well, but their role is primarily the activation of the autoreactive B cells rather than directly attacking host cells. Examples of these autoimmune diseases include the following:

- Autoimmune hemolytic anemia: type II hypersensitivity
- Goodpasture syndrome: type II hypersensitivity
- Hashimoto thyroiditis: type II hypersensitivity
- Rheumatic fever: type II hypersensitivity
- Rheumatoid arthritis: type III hypersensitivity
- Systemic lupus erythematosus: type II and type III hypersensitivity

CLINICAL APPLICATION
Rheumatoid arthritis

Grace D., a 53-year-old woman, presents with a 5-week history of fatigue associated with joint pain of her hands and feet and morning stiffness. She takes ibuprofen and acetaminophen without much relief.

The physical examination is remarkable for tenderness and swelling of the metacarpophalangeal joints bilaterally.

Laboratory examination reveals positive results for rheumatoid factor and anticyclic citrullinated peptide antibodies.

This patient has symptoms and blood tests consistent with rheumatoid arthritis (RA), which is a chronic inflammatory polyarthropathy and may affect many tissues and organs.

Further discussion of this disease and medical treatment options for RA are discussed in Chapter 18.

B. Cell-mediated autoimmune diseases

Type IV hypersensitivity responses involve cell-mediated injury leading to autoimmune disease. These may include cytotoxic T-cell responses or macrophages driven by DTH responses. The inflammation that is generated can eventually involve numerous simultaneously ongoing responses. In some diseases, particular antibodies may also be characteristically present, but they have not been demonstrated to contribute to the disease pathologies. The following are examples of autoimmune diseases involving type IV hypersensitivity responses. Rheumatoid arthritis provides an example of an autoimmune disease that involves both humoral and cell-mediated injury.

- Insulin-dependent diabetes mellitus (type 1)
- Multiple sclerosis
- Reactive arthritis
- Rheumatoid arthritis

V. HLA ASSOCIATION WITH AUTOIMMUNE DISEASES

The risks for many autoimmune diseases appear to be associated with the presence of particular HLA genes (Table 16.2). In some cases (e.g., HLA-B27 and HLA-DR3), a single HLA gene is associated with increased risk for multiple autoimmune diseases. The molecular mechanisms underlying these statistical associations are still uncertain but presumably involve some influence on processing and presentation of self-epitopes to self-reactive T cells.

The strength of the statistical association between a particular HLA gene and a particular autoimmune disease is expressed as the **relative risk**. The relative risk compares the frequency of the particular disease among

Table 16.2
MHC ASSOCIATIONS WITH AUTOIMMUNE DISEASES

Disease	HLA Gene[a]	Relative Risk[b]
Acute uveitis	B27	10
Ankylosing spondylitis	B27	100
Goodpasture syndrome	DR2	15
Graves disease	DR3	4
Hashimoto thyroiditis	DR5	3
Type I insulin-dependent diabetes mellitus	DR3/DR4 heterozygote	20–25
Multiple sclerosis	DR2	5
	DR3	10
Myasthenia gravis	DR3	3
	B8	3
Pemphigus vulgaris	DR4	15
Psoriasis vulgaris	Cw6	5–13
Reiter disease	B27	35
Rheumatoid arthritis	DR4	4
Systemic lupus erythematosus	DR3	6

[a]Studies done in different populations may implicate different genes.
[b]Relative risks can vary among different studies. Values given are typical.

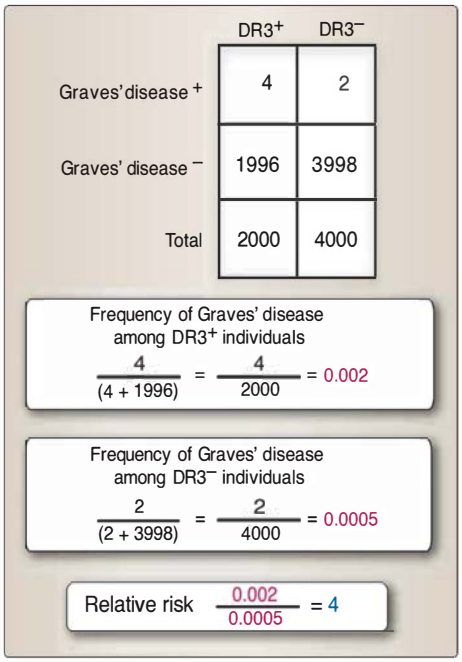

Figure 16.11
Relative risk. The statistical association between an autoimmune disease and a specific HLA gene is expressed as the relative risk. Relative risk is the ratio between the incidence of the disease among carriers of the gene in question and the incidence among noncarriers.

carriers of a particular HLA gene with the frequency among noncarriers (Fig. 16.11). For example, the relative risk of six for the association of SLE with HLA-DR3 means that SLE occurs approximately three times more frequently among $DR3^+$ individuals than among $DR3^-$ individuals. Relative risk calculations are made within defined populations, and results may vary among groups of different ethnic or geographic origin.

Because genetics is only one of several possible factors contributing to the risk of a particular autoimmune disease, most relative risks are modest, in the range of two to five. However, some HLA genes display much higher associations. For example, HLA-B27 and ankylosing spondylitis have relative risks around 100, and over 90% of individuals with ankylosing spondylitis are $B27^+$. The impact of relative risk should also be considered in the context of actual frequency. A disease occurring at a rate of three per million in one group and one per million in the other has a relative risk of three, but the practical impact is diluted by the rarity of the condition.

Chapter Summary

- **Tolerance** is the failure to respond in an aggressive way against an epitope recognized by the immune system.
- **Autoimmunity** results from a loss of **self-tolerance** through the failure to inactivate or eliminate self-reactive cells.
- **Central tolerance** occurs in the primary lymphoid organs (bone marrow and thymus) during the early development of B and T cells.

- **Peripheral tolerance** results from mechanisms that inactivate or eliminate B and T cells that are in circulation.
- **Anergy** (inactivation) of B and T cells occurs when naive lymphocytes bind via their BCR or TCR ("first signal") but fail to receive the second signals provided by T cells (for B cells) and APCs (for T cells) that are necessary for activation.
- Suppressor T cells inhibit responses by other immune cells.
- Loss of self-tolerance may occur through molecular mimicry, epitope spreading, loss of suppression, or the exposure of sequestered antigens.
- **Molecular mimicry** involves the generation of responses to microbial epitopes that may cross-react with host epitopes that are structurally very similar to the microbial ones.
- **Epitope spreading** occurs when a response to an epitope leads to the generation of responses to one or more other epitopes.
- Suppressor T-cell numbers may decline with age, permitting other self-reactive cells to escape regulation and initiate autoimmune diseases.
- Sequestered antigens are located in anatomical sites that are normally sheltered from the immune system by specialized anatomic structures or other mechanisms.
- **Neoantigens** are not self-antigens but may lead to conditions that mimic autoimmunity. If the condition creating the neoantigens is removed, the condition should be resolved. Responses to true self-antigens, on the other hand, should be permanent as a rule.
- Numerous autoimmune diseases have been identified. Their effects are determined largely by the localization of the self-epitope. Some diseases, such as systemic lupus erythematosus and rheumatoid arthritis, are systemic and affect several body sites simultaneously. Others, such as Hashimoto thyroiditis and Sjögren syndrome, affect specific tissues or organs.
- Autoimmune pathology may result from antibody-initiated damage (hypersensitivity types II and III), cell-mediated responses (type IV hypersensitivity), or both.
- Some autoimmune diseases have elevated frequencies in individuals carrying certain HLA genes. The statistical association between the disease and the HLA gene is expressed as the **relative risk**.

Study Questions

16.1. The failure to inactivate or eliminate self-reactive cells results in

A. autoimmunity.
B. positive selection.
C. negative selection.
D. suppression.
E. tolerance.

The correct answer is A. Autoimmunity results from the failure to inactivate or eliminate self-reactive immune cells. Positive selection is the promotion of lymphocytes that can function within the body. Suppression, negative selection, and tolerance are various mechanisms by which the immune system produces tolerance.

16.2. Failure of the immune system to respond against an epitope in an aggressive way is termed

A. autoimmunity.
B. positive selection.
C. negative selection.
D. suppression.
E. tolerance.

The correct answer is E. Tolerance is the failure to generate a destructive response against an epitope that the immune system recognizes.

16.3. Deliberate inactivation or destruction of lymphocytes bearing BCRs or TCRs capable of recognizing and binding specific self-epitopes results in

A. hypersensitivity.
B. autoimmunity.
C. molecular mimicry.
D. positive selection.
E. self-tolerance.

The correct choice is E. The inactivation or destruction of lymphocytes bearing particular antigen receptors is one of the mechanisms producing tolerance. Hypersensitivity responses are heightened and destructive. Autoimmunity results from the absence of self-tolerance. Mimicry is a means of breaking tolerance. Positive selection is the promotion of lymphocytes that bear receptors capable of particular self-molecules.

16.4. Lymphocytes expressing both the CD4 and CD25 markers on their surfaces function as

A. antigen-presenting cells.
B. autoantibody-secreting B cells.
C. cytotoxic T cells.
D. natural killer-like T cells.
E. T regulatory cells

The correct answer is E. $CD4^+CD25^+$ T cells are a regulatory subset of T cells. They do not act as antigen-presenting cells, nor do they secrete antibodies. Cytotoxic T cells are $CD8^+$. They do not belong to the natural killer-like T-cell subset of T cells.

16.5. During an infection with *Streptococcus pyogenes*, an individual generated sufficiently high levels of IgM and IgG antibodies against a *S. pyogenes* antigen with structural similarity with molecules on the heart that cardiac damage was caused. In this example, the microbe contributed to autoimmunity via a process known as

A. anergy.
B. central tolerance.
C. epitope spreading.
D. loss of suppression.
E. molecular mimicry.

The correct answer is E. Molecular mimicry contributes to autoimmunity by triggering responses with microbial molecules that are cross-reactive with host molecules. Anergy and central tolerance are mechanisms for preventing autoimmunity. Epitope spreading involves the generation of responses to a series of different antigens, not to cross-reactive ones. The loss of suppression is a different mechanism by which tolerance can be broken.

16.6. A previously healthy 12-year-old female lost 8 pounds over the past several weeks without dieting. Her parents are concerned about this weight loss and believe that she has an eating disorder. The patient's history reveals polydipsia (excessive thirst), polyuria (excessive urination), and nocturia (need to arise during the night for urination) over the last several weeks. A fasting blood glucose of 460 mg/dL is obtained (reference range: 70 to 100 mg/dL). The patient is diagnosed with an autoimmune disease. On the basis of these findings, which of the following conditions was most likely diagnosed in this patient?

A. Anorexia nervosa
B. Hyperthyroidism
C. Nephrolithiasis (kidney stones)
D. Type 1 diabetes mellitus
E. Urinary tract infection

The correct answer is D. Type 1 diabetes mellitus is the autoimmune disease, among those listed, that impairs regulation of blood glucose levels. Some forms of hyperthyroidism can result from autoimmune diseases attacking thyroid receptors. Anorexia nervosa, nephrolithiasis, and urinary tract infections are not autoimmune diseases.

16.7. In Question 16.6, a defect or deficiency in which of the following is associated with the patient's condition?

A. Adipose tissue
B. Kidney tubules
C. Pancreatic β cells
D. Thyroid gland
E. Skeletal muscle

The correct answer is C. Destruction of pancreatic β cells reduces insulin production. The other tissues listed are not targets of the autoimmune attack, although they may incur later secondary damage if the primary disease is not appropriately treated and controlled.

16.8. A previously healthy 65-year-old female presents with complaints of frequent bowel movements, weight loss, and nervousness. Her physical examination was remarkable for slight exophthalmos (protrusion of the eyeball) and atrial fibrillation (abnormal heart rhythm). Laboratory findings supported a diagnosis of Graves disease. Which of the following tissues/organs will be most affected by the ensuing immune reactions?

A. Connective tissue
B. Joints of lower extremities
C. Heart valves
D. Kidneys
E. Thyroid gland

The correct answer is E. Graves disease results from autoimmune responses targeting the thyroid gland. The other tissues and organs listed are not targets of the autoimmune responses producing Graves disease.

16.9. Graves disease is an example of which of the following immunologic processes?

A. Autoimmune disease associated with HLA gene B27
B. Autoimmune disease associated with HLA gene DR3
C. Immune deficiency associated with HLA gene DR2
D. Immune deficiency associated with HLA gene DR4
E. Type III hypersensitivity associated with HLA gene Cw6

The correct answer is B. Graves disease is an autoimmune disease that is associated with the presence of the HLA-DR3 gene. It is not associated with HLA-B27, -DR2, -DR4, or -Cw6. It does not result from immunodeficiency.

16.10. A 35-year-old male presents with symptoms of fatigue, paresthesia (numbness and tingling) of his arms and legs, and occasional blurred vision of 2 months' duration. Tests reveal several areas of demyelination within the central nervous system. Diagnosis of which of the following conditions is supported by these findings?

A. Ankylosing spondylitis
B. Hashimoto thyroiditis
C. Multiple sclerosis
D. Reactive arthritis
E. Systemic lupus erythematosus

The correct answer is C. Multiple sclerosis is an autoimmune disease that results in demyelination within the central nervous system. Ankylosing spondylitis and reactive arthritis involve joints, Hashimoto thyroiditis involves the thyroid gland, and systemic lupus erythematosus is a systemic disease with primary effects on joints, muscles, skin, and kidneys.

16.11. Which of the following is the underlying immunological process in ankylosing spondylitis?

A. Autoimmune disease associated with HLA gene B27
B. Development of autoantibodies against nucleic acids
C. Immune-mediated destruction of neurons
D. Immune deficiency associated with HLA gene DR4
E. Molecular mimicry of the acetylcholine receptor

The correct answer is A. Ankylosing spondylitis is an autoimmune disease in which over 90% of people with the disease carry the HLA-B27 gene. The autoimmune response does not target nucleic acids or acetylcholine receptors. It is not an immune deficiency disease.

16.12. A 30-year-old female presents with fatigue, weight loss, arthritis of her hands, and a malar ("butterfly") rash. Blood tests reveal decreased hemoglobin and the presence of antinuclear antibodies. These findings support which of the following diagnoses paired with its underlying immunologic process?

A. Graves disease: autoantibodies to thyroid-stimulating hormone receptor
B. Myasthenia gravis: autoimmunity associated with HLA gene DR3
C. Reiter syndrome: immune-mediated destruction associated with HLA gene B27
D. Rheumatoid arthritis: immune deficiency associated with HLA gene DR4
E. Systemic lupus erythematosus: autoantibodies to chromosomal proteins

The correct answer is E. Systemic lupus erythematosus results from the generation of autoimmune antibodies against chromosomal proteins (and nucleic acids). It is associated with the presence of HLA-DR3, but not -B27 or -DR4. Myasthenia gravis results from autoantibodies against acetylcholine receptors on muscle cells. Reiter syndrome and rheumatoid arthritis target joints. The thyroid gland is not a target of the antinuclear antibodies.

16.13. A 55-year-old female presents with complaints of pain and stiffness in her hands and wrists that occurs mainly in the morning. Examination reveals tenderness and swelling in both wrists and hands. Testing reveals the presence of rheumatoid factor. The patient is diagnosed with rheumatoid arthritis. Resulting injury that will likely occur in this patient will result from

A. both cell mediated and humoral immunity.
B. both type II and type III hypersensitivity.
C. IgE-mediated immune responses only.
D. self-tolerance.
E. type II hypersensitivity only.

The correct answer is A. Rheumatoid arthritis involves damage inflicted by both antibody-driven type III hypersensitivity responses and cellular type IV hypersensitivity responses. It does not involve type II hypersensitivity responses or IgE mediated (type I) responses. It results from the loss of self-tolerance.

16.14. A 47-year-old-male has a history of end-stage renal failure and required a kidney transplant. Approximately 4 weeks after receiving his transplanted kidney, he developed oliguria (decreased production of urine), fever, hypertension, and pain or tenderness over the allograft. On the basis of these findings, the most likely underlying immunological process is

A. autoimmunity.
B. acute rejection.
C. chronic rejection.
D. hyperacute rejection.
E. peripheral tolerance.

The correct answer is B. The time span is appropriate for acute rejection of the transplanted organ but not for chronic or hyperacute rejection. There is no information suggesting autoimmunity. Peripheral tolerance is a mechanism for preventing responses to self-antigens.

16.15. A 20-year-old woman presents with right lower abdominal cramp-type pain associated with diarrhea and weight loss. Blood tests reveal a low hemoglobin level and high white blood cell counts. She is diagnosed with Crohn disease. The tissue that is most affected in this autoimmune disease is

A. connective tissue.
B. erythrocytes.
C. pancreatic β cells.
D. the small intestine.
E. the thyroid.

The correct answer is D. Crohn disease targets the small intestine. It is not directed at connective tissue, erythrocytes, pancreatic β cells, or the thyroid gland.

Transplantation 17

I. OVERVIEW

The ability to replace or restore damaged tissues, or even entire body parts, has long been a dream of the healing professions. The broad application of transplantation in human medicine has been available only for the past five or six decades. Among the obstacles that had to be overcome were infection control, the genetic matching of donors with hosts, an understanding of the immunologic processes involved, and the development of agents that could inhibit the immune system. The development of antiseptic techniques coupled with antibiotics reduced the risk of infection, whereas tissue typing and immunosuppressive drugs increased the probability of transplant success.

II. GENETIC BASIS OF TRANSPLANTATION

The genetic basis for transplantation was recognized in the early twentieth century by pioneers such as Loeb, Tyzzer, and Little. The genetic match (similarity/disparity) between the donor and the host is perhaps the most important factor determining the likelihood of a successful transplant. The recipient's immune system looks for certain genetically encoded molecules (**histocompatibility antigens**) on the surfaces of the donor cells. Thus, the response against transplanted cells and tissues has parallels to the body's response to foreign infectious organisms.

A. Histocompatibility genes and antigens

Histocompatibility genes encode histocompatibility antigens. It is estimated that there are several scores of such loci, probably more than a hundred. Among these are the MHC class I and II molecules encoded within the **major histocompatibility complex** (**MHC**). With the possible exception of a few loci whose expression is not understood, the products of histocompatibility genes are codominantly expressed. **Codominance** means that they are expressed whether present as a single copy (heterozygous or hemizygous) or two copies (homozygous). Thus, an individual heterozygous at a particular histocompatibility locus (e.g., $H1^a/H1^b$) would simultaneously express both $H1^a$ and $H1^b$ molecules on the same surface cell surface (Fig. 17.1). The same would be true for other histocompatibility loci (e.g., $H2^a/H2^b$, $H3^a/H3$). The terminology here is that applied to humans. The H2 in humans should not be confused with the H2 of mice, which is the murine MHC. The MHC of humans is termed HLA (see Chapter 6).

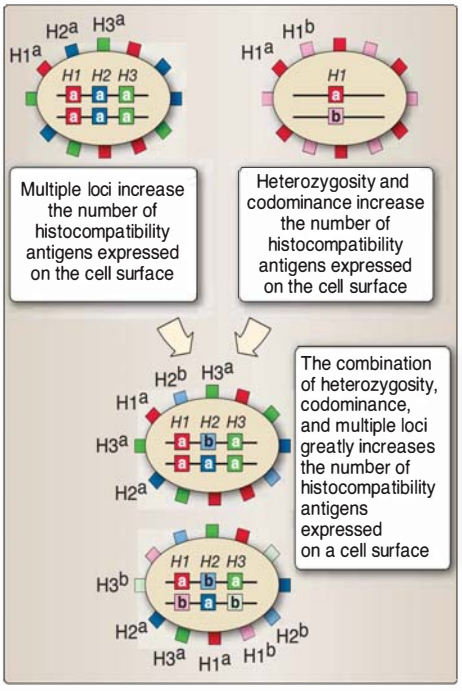

Figure 17.1
Histocompatibility antigens.

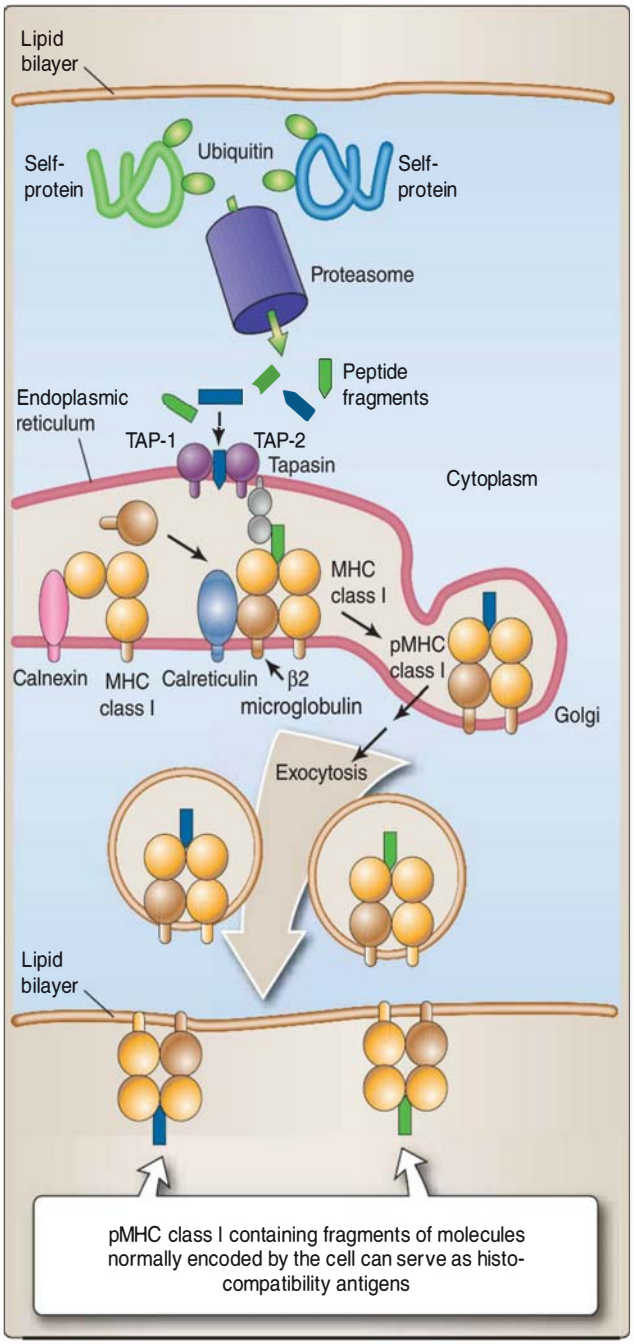

Figure 17.2
Display of histocompatibility antigens. Peptide fragments that result from proteasome degradation of cytoplasmic molecules and their subsequent loading onto MHC I molecules in the endoplasmic reticulum are present on the surface of all nucleated cells.

The structures and functions are known for only a very few of these molecules, namely, the MHC class I and II molecules. Little is known about the other non-MHC histocompatibility antigens except that they include molecules encoded by a large number of genes scattered among all of the chromosomes (including X and Y). In principle, any peptide fragment brought to the cell surface and presented by either MHC class I or II molecules could serve as a histocompatibility antigen (Fig. 17.2). Such fragments could be derived from cytosolic proteins

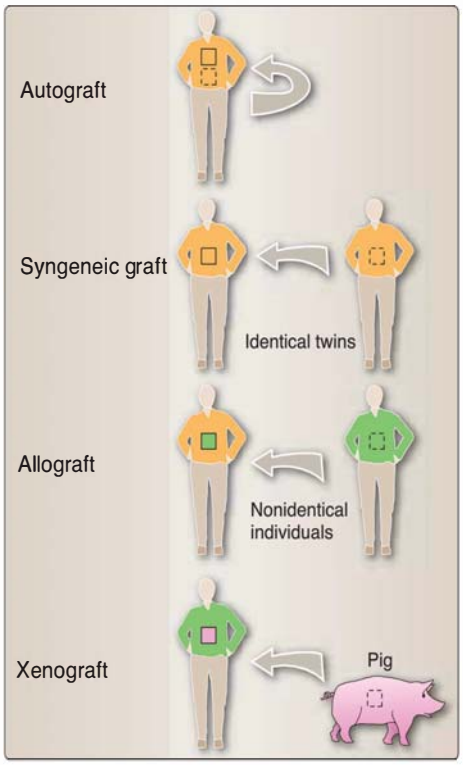

Figure 17.3
Classification of grafts by donor–recipient genetic relationship.

or from cell debris ingested and degraded by phagocytic cells. The important distinction is that the molecules are encoded within the transplanted donor cells and not derived from infectious agents.

B. Types of grafts

Transplants may be categorized by location or by the genetic relationship between the recipient and the donor. With respect to location, tissues or organs that are placed in their normal anatomic location are called **orthotopic** grafts. However, many transplanted tissues or organs can function quite well in other sites as well. Grafts that are placed into a site other than their normal one are called **heterotopic** grafts. Heterotopic grafts are especially useful in cases in which orthotopic placement may be technically difficult.

Classification of grafts by the donor–recipient genetic relationship (Fig. 17.3) is more complex. **Autografts** are those transferred from one part of an individual to another location on that same individual. **Syngeneic** grafts are those transferred between different individuals who are genetically identical or nearly so (e.g., identical twins or members of an inbred strain). **Allogeneic** grafts (or **allografts**) are transferred between two genetically disparate individuals of the same species (e.g., brother and sister, parent and child, or totally unrelated individuals). Finally, **xenogeneic** grafts (or **xenografts**) are those exchanged between members of different species (e.g., the placement of primate hearts into human recipients).

C. The laws of transplantation

The **laws of transplantation** were originally established in experimental studies, particularly in mice, but are applicable to human transplantation as well. Genetic diversity in humans virtually ensures that no two individuals are genetically identical (identical twins are an exception). The histocompatibility antigens of concern in transplantation vary from one case to another, depending on what specific genetic differences are present in each donor–recipient combination (Fig. 17.4). Experimental animals and plants can be deliberately bred to reduce their genetic heterogeneity so that genetic variability becomes a controlled variable rather than an uncontrolled one. This process, called **inbreeding**, is accomplished by mating of closely related individuals. When laboratory mice are subjected to brother–sister matings for 20 or more consecutive generations, **inbred strains** are produced. The animals within a given inbred strain are hypothetically homozygous for more than 99% of their genetic loci and, for practical purposes, are all genetically identical.

Transplants between members of the same inbred strains and between members of different inbred strains were used to deduce the laws of transplantation, which can be summarized as *a host can recognize as foreign and mount a response against any histocompatibility antigen not encoded within its own cells* (Fig. 17.5). Grafts exchanged between individuals of the same species who are completely different (homozygous for different alleles) at a histocompatibility locus can potentially be rejected. Such differences do not necessarily cause rejection on every occasion, for various reasons,

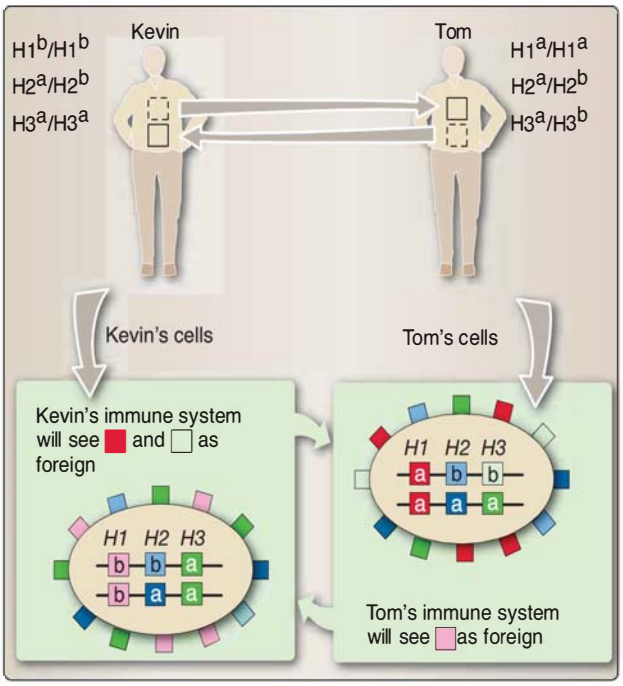

Figure 17.4
Histocompatibility differences vary among donor–recipient combinations. Which donor antigens stimulate the recipient immune response depends on the specific combination of donor and recipient histocompatibility genes involved.

but the potential is always present. Each member in the exchange will recognize the allelic form of the histocompatibility antigen expressed by the other as foreign. Heterozygous recipients, on the other hand, will see nothing foreign on grafts received from homozygous parental donors. Heterozygous grafts placed onto either type of homozygous parental type recipients will be rejected, as they express histocompatibility antigens that are foreign to one or the other parental recipient.

The utility of inbred strains can be extended by further subjecting them to programs of selection and breeding that use normal genetic recombination for the transfer of small chromosomal segments from one inbred strain to another. These new sets of inbred animals are called **congenic strains**, and they permit comparisons among organisms that differ from one another by only a small section of a chromosome or, conversely, that have only a small chromosomal segment in common (Fig. 17.6). Comparisons among congenic strains allow the mapping and analysis of individual histocompatibility genes within the transferred segment.

The most thoroughly characterized histocompatibility genes are those encoding the MHC class I and II molecules. As was discussed in Chapter 6, the MHC class I and II molecules are normally quite polymorphic within populations. As a result, MHC class I and II molecules (or, more precisely, fragments of different MHC I and II molecules being presented on intact and normally functioning MHC class I and II molecules) that differ between a host and a donor are readily recognized as foreign and trigger host immune responses directed against the donor

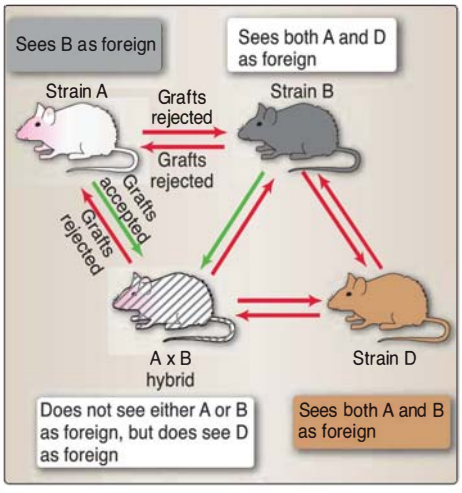

Figure 17.5
Laws of transplantation.

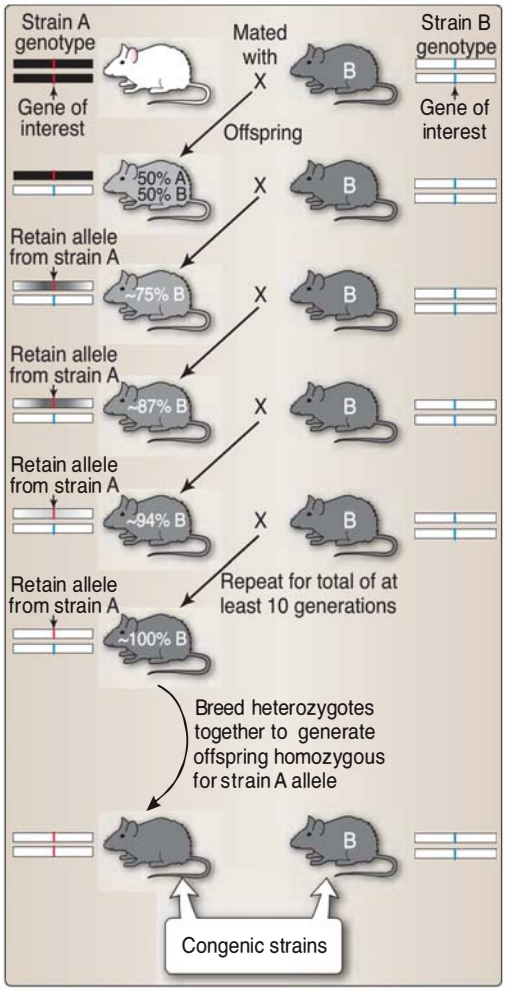

Figure 17.6
Congenic strains. Congenic strains, attained by systemic breeding and selection, differ only by small chromosomal regions.

cells (Figs. 17.7A and 17.7B). Foreign MHC molecules (especially the class I molecules) present a strong barrier to transplant survival, and it has been estimated that 5% to 10% of an individual's $CD8^+$ T cells can recognize and bind fragments of foreign MHC class I.

Several different characteristics have been noted that distinguish the effects on transplantation of differences between host and donor at MHC I and II loci from those of differences at **non-MHC** (or **minor**) histocompatibility loci (Table 17.1). Although exceptions can often be found, valid generalizations can be made.

III. TISSUE REJECTION

The recipient immune system recognizes peptide fragments presented by MHC class I or II molecules, whether those fragments are derived from infectious organisms or from the degradation of self-molecules encoded by host genes (see Figs. 10.6 and 10.7). In the case of transplanted tissues, the genes of the engrafted cells may encode nonself

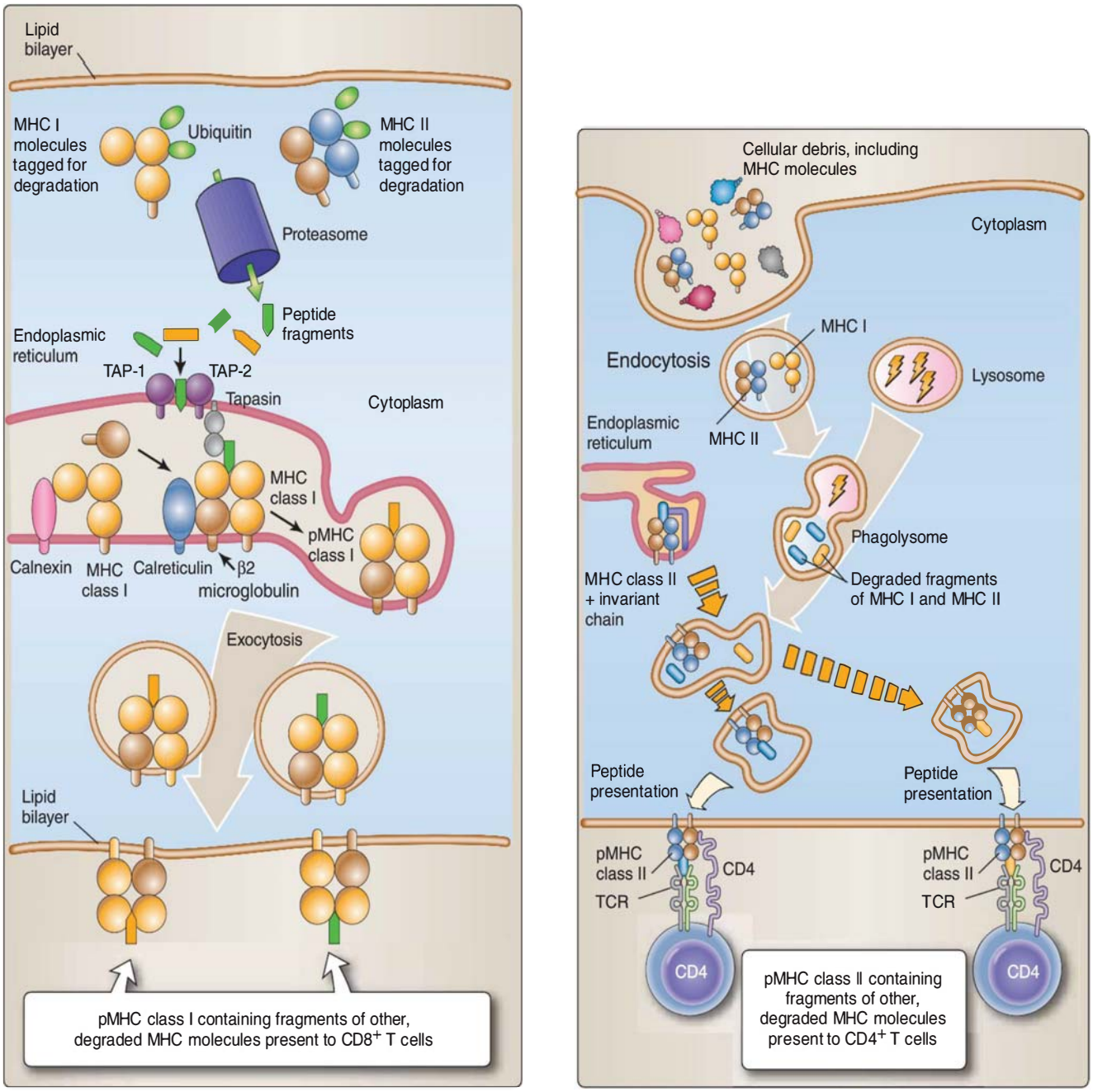

Figure 17.7

Fragments of MHC I and II molecules can be presented as histocompatibility antigens by intact MHC I and MHC II molecules. **A.** Erroneously translated, misfolded or, otherwise damaged cytoplasmically synthesized MHC class I and II molecules may be ubiquinated and degraded by proteasomes. The resulting fragments can be transported into the endoplasmic reticulum by TAP and loaded onto nascent MHC I molecules for eventual presentation to $CD8^+$ T cells. **B.** Ingested MHC class I and II molecules may be degraded and loaded onto MHC II molecules for presentation.

Table 17.1
HISTOCOMPATIBILITY GENES AND ANTIGENS

Major	Characteristics	Minor
5–10	Number of loci	~100
High degree, except for DR4	Polymorphism	Low
Located within the MHC	Chromosome locations	Located on almost all chromosomes including X and Y
Antigen presentation to T cells	Function(s)	Unknown, probably diverse
Acute (typical), hyperacute, chronic (sometimes)	Types of initial rejections	Acute or chronic depends upon donor–recipient differences
Strong	Cell-mediated immune responses	Variable intensity
Readily induced to MHC molecules	Host antibody production to graft	Difficult to induce
Difficult	Ease of tolerance induction	Relatively easy

molecules that also can be detected by the recipient immune system and function as histocompatibility antigens. T cells can detect and be activated against histocompatibility antigens through two different pathways of recognition: direct or indirect (Fig. 17.8). Direct recognition involves antigen presentation by donor antigen-presenting cells (APCs) to recipient T cells, whereas indirect recognition involves antigen presentation by recipient APCs to recipient T cells.

Direct recognition can occur only when some of the MHC class I or II molecules on the donor cells are identical to those on recipient cells. Like other cytosolic proteins, MHC class I and II molecules can be degraded by proteasomes and the resulting fragments presented on the cell surface by intact MHC class I molecules. If the donor and recipient have MHC class I molecules in common, APCs of donor origin may be able to present those peptide fragments directly to the TCRs of recipient $CD8^+$ T cells. Because the MHC class I molecules on the donor cells are the same as those present in the host thymus during thymic education, the recipient TCRs are able to recognize and bind the pMHC I molecules on the donor cells. Direct recognition may also occur if donor APCs ingest cellular debris of donor origin and process/present it via MHC class II molecules to recipient $CD4^+$ T cells. **Indirect recognition** occurs when recipient APCs process and present peptide fragments derived from the ingestion, processing, and presentation of cellular debris from donor cells—debris that contains the donor histocompatibility antigens—and present it to recipient T cells.

Thus, the recognition of foreign histocompatibility antigens and the activation of T cells against them involve processes very similar to those involved in the initiation of responses against antigens derived from infectious organisms. Indeed, the recipient immune system may view the transplanted cells as just another batch of infected cells—infected by nonself-genes.

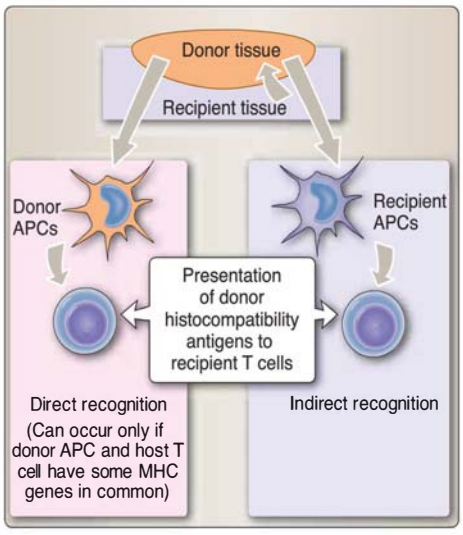

Figure 17.8
Direct recognition and indirect recognition.

A. Types of rejection

Rejection responses fall into three general categories—chronic, acute, and hyperacute—depending on timing and intensity. Each type involves particular sets of immune responses and is determined in part by the genetic mismatch between donor and recipient.

B. Immune responses involved in rejection

Chronic rejections are the slowest and the least vigorous type of rejection. The transplanted tissues or organs establish a vascular connection and proceed to function for weeks, months, and even years before signs of deterioration due to immune attack become evident. Even after the first signs of rejection appear, the graft destruction proceeds slowly and gradually as the graft tissue is replaced by intracellular matrix and scar tissue. Chronic rejections are typical of situations in which the donor and recipient differ by only non-MHC histocompatibility gene differences, although there are exceptions.

Acute rejections occur much sooner after graft emplacement than do chronic rejections. The grafts establish vascular connections and function normally for a relatively short period (e.g., 2 to 4 weeks) before the first signs of rejection appear. Unlike chronic rejections, acute rejections proceed rapidly once underway. The grafts become edematous and inflamed, with an influx of blood and mononuclear cell infiltrates, and complete destruction and sloughing of the grafted tissues may take only a very few days following the first signs of deterioration. Acute rejections are commonly seen when the donor and recipient differ at MHC histocompatibility genes, especially those involving the MHC class I loci.

CLINICAL APPLICATION
Renal transplantation

Doug, a 42-year-old male, presented initially 3 years ago with weakness. He developed type 1 diabetes at age 18 and hypertension at age 32. He had been taking insulin and an antihypertensive medication. Blood tests revealed low hemoglobin and decreased renal function. He was diagnosed with anemia associated with chronic kidney disease. He was referred to a nephrologist, who managed the patient's hypertension with an angiotensin-converting enzyme inhibitor, erythropoietin for anemia, dietary protein restriction, and vitamin D supplementation. Now, 3 years later, he has developed end-stage renal disease with worsening renal function requiring replacement therapy. The patient is advised to undergo dialysis or renal transplantation. He is advised that renal transplantation provides a good quality of life and is less expensive overall than chronic hemodialysis.

Fortunately, his brother has volunteered to be a kidney donor and is found to be an appropriate genetic match. The patient received his brother's healthy kidney together with immunosuppressive therapy. The kidney is functioning satisfactorily as he recovers from surgery.

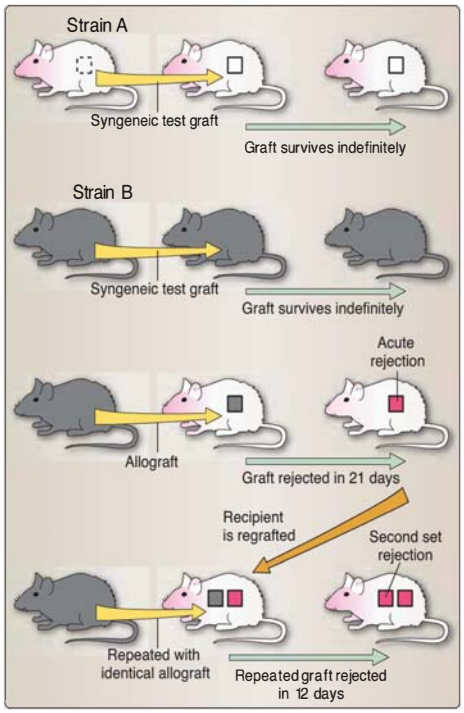

Figure 17.9
Second set rejections. Initial allografts between different inbred strains usually undergo acute rejection. If the rejected graft combination is repeated, the newly placed graft is rejected in an accelerated ("second set") manner.

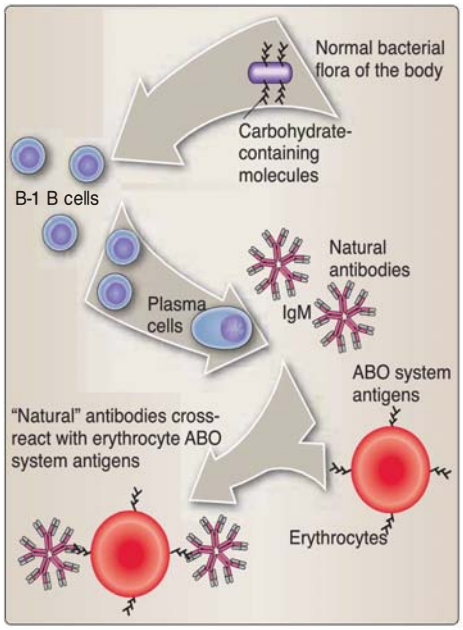

Figure 17.10
Naturally occurring antibodies. Naturally occurring antibodies against A and B antigens were so named because they were already present at the time of transfusion, prior to any known exposure or immunization.

Hyperacute rejections are the most rapid type of rejection. They are initiated and completed within a few days of graft placement, usually before the grafted tissue or organs can establish connections with the recipient vasculature. The immune attack is typically directed at the vasculature of the graft and is mediated (in various situations) by complement, natural killer (NK) cells, and/or preexisting antibodies. Hyperacute rejections have also been called "white grafts" because in the case of skin, the failure to establish a vascular connection gives the engrafted skin a blanched appearance. The term can be misleading; it does not describe the comparable condition of other rejected tissues. A hyperacutely rejected kidney, for example, may be bluish in color owing to the large amount of deteriorating blood trapped within it.

Like responses to infectious organs, immune responses against transplanted tissues or organs can display memory. Attempts to repeat grafts that have previously been rejected usually result in an accelerated graft rejection, a phenomenon termed **second set rejection** (Fig. 17.9). Grafts that are rejected chronically on the initial occasion may be rejected acutely when repeated. During the initial rejection, activated T and B lymphocytes can generate populations of memory cells that provide the basis for accelerated and heightened secondary responses. Second set responses are therefore simply secondary immune responses directed against histocompatibility antigens.

Although not every type of immune response is necessarily generated for every allograft or xenograft, almost every relevant type of immune response has been observed among various rejection episodes: antibodies, T-cell responses, complement, and even NK cells.

Antibodies against graft antigens occur from two primary sources. **Natural antibodies** are preexisting antibodies that are present in the absence of known exposure or immunization. They provide, for example, the basis for transfusion reactions against ABO antigens on red blood cells, a topic that is discussed later in this chapter. Natural antibodies are produced, probably by B-1 B cells, following stimulation by antigenic molecules on the natural flora found in the body (Fig. 17.10). They are of the IgM isotype and are directed against carbohydrate antigens. These antibodies are stimulated by microbial carbohydrate molecules but may cross-react with carbohydrate molecules on eukaryotic cells (e.g., human). Thus, for example, they can act immediately to damage erythrocytes in transfusions that are mismatched for carbohydrate ABO antigens. Similarly, in the case of xenografts, they can bind immediately to some carbohydrate molecules associated with the graft vasculature and initiate fatal damage to the graft.

The second source of antibodies involved in graft rejection occurs by the activation of B cells and generation of plasma cells synthesizing antibodies against histocompatibility antigens on graft tissue. Typically, sufficient amounts of antibodies to affect graft survival are generated only after prolonged or repeated exposures. Antibodies usually have little or no role in chronic or acute rejections unless they have been elevated by previous rejections of grafts bearing the same

histocompatibility antigens. Acute rejection of first-time grafts is mediated by T-cell responses. Although it is relatively easy to generate significant levels of antibodies against MHC class I and II molecules by repeated exposures to allogeneic grafts (or injected cells), it has been difficult to demonstrate the consistent generation of antibodies against minor (non-MHC) histocompatibility antigens. Binding of antibodies to graft cells can initiate destructive actions such as complement activation, opsonization, and antibody-dependent cell-mediated cytotoxicity. The effects of these actions can vary depending on the nature of the targeted tissue.

Development of delayed (-type) hypersensitivity (DTH) and cytotoxic T-lymphocyte (CTL) responses directed against histocompatibility antigens has been demonstrated in both acute and chronic rejections. The inflammatory nature of the DTH response, with the recruitment and activation of macrophages, suggests that it plays a significant role. Although CTLs specifically directed against histocompatibility antigens are clearly generated, how much they contribute to a given rejection can be difficult to discern because their killing is directed against a single target cell at a time. Both DTH and CTL responses can be generated against MHC (class I and II) and non-MHC histocompatibility antigens.

Complement activation and the ensuing inflammation can inflict considerable injury and even death on grafted cells. As was mentioned, this inflammation can be targeted through the attachment of graft-specific IgG and IgM molecules. However, complement has also been found to have an important impact on xenografts that does not involve the classical pathway of activation. Host cells are protected from the potential threat of deposition of complement fragments (e.g., C3b and C4b) on host cell membranes by the presence of various cell receptors and membrane-associated enzymes that continuously break them down and remove them. These protective mechanisms, however, are species-specific. Thus, when a graft from a miniature swine is placed on a human recipient, the enzymes and receptors that effectively protect the pig cells from pig complement are not effective against human complement, and the graft cells can be rapidly attacked by fragments of human complement initiating opsonization and formation of the membrane attack complex. The rapid action of these preexisting complement components leads to hyperacute rejection of xenografts.

NK cells recognize molecules produced by damaged or stressed cells and prepare to kill those cells. They refrain from doing so, however, if they recognize sufficient levels of appropriate MHC class I molecules on the targeted cells. In the case of xenografts, host NK may recognize stress molecules on graft cells but will not find appropriate host MHC class I molecules on the graft cells to inhibit them. As a result, host NK cells can cause considerable injury to the graft and constitute another significant barrier to successful xenotransplantation.

C. Therapeutic intervention

The initial effort to minimize the risk of rejection is to genetically match the donor and recipient as closely as possible. However, some degree

of mismatch is present in most transplants. The next step that can be taken is to inhibit the ability of the recipient immune system to attack and damage the engrafted tissues. This inhibition is approached in two general ways:

- **Specific immune tolerance** involves a selective inhibiting of the responsiveness to a given antigen or set of antigens.
- **Immune suppression** (or **immunosuppression**) involves inhibiting general immune responsiveness without regard to the specificity.

Although specific immune tolerance to foreign grafts can be induced in experimental systems, it usually requires some advance information about the precise genetic differences involved and sufficient lead time to prepare the recipient. These requirements have limited its use in humans so far. In addition, some of the techniques are ethically inappropriate in humans. Therefore, immunotherapy for transplant patients still relies on immunosuppression.

Immunosuppressive techniques such as whole-body irradiation or the use of toxic drugs effectively eliminate immune responses that could damage transplanted organs and tissues (Table 17.2). The treated recipients, however, are then open to opportunistic infections that can be fatal if not successfully monitored and controlled. Over the past few decades, additional drugs (e.g., cyclosporine, tacrolimus, and rapamycin) have been developed that have more restricted effects on the immune system. Their effects are targeted more closely on cells that react to graft antigens while leaving the remainder of the immune system relatively uninhibited in its ability to deal with infectious agents. They are not without risk, however. Patients must often receive the drugs for an extended period. If a significant infection occurs during this period, the immune cells

Table 17.2
IMMUNOSUPPRESSIVE AGENTS RELEVANT TO TRANSPLANTATION (ALSO SEE CHAPTER 18)

Agent	Affected Cells	Mode of Action
Azathioprine	Multiple cell types	Inhibition of nucleotide synthesis
Corticosteroids (e.g., prednisone)	Multiple cell types	Inhibition of transcription for numerous cytokines and other products involved in inflammation
Cyclophosphamide	Multiple cell types	Inhibition of nucleotide synthesis
Cyclosporine	Lymphocytes	Inhibition of transcription for multiple cytokines (e.g., IL-2, IL-4)
Mycophenolate mofetil	Lymphocytes	Inhibition of lymphocyte nucleotide synthesis and proliferation
Sirolimus (rapamycin)	T cells	Inhibition of some signal transduction induced by cytokines (e.g., IL-2)
Tacrolimus (FK506)	T cells	Inhibition of gene transcription in lymphocytes, inactivation of calcineurin
Antibodies against the IL-2 receptor	T cells	Inhibition of IL-2 mediated activation of lymphocytes
Irradiation	Many cell types	Induction of DNA damage, especially in rapidly proliferating cells
Antibodies against lymphocytes or against T cells	Lymphocytes, T cells	Destruction or inhibition of lymphocytes or lymphocyte subsets
Anti-CD4 antibodies, anti-CD8 antibodies	$CD4^+$ T cells, $CD8^+$ T cells	Interference with TCR binding
Anti-MHC I/II antibodies	Antigen-presenting cells	Interference with antigen presentation and T-cell activation by blockading

responding to the infectious agent could be inhibited in the same way as those responding to graft alloantigens. In addition, extended use of these drugs is sometimes associated with damage to organs such as the liver. These and other therapeutic drugs are discussed in greater detail in Chapter 18.

A second approach to inducing a less than global inhibition of the immune response has been the use of antibodies directed at molecules on the surface of the cells involved in immune responses, particularly lymphocytes and APCs. Antibodies against MHC class I or class II molecules can inhibit with T-cell activation. Antibodies against CD4 or CD8 molecules, when administered during active rejection, have been shown to inhibit or destroy T cells and halt the rejection at least temporarily; however, antibodies against broad categories of T lymphocytes (e.g., anti-CD3 antibodies) have problems similar to those seen with immunosuppressive drugs, and their long-term use can reduce the body's ability to respond to infectious agents.

IV. TISSUE-SPECIFIC CONSIDERATIONS

Special problems may arise when particular tissues are transplanted. We will discuss two of these situations: those involving blood transfusions and the transfer of bone marrow.

A. Transfusion

Transfusion is essentially the transplantation of blood. Erythrocytes and white cells in the transfused blood bear hundreds of molecules that can vary among individuals and act as histocompatibility antigens on these cells. Erythrocytes alone are estimated to express over 400 such types of antigens. Fortunately, mismatches for most of these antigens seldom have clinical consequences, and those tend to be of minimal severity when they do occur. There are, however, two antigen systems that are of major clinical concern: the ABO and Rh systems.

1. **ABO:** The **ABO antigen system** is a set of carbohydrate structures on erythrocyte surfaces and on some endothelial and epithelial cells. They are synthesized by glycosyl transferases encoded by two loci: the H locus and the ABO locus (Fig. 17.11) (Table 17.3). The H locus has two alleles: dominant H and recessive h. The recessive h allele encodes a nonfunctional product, but the H allele encodes a fucosyl transferase that attaches fucose to a precursor molecule normally present on erythrocyte surfaces to produce H substance. H substance is the precursor for the glycosyltransferases encoded by the alleles of the ABO locus that modify the H substance to produce A and B antigens (Fig. 17.11).

   A and B antigens are recognized and bound **by natural antibodies** (also called **naturally occurring antibodies**) present in the serum without any stimulation from prior transfusions or intentional immunizations. These natural antibodies, of the IgM isotype, are probably generated against carbohydrates on normal body flora, and their role in transfusion is probably because of cross-reaction

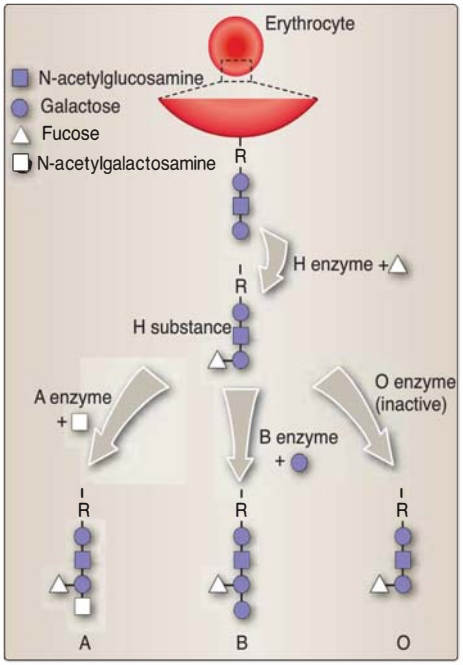

Figure 17.11
Synthesis of ABO blood group antigens.

Table 17.3
ABO ANTIGEN SYSTEM

Genotype of Individual		Phenotype of Individual	Natural Antibodies Present in Serum
H Locus	*ABO* Locus		
HH or Hh	*AA*	A	Anti-B
HH or Hh	*AO*	A	Anti-B
HH or Hh	*AB*	AB	None
HH or Hh	*BB*	B	Anti-A
HH or Hh	*BO*	B	Anti-A
HH or Hh	*OO*	O	Anti-A and anti-B
hh	*AA*	O	Anti-A and anti-B
hh	*AO*	O	Anti-A and anti-B
hh	*AB*	O	Anti-A and anti-B
hh	*BB*	O	Anti-A and anti-B
hh	*BO*	O	Anti-A and anti-B
hh	*OO*	O	Anti-A and anti-B

with certain carbohydrates on erythrocytes that share structural similarities with those on the microbial flora. Individuals who have neither A nor B on their own erythrocytes generate IgM antibodies against both A and B. Individuals of blood type A, tolerant to their own A antigens, will produce only anti-B antibodies. Similarly, type B individuals are tolerant to their own B antigens and therefore generate only anti-A antibodies.

Mismatched transfusions (e.g., type A erythrocytes given to a type B recipient) can have serious consequences. The naturally occurring IgM antibodies react almost immediately with the transfused erythrocytes to initiate agglutination and complement-mediated lysis. It is the agglutination that produces the clumping seen in demonstrations of ABO typing commonly performed in laboratories (see Chapter 20). ABO mismatching can result in massive destruction of transfused red blood cells (**transfusion reaction**) and, if severe enough, can produce a type of transfusion reaction known as an acute hemolytic reaction within 24 hours of transfusion. This reaction is caused by widespread hemolysis within the vasculature from the binding of IgM to erythrocytes and the ensuing complement activation. Clinical signs include fever, chills, shortness of breath, and urticaria. If it is extensive enough, a potentially fatal condition known as disseminated intravascular coagulation can develop.

Such situations emphasize the necessity of correct typing and matching of donors and recipients. Type A individuals can safely be given blood of phenotypes A and O, whereas type B recipients can safely receive blood of phenotypes B or O (Table 17.3). Type O recipients should receive erythrocytes only from other type O donors. AB individuals are “universal recipients” and can safely receive transfusions from donors of phenotypes A, B, O, or AB (Table 17.4).

Table 17.4
PERMISSIBLE ABO HOST–DONOR COMBINATIONS

Recipient Phenotypes	Can Accept Erythrocytes from Donors of Phenotypes
A	A, O
B	B, O
AB[a]	AB, A, B, O
O	O[b]

[a]Because they can safely accept erythrocytes from all donor types, type AB individuals are called *universal recipients*.

[b]Because they can safely donate erythrocytes to all recipient types, type O individuals are called *universal donors*.

2. **Rh:** The **Rh ("Rhesus") antigens** on erythrocyte surfaces are proteins. When an Rh-negative (Rh^-) individual is exposed to Rh-positive (Rh^+) erythrocytes, he or she can generate antibodies, some of which are of the IgG isotype. Rh antigens can be typed prior to transfusion, and Rh-related transfusion reactions can be avoided by avoiding the transfusion of Rh^- recipients with Rh^+ blood. Rh incompatibility during pregnancy presents a special concern for an Rh^- mother who carries an Rh^+ fetus. Fetal blood immunizes the mother's immune system to make IgG antibodies that may cross the placenta and destroy fetal erythrocytes in utero.

   Rh antigens are encoded by a series of closely linked loci (D and CE) with dominant alleles (e.g., D) and recessive alleles (e.g., d), the most important of which is D. DD or Dd individuals have the Rh^+ phenotype, whereas those with dd are Rh^- (Table 17.5). When the father is Rh^+, an Rh^- mother may carry an Rh^+ fetus (Fig. 17.12). The maternal immune system is exposed to fetal blood as early as the first trimester of pregnancy and begins to generate anti-Rh IgG antibodies. The first Rh^+ fetus is rarely at risk because of the time needed for injurious levels of anti-Rh antibodies to develop. However, subsequent Rh^+ fetuses are at risk because maternal anti-Rh

CLINICAL APPLICATION
Blood transfusion reaction

Aileen, a 55-year-old female, has had breast cancer for several years requiring chemotherapy. She is hospitalized for chemotherapy-induced anemia requiring a blood transfusion.

Within minutes after beginning the blood transfusion, she develops fever, nausea, back pain, and hypotension. The blood transfusion is immediately stopped. She is given intravenous fluid and acetaminophen. The patient's blood type is retested, and the original typing is found to be erroneous, confirming that the reaction was caused by a transfusion reaction. Fortunately, her symptoms resolve without any complications, such as acute kidney failure.

Table 17.5
RH ANTIGEN SYSTEM

Rh Genotype of Individual		
***D* locus (alleles *D* and *d*)**	***C* locus + *E* locus (alleles *C* or *c* and *E* or *e*)**	**Rh phenotype of individual**
DD	All combinations (*C* + *E*, *C* + *e*, *c* + *E*, or *c* + *e*)	Rh^+ (positive)
Dd	All combinations (*C* + *E*, *C* + *e*, *c* + *E*, or *c* + *e*)	Rh^+ (positive)
dd	All combinations (*C* + *E*, *C* + *e*, *c* + *E*, or *c* + *e*)	Rh^- (negative)

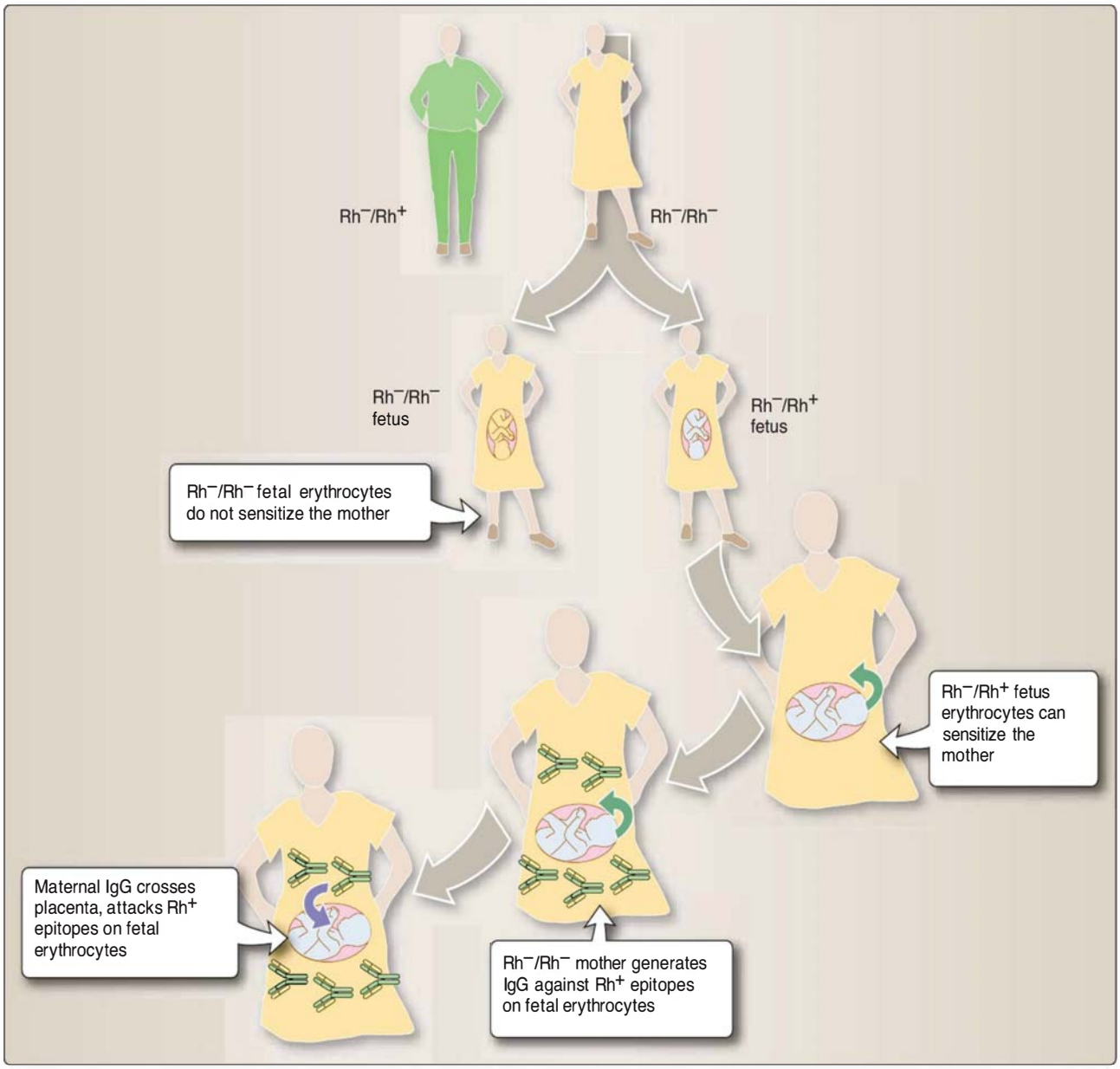

Figure 17.12
Hemolytic disease of the newborn. An Rh^- mother carrying an Rh^+ fetus can be exposed to fetal erythrocytes during pregnancy and delivery. The maternal immune system can generate anti-Rh IgG antibodies that cross the placenta and bind to Rh^+ fetal erythrocytes. Upon binding, these antibodies can induce destruction of fetal erythrocytes that may lead to anemia and other consequences.

antibodies can increase rapidly and enter the fetus. Binding to fetal erythrocytes can lead to anemia and damage to other fetal organs. This is called **hemolytic disease of the newborn** (**HDN**) or sometimes **erythroblastosis fetalis**. The Rh antigen is a protein and elicits an IgG response. Every conception between an Rh^+ male and an Rh^- female has the potential to produce an Rh-incompatible fetus. Aborted (spontaneous or induced) conceptions can also lead to the development of an IgG antibody response to Rh_0 (*D*).

In HDN, binding of anti-Rh antibodies to erythrocytes activates fetal complement, causing lysis of erythrocytes. The resulting anemia may become so severe that the fetus sustains severe damage or dies in utero. To compensate for the anemia, the fetal bone marrow releases immature erythrocytes (or erythroblasts). The abnormal presence of these erythroblasts in the fetal circulation is the hallmark of the disease (hence the term erythroblastosis fetalis).

Preventive therapy, especially the use of Rh_0 (D) immune globulin to minimize the risk of the mother becoming sensitized against Rh, is now routinely available for this situation. This involves the injection of a high-titer anti-Rh antibody preparation such as RhoGAM or MICRhoGAM. These preparations contain pooled anti-Rh antibodies, prepared from human serum obtained from mothers who have made antibodies to Rh antigens. Rh_0 (D) immune globulin should be administered after the 12th gestational week for ongoing pregnancy was well as for spontaneous or induced abortion. RhoGAM and MICRhoGAM remove fetal cells from the maternal circulation quickly enough to avoid sensitizing the mother's own immune system against Rh. Use of Rh_0 (D) immune globulin may also be appropriate after a blood transfusion of an Rh^- female.

CLINICAL APPLICATION
Hemolytic disease of the newborn

Kim, a 30-year-old female is pregnant for the third time. Her first pregnancy resulted in a miscarriage, and she did not follow-up with any additional testing. During her second pregnancy, the baby was jaundiced at birth and exhibited anemia and hepatosplenomegaly consistent with hemolytic disease of the newborn. Kim was found to be Rh^-, and the baby's father was Rh^+. Elevated levels of anti-Rh antibodies were found in Kim's blood.

During her third pregnancy, she has been very concerned. To prevent complications, she receives injections of RhoGAM, a high-titer anti-Rh antibody prepared from human serum from mothers who have made antibodies against Rh antigens. RhoGAM is given at 28 weeks of pregnancy and again within 72 hours of delivery if the baby is Rh^+. Kim delivers a healthy baby boy.

Although apparently healthy, the child should be followed to check for sequelae that may not be apparent at birth. Where appropriate prenatal care is observed, HDN has become rare. However, it is still a danger where appropriate prenatal care is avoided or unavailable.

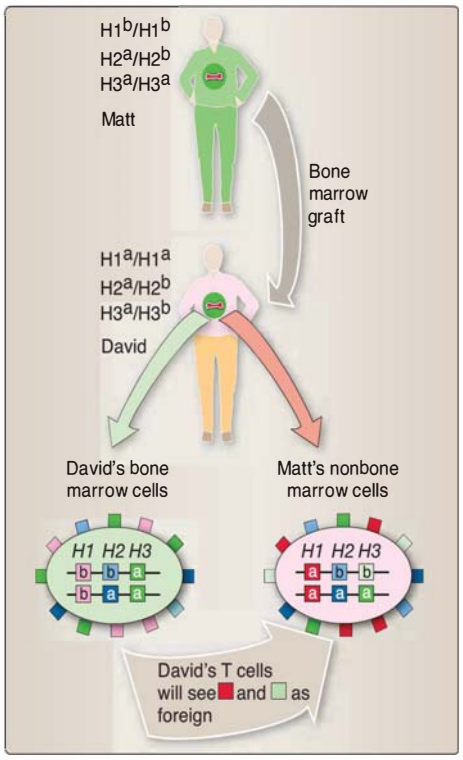

Figure 17.13
Bone marrow transplantation. Immunocompetent T cells in the donor bone marrow may recognize host antigens as foreign and initiate a graft-versus-host (GVH) response. The risk of GVH can be greatly reduced by removing mature T cells from the bone marrow inoculate prior to its introduction.

B. Bone marrow

The bone marrow carries stem cells for the entire hematopoietic system and (at least hypothetically) could be used to treat individuals in whom some or all of these tissues are intrinsically defective or may have been damaged. Examples include those with immune deficiency diseases, some anemias, and the effects of cancer therapies. Indeed, transplantation of bone marrow can provide benefits to some of these patients, but it also carries unique risks. Bone marrow transplantation involves the placement of an immunocompetent tissue into a recipient who is usually immunodeficient for natural or therapeutic reasons. Even recipients with intact immune systems, however, undergo procedures that deliberately damage their immune systems to enable the transplanted bone marrow to establish itself in its new environment.

Under these circumstances, the immunocompetent cells in the transplanted bone marrow may recognize histocompatibility antigens on recipient cells as foreign and attack the host tissues (Fig. 17.13). This is a **graft-versus-host** (**GVH**) response, and the resulting damage is **graft-versus-host disease** (**GVHD**), which can be potentially fatal. GVHD can develop from two sources within the transplanted bone marrow: the stem cells and the mature T cells present in the implanted bone marrow. The most immediate and serious threat comes from the mature T cells because they are capable of generating rapid and severe GVH responses. These responses can be minimized by pretreatment of the bone marrow inoculate to remove the T cells prior to implantation. It is hoped that lymphocytes generated from the implanted stem cells will become tolerant to host histocompatibility antigens as they undergo positive and negative selection in the recipient thymus. Tolerance is sometimes imperfect, but when GVH responses do result from the activity of donor stem cell-derived lymphocytes, they are usually transient and less severe than the GVH responses initiated by mature T cells within the bone marrow inoculum.

Although genetic matching of donor and recipient can minimize the risk of GVHD, it is also important for another reason. T cells generated by implanted stem cells must undergo thymic education in the recipient thymus. Some degree of matching between the MHC class I and II genes of the host and donor is required for the positive and negative selection events of thymic education to proceed effectively. Bone marrow recipients are also vulnerable to opportunistic infection while the new marrow becomes established and must be carefully monitored for infection and treated appropriately. Once established and functioning, the transplanted hematopoietic stem cells can often provide a normal or near-normal condition to recipients for the remainder of their lives.

C. Immune-privileged sites

Some anatomic sites are "permissive" in tolerating genetic mismatches between donor and recipient that would lead to prompt rejection in most parts of the body. Allogeneic and xenogeneic grafts that would be rapidly rejected at most sites in the body can often survive when placed into these areas. These sites are termed **immune-privileged**

sites, and each has features that limit the immune response to cells and molecules within them. The immune-privileged sites include the eye, the testicular tubules, the brain, and perhaps the placenta.

The eye has several features that make it a privileged site. The aqueous humor of the anterior chamber allows cells and molecules to exist without close contact with the vasculature, thus hiding them from the immune system to some extent. In addition, the immunologic processes that inhibit immune responses, such as the apoptotic death of lymphocytes attacking tissues in the eye, operate very rapidly, perhaps protecting the eye from inflammatory damage. This mechanism may also account, at least in part, for the ease with which corneas can be transplanted between individuals with genetic differences that would be difficult to overcome with other tissues.

The lumen of the testes also provides an immunologically privileged site. The testicular tubules are developed and closed prior to the development of the immune system. Because the Sertoli cells and other tubular elements prevent any subsequent passage of immune cells into the testicular tubules, the molecules and cells that are unique to that environment (e.g., spermatogonia and developing sperm) are never recognized as self by the immune system. As a result, if the testicular tubules are breached by infection, injury, or surgical intervention, the immune system can react against the seemingly foreign antigens that become exposed. It is estimated that a portion of male infertility cases may stem from immune responses against exposed testicular tubule elements.

The brain is sometimes cited as an immune-privileged site, because the blood–brain barrier can limit the exchange of cells and large molecules between the vasculature and the nervous system. The extent of this isolation is still somewhat unclear, as is the extent to which the cells of the immune system recirculate through nervous tissue. It appears that mechanisms that rapidly suppress potentially dangerous immune-mediated injury, similar to those seen in the eye, may also exist in the brain.

The placenta presents an interesting conundrum. The developing fetus typically expresses numerous histocompatibility antigens that are foreign to the mother. Why, therefore, does the maternal immune system not attach and destroy the fetus? Although the basis for the sheltering of the fetus from the maternal immune system (aside from maternal IgG crossing the placenta to provide passive protection to the fetus) has yet to be clarified, several structural and biochemical features of the fetal/uterine environment have been suggested as contributing factors.

V. TISSUE SOURCES

Tissues available for transplantation can come from various different sources. Traditionally, they have been harvested from voluntary living donors or from cadavers. In the case of cadaver donors, permission must usually be obtained through the documented permission of the donor

given prior to death or through the agreement of family or guardians. Depending on the nature of the tissue, donated cells can sometimes be expanded or modified in vitro prior to implantation. Increasing research into the use of stem cells, either from adult or embryonic sources, provides yet another potential source but has had limited use in humans to this point. Finally, the search for available organs has been extended to other species, and the use of primate and swine donors has provided some benefits, although it has been limited by other problems inherent in xenogeneic exchanges.

A. Human tissues and organs

The total number of transplants that have been performed now exceeds a half million worldwide. The increased efficacy of transplantation has been made possible by continual improvements in techniques, in the ability to genetically match donors and recipients, and in the ongoing development of immunosuppressive and antibiotic agents that can be used to manipulate the recipient immune system to permit graft survival without an accompanying overwhelming sepsis.

1. **Organ procurement and distribution:** A growing imbalance exists between the number of organs available for transplantation and the number of patients awaiting them, and the effective distribution of available organs has become increasingly complicated. In the United States, organ distribution is managed through the United Network for Organ Sharing (UNOS), the organization that administers the federally funded Organ Procurement and Transplantation Network. UNOS uses various factors, including the degree of genetic matching, potential benefit to the recipient, and geographical priorities to prioritize the assignment of donated organs as they become available. UNOS maintains a regularly updated web site available to the public that details the types of organs, number of transplants performed, success rates, waiting lists, and other criteria.

2. **Stem cell and fetal sources:** The ability to transfer healthy stem cells that are self-renewing and capable of generating new cells and/or tissues offers benefit to various injuries (e.g., burn wounds, spinal cord injuries) and diseases (e.g., arthritis, diabetes, cardiovascular disease, and neurologic diseases such as Alzheimer disease and Parkinson disease). In some cases, these represent new forms of therapy; in other cases, they extend the effectiveness of previous therapies. For example, transplantation of pancreatic islet cells has been used to treat diabetes, but the transplanted cells have finite life spans. The transplantation of stem cells that are capable of generating these cells provides a potentially permanent replacement therapy.

   Adult stem cells have already been used in a limited number of human cases, but their ability to generate various new tissues is more limited. In addition, much has yet to be learned about how best to obtain and prepare them for use. Their primary application thus far has been the use of hematopoietic stem cells in bone marrow transplantation. **Embryonic stem cells** have a broader

capacity for regeneration, as has been demonstrated in experimental animal models, but their use in humans has been restricted by practical and ethical considerations.

3. **Ethical considerations:** Transplantation involves decisions that may create ethical difficulties for some individuals. In some cases, cultural or religious customs forbid individuals from participating as either donors or recipients of transplantation and even blood transfusion. Even when there are no such general limitations, individuals are often personally reluctant to offer themselves as potential donors. As a result, the need for donated organs greatly exceeds the supply, creating the need for a system such as UNOS that regulates their distribution to prevent availability from becoming dependent on a potential recipient's wealth or social/political influence.

   The potential use of embryonic stem cells faces social and religious opposition from some segments of the scientific, religious, and general communities. Currently, this opposition has imposed severe limitations on obtaining and using human embryonic stem cells for either research or therapeutic use.

B. Nonhuman (xeno-) tissues and organs

The shortage of available human organs has spurred research into the use of nonhuman alternatives. Numerous attempts have been made to use animal donors. Primates are an obvious donor choice because of their close genetic relationship to humans. Pigs have many physiologic similarities to humans, and some breeds have organs that are an appropriate size for use in human recipients. Pig skin has also been used on occasion for temporary coverage of damaged areas in human burn victims.

Xenotransplantation has not been very successful or widely used, however. Xenografts face significant immunologic obstacles. Concern also exists about the potential for introducing zoonotic infections (infections passed from one species to another) through xenotransplantation. Finally, some individuals oppose the use of xenografts on ethical grounds.

Naturally existing antibodies in human serum, such as those against ABO antigens on human erythrocytes, can react with xenogeneic tissues to produce hyperacute rejections. NK cells can detect stress molecules on xenograft cells and bind to them via their killer activation receptors. However, the absence of human MHC class I molecules on the xenografts prevents the NK cells from ceasing the killing response through binding of their killer inhibition receptors. Xenogeneic cells lack enzymes that protect them against the attachment of human complement components that lead to cell lysis. These various mechanisms often destroy xenografts before the T cell-mediated responses typically associated with allograft rejection are even generated. Attempts to resolve these problems have used genetic engineering of the animal donors to introduce various human genes. Although there have been promising experimental advances, they have not yet significantly increased the clinical application of xenotransplantation.

Chapter Summary

- The genetic match (similarity/disparity) between the donor and the host is a very important factor in determining the likelihood of a successful transplant.
- **Histocompatibility genes** encode histocompatibility antigens. Among these are the MHC class I and II molecules encoded within the **major histocompatibility complex** (**MHC**).
- Grafts that are placed in their normal anatomic location are called **orthotopic** grafts. Grafts that are placed into a site other than their normal one are called **heterotopic** grafts.
- **Autografts** are those transferred from one part of an individual to another location on that same individual. **Syngeneic** grafts are those transferred between different individuals who are genetically identical or members of the same inbred strain of experimental animals. **Allogeneic** grafts (or **allografts**) are transferred between two genetically disparate individuals of the same species. **Xenogeneic** grafts (or **xenografts**) are those exchanged between members of different species.
- The **laws of transplantation** can be summarized as follows: *A host can recognize as foreign and mount a response against any histocompatibility antigen not encoded within its own cells.*
- The recipient immune system recognizes peptide fragments presented by MHC class I or II molecules. In the case of transplanted tissues, the genes of the engrafted cells may encode molecules that also can be detected by the recipient immune system and function as histocompatibility antigens. The recognition of foreign histocompatibility antigens and the activation of T cells against them involve processes that are very similar to those involved in the initiation of responses against antigens derived from infectious organisms.
- **Chronic rejections** are the slowest and the least vigorous type of rejection. Chronic rejections are typical of situations in which the donor and recipient differ by only non-MHC histocompatibility gene differences. **Acute rejections** occur much sooner after graft emplacement than do chronic rejections (e.g., 2 to 4 weeks). **Hyperacute rejections** are the most rapid type of rejection. They are initiated and completed within a very few days of graft placement, usually before the grafted tissue or organs can establish connections with the recipient vasculature. **Second set rejection** are grafts that are rejected more rapidly when repeated on a recipient who rejected the same type of graft on a previous occasion.
- Development of delayed (-type) hypersensitivity (DTH) and cytotoxic T-lymphocyte (CTL) responses directed against histocompatibility antigens have been demonstrated in both acute and chronic rejections.
- Steps can be taken to inhibit the ability of the recipient immune system to attack and damage the engrafted tissues. **Specific immune tolerance** involves a selective inhibition of the responsiveness to a given antigen or set of antigens. **Immune suppression**

(or **immunosuppression**) is a broad and general inhibition of immune responsiveness without regard to specificity. A second approach to inducing a less than global inhibition of the immune response has been the use of antibodies directed at molecules on the surface of the cells involved in immune responses, particularly lymphocytes and antigen-presenting cells.

- ABO mismatching can result in massive destruction of transfused red blood cells (**transfusion reaction**) and, if severe enough, can produce a type of transfusion reaction known as an **acute hemolytic reaction** within 24 hours of transfusion.
- When an Rh-negative (Rh^-) individual is exposed to Rh-positive (Rh^+) erythrocytes, he or she can generate antibodies, some of which are of the IgG isotype. In the case of an Rh^- mother carrying an Rh^+ fetus, the maternal anti-Rh IgG antibodies can cross the placenta and bind to fetal erythrocytes. This can lead to **hemolytic disease of the newborn**.
- **Graft-versus-host disease** (**GVHD**) can develop from two sources within transplanted bone marrow: the stem cells and the mature T cells present in the implanted bone marrow. The latter present the most serious risk of developing GVHD, but the risk can be minimized by removing them from the bone marrow inoculate prior to its infusion.
- Tissues available for transplantation can come from various different sources. Traditionally, they have been harvested from voluntary living donors or from cadavers.

Study Questions

17.1. A 23-year-old female has HLA genotype A3/A8, B1/B8, C4/C1. For each locus, the maternal allele is listed first and the paternal allele second. Several potential donors are available for an organ graft. Which of the following donors would be the closest match?

A. Donor A: A8/A27, B24/B8, C4/C9
B. Donor B: A3/A3, B27/B8, C1/C1
C. Donor C: A8/A6, B44/B8, C4/C1
D. Donor D: A6/A27, B1/B8, C4/C2
E. Donor E: A3/A8, B1/B27, C9/C4

The answer is B. The closest match will have the fewest mismatched HLA genes not present in the recipient. For donor B, only HLA B27 is not already present in the recipient. Donor A has three mismatches, Donor C has two mismatches, Donor D has three mismatches, and Donor E has two mismatches.

17.2. After receiving a kidney transplant from the most appropriate available donor, a 38-year-old female is administered immunosuppressive drugs, including cyclosporine, in order to

A. decrease T-cell production of IL-2.
B. destroy stem cells in her bone marrow.
C. induce involution of her thymus.
D. inhibit macrophage release of IFN-γ.
E. reduce plasma cell secretion of IgG antibodies.

The answer is A. Cyclosporine decreases T-cell production of IL-2, resulting in decreased T-cell proliferation. Cyclosporine treatment does not destroy bone marrow stem cells, nor does it induce thymic involution. Neither macrophage release of IFN-γ nor plasma cell secretion of IgG antibodies is affected by cyclosporine.

17.3. A 6-year-old male receives a bone marrow transplant from his father during treatment for acute myelogenous leukemia. Of primary concern will be the potential development of

A. acute rejection.
B. an allergic reaction.
C. autoimmune responses.
D. graft-versus-host disease.
E. immediate hypersensitivity.

The answer is D. Graft-versus-host (GVH) disease is a risk because bone marrow contains immunocompetent tissue. The GVH response is directed against host antigens that are not present in the donor bone marrow. Recipients of bone marrow transplants are usually immunocompromised or immunosuppressed, resulting in little risk for development of host-versus-graft responses such as acute rejection. Allergic reactions, also described as type I or immediate hypersensitivity reactions, do not occur in response to bone marrow transplantation. An autoimmune response is one directed by the immune system against self-antigens.

17.4. With no therapeutic intervention, the most likely outcome for a transplanted skin graft obtained from an unrelated donor who is HLA identical to the recipient is

A. acute rejection.
B. chronic rejection.
C. graft-versus-host disease.
D. hyperacute rejection.
E. long-term success.

The answer is B. Chronic rejection is most likely to occur, over months to years, in such a situation. Unrelated HLA identical individuals will have numerous mismatches of minor histocompatibility genes. Because the major histocompatibility genes match, hyperacute and acute rejections are unlikely to occur. Skin does not contain immunocompetent tissue and cannot mount a graft versus host response. Even with identical major histocompatibility genes, long-term success of a transplanted skin graft will require immunosuppressive therapy.

17.5. What are the possible ABO blood types of children to the union of a man who has blood type AB and a woman who has blood type O?

A. A only
B. A and B only
C. A, B, and AB only
D. A, B, AB, and O
E. O only

The answer is B. Blood types A and B are both possible in children of parents with type AB and type O. The genders of the parents and of the children are inconsequential because inheritance of ABO blood group is autosomal. A and B are codominant and are both dominant to O. In this example, children will inherit either the A or B allele from the father and the O allele from their mother and will have either blood type A or blood type B. Inheritance of both A and B or of O only is not possible, eliminating types AB and O as possible blood types among the children of this couple.

Tumor Immunity 19

I. OVERVIEW

Cell growth and cell death are normally balanced so that a stable number of cells are maintained in a given tissue. Occasionally, however, cells arise that no longer respond to the usual checks and balances for division and death. These are tumor cells. Development from a normal cell to a cancerous one requires several transformation steps. Transformed tumor cells express characteristic cell surface antigens, and these antigens often initiate immune responses. Therapeutic approaches, which attempt to exploit these normal immune responses to tumors, continue to be investigated. However, tumors also evade recognition by the immune system, and at times, tumor growth appears to be enhanced by immune mediators produced against that very tumor.

II. CANCER

A **tumor**, or **neoplasm**, is a collection of the clonal descendants of a cell whose growth has gone unchecked. When a tumor continues to grow and to invade healthy tissue, it is considered to be a **cancer**.

A. Terminology and definitions

Malignant tumors are distinguished from **benign** tumors by their progressive growth and invasiveness. **Metastasis** is a characteristic of many malignant tumors (cancers). Metastatic cells become dislodged from the main tumor, invade blood or lymphatic vessels, and travel to other tissues, where they continue to grow and to invade. In this way, tumors at one site can give rise to secondary tumors at other sites within the body (Fig. 19.1).

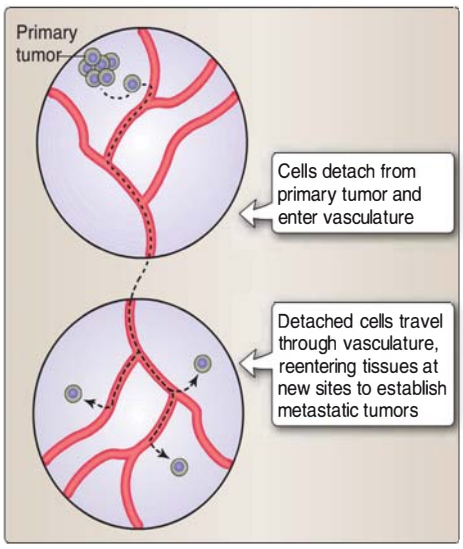

Figure 19.1
Metastasis. Tumor cells can detach from the primary tumor and travel through the vasculature to establish metastatic tumors at other sites.

Classification of tumors is based on the embryonic origin of the tissue from which the malignant cells are derived. **Carcinomas** develop from endodermal or ectodermal tissues (e.g., skin, glands) and constitute most malignant tumors, including cancers of the breast, colon, and lung. **Sarcomas** develop from bone and cartilage and have a much lower incidence than carcinomas. **Leukemias** are malignant cells of hematopoietic lineage that proliferate as individual cells, whereas **lymphomas** arise from malignant hematopoietic cells but grow as solid tumors.

B. Malignant transformation

Experiments with cultured cells have allowed researchers to trace the development of tumors. Cells that are infected with certain viruses

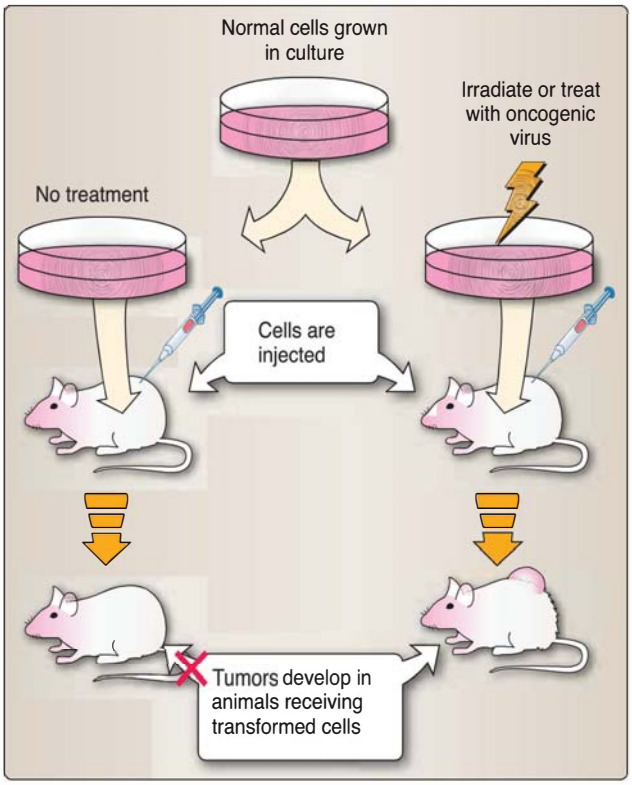

Figure 19.2
Malignant transformation. Transfection or irradiation of normal cultured cells alters them in such a way that they will induce the formation of tumors when injected into experimental animals.

(e.g., SV40 or Rous sarcoma virus), irradiated (ultraviolet light or ionizing radiation), or treated with certain DNA-altering chemicals show altered growth properties and often induce tumors when injected into animals (Fig. 19.2). Such transformed cells can be grown in culture almost indefinitely. In some cases when retroviruses (RNA viruses) induce such growth change in cells, the process is related to the presence of **oncogenes** (cancer-producing genes) of the virus. Change from a normal cell to a tumor cell is known as **malignant transformation**. The process of malignant transformation requires at least two distinct phases. The first phase is **initiation**, which changes the genome of the cell; the second is **promotion**, which results in stimulation of cell division.

C. Tumors of the immune system

Lymphomas and **leukemias** are tumors of immune cells. Lymphomas are solid tumors within lymphoid tissues such as bone marrow and lymph nodes. Hodgkin and non-Hodgkin lymphomas are examples. Leukemias are composed of dispersed single cells that arise from the bone marrow and may involve cells from either lymphoid or myeloid lineages. Acute leukemias arise from less mature cells and are found in both children and adults. Chronic leukemias are tumors of more mature cells that develop slowly and are seen only in adults.

D. Oncogenes and cell growth

In some cases, malignant transformation induced by retroviruses (or RNA viruses) has been linked to the presence of cancer-causing genes called **oncogenes** within the retrovirus. The viral oncogene *Src* (v-*Src*) from the Rous sarcoma virus is an example of this type of gene. Inserting this virus into normal cells in culture results in malignant transformation. Cells have genes, referred to as proto-oncogenes or cellular oncogenes, that are counterparts of retroviral oncogenes. Conversion of a cellular proto-oncogene (e.g., c-*Src*) into a cancer-promoting oncogene (e.g., v-*Src*) can occur by mutation. This change is generally accompanied by a change in cellular growth because the cellular oncogenes normally code for growth-controlling proteins.

1. **Stimulators of cell division:** Oncogenes that function as stimulators of cell division include those that encode growth factors and growth factor receptors. Oncogenes may also code for proteins involved in signaling pathways, particularly via tyrosine phosphorylation, and those that function as transcription factors. Increased activity of proteins encoded by oncogenes in this category can result in uncontrolled cellular proliferation. Examples include *sis*, which encodes a chain of platelet-derived growth factor, and *erb-b*, which encodes epidermal growth factor receptor (Table 19.1). *Src* and *Abl* in their proto-oncogenic (cellular) forms encode tyrosine kinases that regulate cell division. In their oncogenic forms, the regulatory function of these proteins has been lost, and the affected cells will have unregulated proliferation. *Ras* codes for a GTP-binding protein; continued stimulation of division occurs when the oncogene form of

Table 19.1
ONCOGENES

Classification	Gene	Function
Stimulators of cell division	*Abl*	Tyrosine kinase
	erb-b	Receptor for epidermal growth factor
	Fms	Receptor for colony-stimulating factor
	fos	Component of a transcription factor
	Jun	Component of a transcription factor
	Myc	DNA-binding protein
	Ras	GTP-binding protein
	Sis	Altered form of platelet-derived growth factor
	Src	Tyrosine kinase
Inhibitors of cell division: tumor suppressors	*NF1*	Suppressor of neurofibromatosis
	Rb	Suppressor of retinoblastoma
	p53	Nuclear protein that suppresses tumor growth
Apoptosis regulators	*Bax*	Stimulator of programmed cell death
	Bcl-2	Inhibitor of programmed cell death

ras remains active. Transcription factors are encoded by the *fos*, *jun*, and *abl* oncogenes.

2. **Tumor suppressor genes:** Oncogenes that are inhibitors of cell division and are sometimes referred to as *anti-oncogenes* function as tumor suppressor genes. When a tumor suppressor is inactivated through mutation, the ability to suppress cell growth is lost, and uncontrollable cell proliferation can result. Mutated forms of the tumor suppressor *p53* have been found in many human tumor cells. Mutation of the tumor suppressor *Rb* can lead to development of the malignant retinal tumors in children with hereditary retinoblastoma.

3. **Regulators of apoptosis:** A third category of cancer-related genes are those that regulate apoptosis. Some members of this group prevent programmed cell death (apoptosis), whereas others induce it. *Bcl-2*, an antiapoptotic oncogene discovered in a B-cell follicular lymphoma, normally regulates cell survival of selected lymphocytes during development. When *Bcl-2* is inappropriately expressed, a cell that would normally die via apoptosis instead survives, resulting in unregulated cell proliferation. One of several proteins related to the prosurvival *Bcl-2* is *Bax*, which is pro-apoptotic. The ratio of *Bcl-2* to *Bax* proteins within a cell determines whether that cell will survive or undergo programmed cell death.

E. Tumor antigens

Tumor cells express antigens on their surfaces that are often the targets of immune responses. Many tumor antigens are cellular peptides presented by MHC molecules that stimulate antigen-specific T-cell proliferation (Table 19.2). Some antigenic molecules on tumor cells are variant forms of normal proteins that result from mutation of the gene encoding the protein. Others are normally found only on cells of certain developmental stages or lineages and are antigenic when expressed out of their usual context. Still, other tumor antigens are simply molecules found at higher than normal concentration on tumor cells, whereas a few others are proteins encoded by genes unique to tumors.

1. **Tumor-specific transplantation antigens (TSTAs):** TSTAs are not found on normal somatic cells but result from mutations of genes and the resulting altered proteins that are expressed by the tumor cells. Identification of TSTAs on naturally occurring tumors has proved difficult, most likely because the immune response generally eliminates cells that express TSTAs at levels great enough to be antigenic. However, TSTAs have been identified on tumors induced in culture by viral transformation or treatment with carcinogenic chemicals. When introduced into syngeneic mice, TSTAs induce cell-mediated immune responses that attack the tumor cells (Fig. 19.3).

2. **Tumor-associated transplantation antigens (TATAs):** TATAs are not unique to tumor cells; rather, their expression on tumor cells is altered. For example, the tumor antigen may be found in

Table 19.2
TUMOR-ASSOCIATED TRANSPLANTATION ANTIGENS (TATAs)

Antigen	Expression
HER2/*neu*	Low expression in normal epithelial tissue/over expression in breast tumors
AFP	Serum of fetuses and patients with liver cancer
CEA	Fetal liver and serum of patients with colorectal cancer
BAGE	Melanoma/normal testis
GAGE-1 and 2	Melanoma/normal testis
MAGE-3	Melanoma/normal testis
RAGE	Melanoma/normal testis
P15	Wide expression
PRAME	Wide expression
SART-1	Wide expression

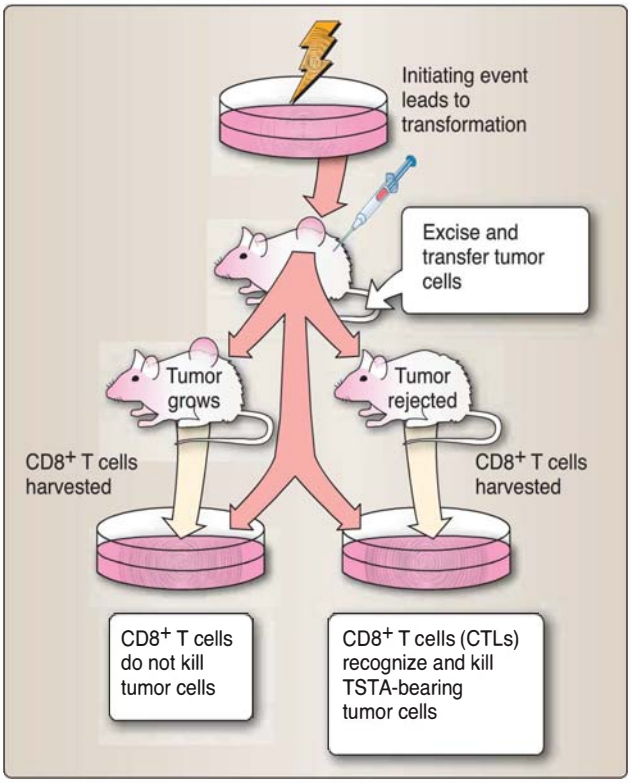

Figure 19.3
Identification of TSTAs. Transformed cells injected into syngeneic mice sometimes induce tumor formation but sometimes do not. When a nontumorigenic line is generated (tumor rejected) and $CD8^+$ CTLs are harvested from that animal, those CTL cells can recognize TSTA-bearing tumor cells.

excessive amounts or may be expressed on a cell type where it would not normally exist. Human breast cancer cells often have high levels of the growth factor receptor *HER2/neu*, which is found in very low concentrations on normal cells but is overexpressed on approximately 20% to 30% of primary breast tumors. HER2+ tumors are aggressive with high chance of recurrence (see Table 19.2). MAGE-1, BAGE, and GAGE-2 are examples of oncofetal antigens because they are expressed on tumors and on normal fetal cells. After the fetal stage of development, normal differentiated cells do not express these oncofetal antigens, except for germline cells of the testis. However, oncofetal antigens are also displayed on human melanomas, gliomas, and breast carcinomas. Another oncofetal antigen, alpha-fetoprotein, is found in fetal liver cells and liver carcinoma cells (and serum of individuals with liver cancer). Other tumor cells may express greater than normal levels of tissue-specific molecules (e.g., MART-1 and gp75 are overexpressed by melanoma cells), whereas still other tumor cells express aberrant forms of such molecules. An example is MUC-1, a glycosylated (carbohydrate-containing) mucin that is found with decreased glycosylation on pancreatic tumors. Decreased levels of carbohydrates may reveal hidden MUC-1 epitopes.

III. IMMUNE SURVEILLANCE

The immune surveillance theory suggests that cancer cells frequently arise within the body but are normally eliminated before they multiply sufficiently to become clinically detectable. Accordingly, through the workings of an effective immune system that patrols the body and mounts responses against abnormal cells, most transformed cells never become true cancers. Tumors arise only if they are able to escape immune surveillance (Fig. 19.4). Evidence supporting the immune surveillance theory comes from immunosuppressed and immunodeficient individuals who have increased tumor incidence.

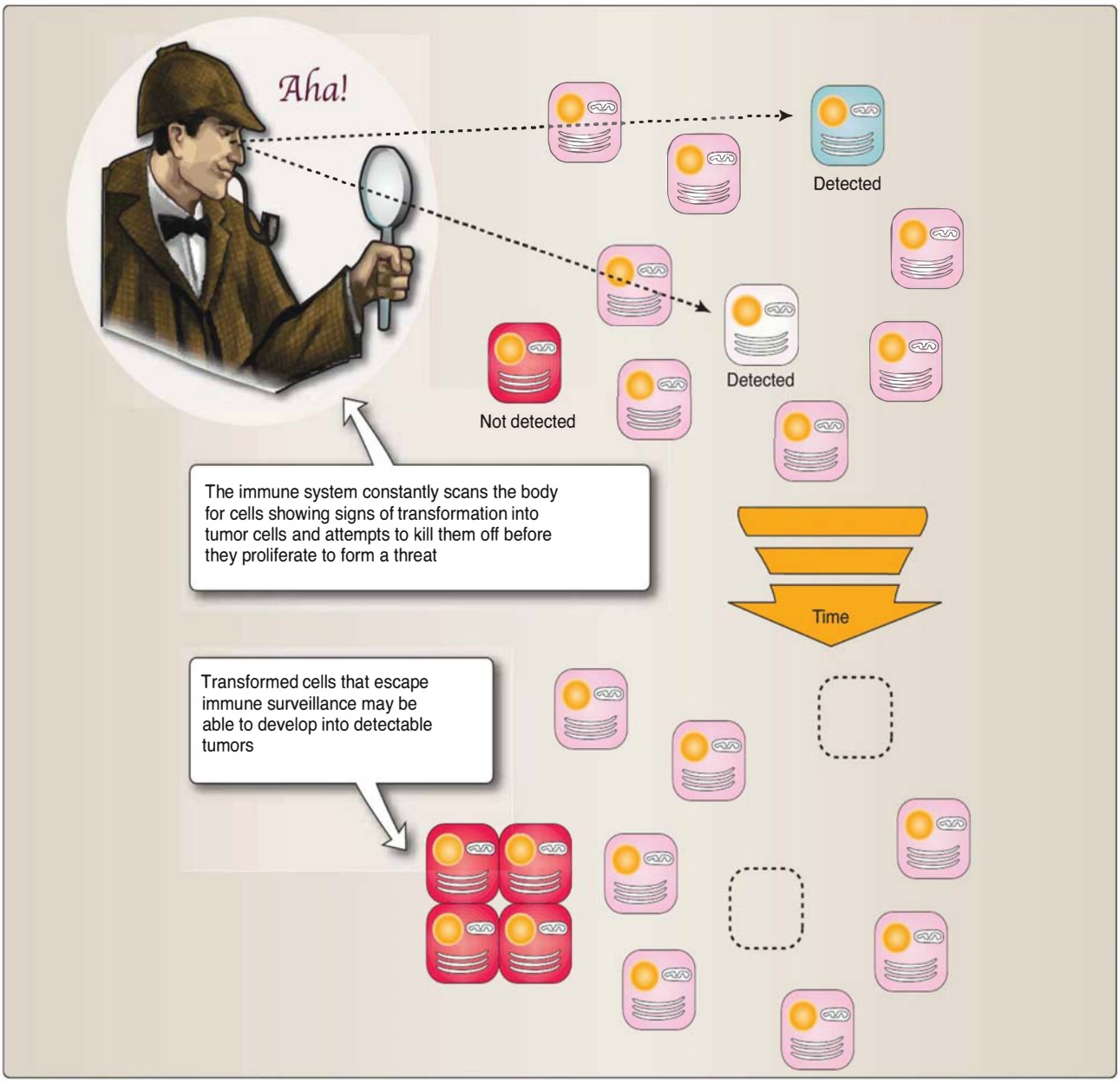

Figure 19.4
Immune surveillance. The immune system is on patrol for abnormal cells, often halting malignant cell growth before tumors arise. Only those malignant cells that escape immune detection become clinical tumors.

A. Innate

The first line of immune defense against tumors comes from the less specific component of the immune response, the innate immune system. These mechanisms prevent spread of malignant disease and are not specific to particular tumor antigens but recognize broad characteristics of tumor cells.

1. **NK cells:** NK cells have a limited ability to discriminate between tumor cells and normal cells. Recall that NK recognition of targets occurs via killer activation receptors (KARs) and killer inhibitory receptors (KIRs) (see Chapter 5). KIRs recognize human MHC class I molecules: HLA-B and HLA-C. Another inhibitory NK receptor, CD94, recognizes another class I molecule called HLA-E. When a KAR is engaged by binding to its carbohydrate ligands on target cells, the "kill" signal to the NK cell is activated (Fig. 19.5). However, if the KIR receptors are engaged by binding

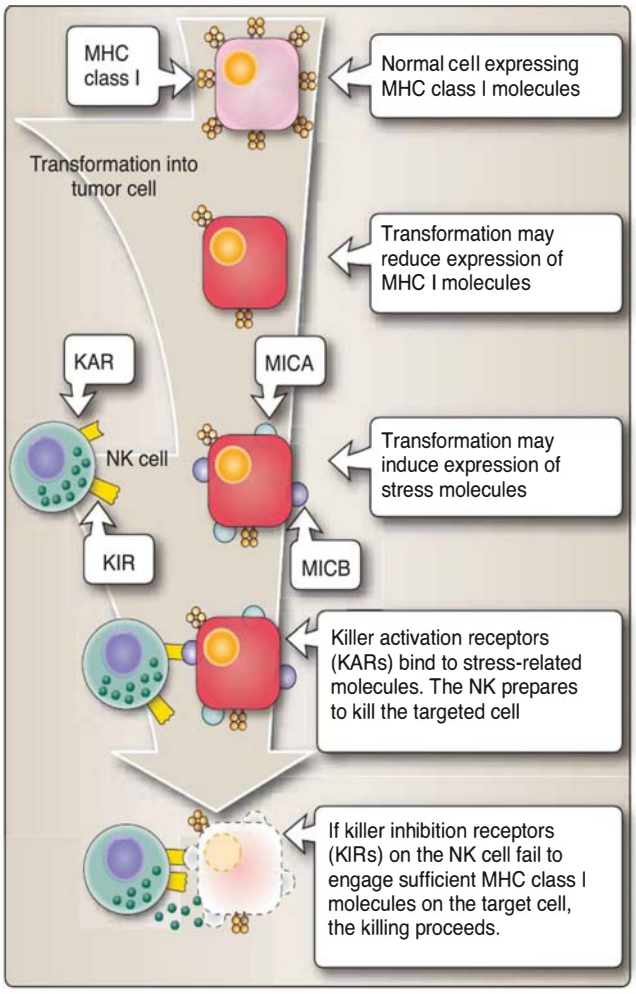

Figure 19.5
NK recognition of tumor cell targets. Transformed cells may have fewer MHC I molecules per cell and express stress molecules that are recognized by KARs on NK cells, allowing the NK cell to kill that target cell. Decreased MHC I expression decreases NK-KIR binding, permitting killing of that target cell.

of ligands on the surface of a target cell, then the "do not kill" signal is received by the NK cell, and the target cell survives. Failure to engage the KIR will result in NK-induced lysis of the target cell. When expression of MHC I molecules on the cell surface is abnormally low, as is the case in some malignant cells, KIRs might not recognize ligands on the target (malignant) cell and might proceed to kill it. In some cases, Fc receptors on NK cells can bind to antibody present on tumor cells (produced as part of the adaptive response against the tumor cell), leading to antibody-dependent cellular cytotoxicity.

NK cells that attack malignant cells are sometimes referred to as **lymphokine-activated killer cells** (**LAKs**). These cells are generated in the presence of high concentrations of interleukin-2 and are able to kill fresh tumor cells. **Tumor-infiltrating lymphocytes** (**TILs**) are T lymphocytes, often $CD8^+$ CTLs. They may also include some $CD4^+$ T cells and NKT cells. A therapeutic strategy against malignant melanoma involves obtaining tumor-specific TILs from tumor biopsies and expanding the cells by stimulating with interleukin-2. These cells are then injected back into the patient. In some cases, partial regression of the tumors has been observed.

2. **Cytokines:** Cytokines with antitumor activity are secreted by macrophages, which are often found in the vicinity of tumors (Fig. 19.6). **Tumor necrosis factor** (**TNF**) is one such antitumor cytokine. When injected into animals with tumors, TNF-α and TNF-β can stimulate necrosis of the tumor cells. TNF-α also inhibits angiogenesis, the growth of new blood vessels by decreasing blood flow to the tumor. **Interferons** are another group of cytokines with antitumor activity. IFN-α, IFN-β, and IFN-γ have all been shown to increase MHC I expression on tumor cells (which often downregulate MHC I expression to evade the immune response). Increasing the MHC I expression can increase susceptibility of the tumor cells to CTLs. IFN-γ may also directly inhibit proliferation of tumor cells.

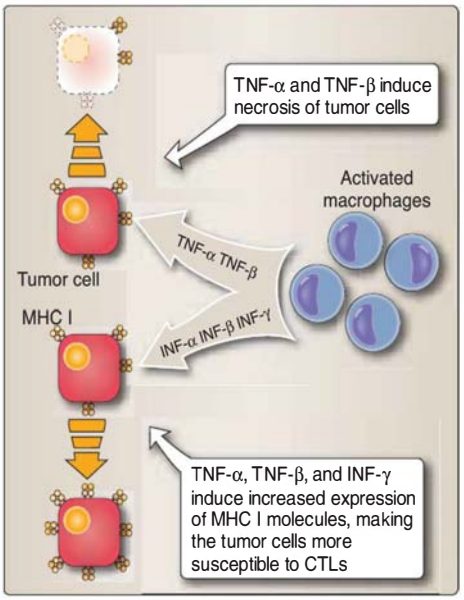

Figure 19.6
Cytokines with antitumor activity. Activated macrophages release TNF-α and TNF-β, which induce tumor cell necrosis and also release IFN-α, IFN-β, and IFN-γ, which increase tumor cell MHC I molecules on tumor cells, allowing them to become targets of CTL killing.

B. Adaptive

Specific antigen-dependent immune responses can develop to antigens on tumor cells. Although they are not always effective in halting progression of a tumor, evidence exists that both humoral and cell-mediated immune responses can be induced in response to the presence of malignant cells (Fig. 19.7).

- **Antibodies** are known to be generated against certain tumor-specific antigens present on the surface of malignant cells.
- **CTLs** can sometimes kill tumor cells by direct contact.
- **DTH** reactions involve Th1 cells recruiting and activating macrophages, which attack and kill tumor cells.

IV. IMMUNE EVASION

Although both innate and adaptive immune responses are evoked by malignant cells, tumor cells often escape the immune system and go on to produce tumors and diseases that are often fatal. Several mechanisms

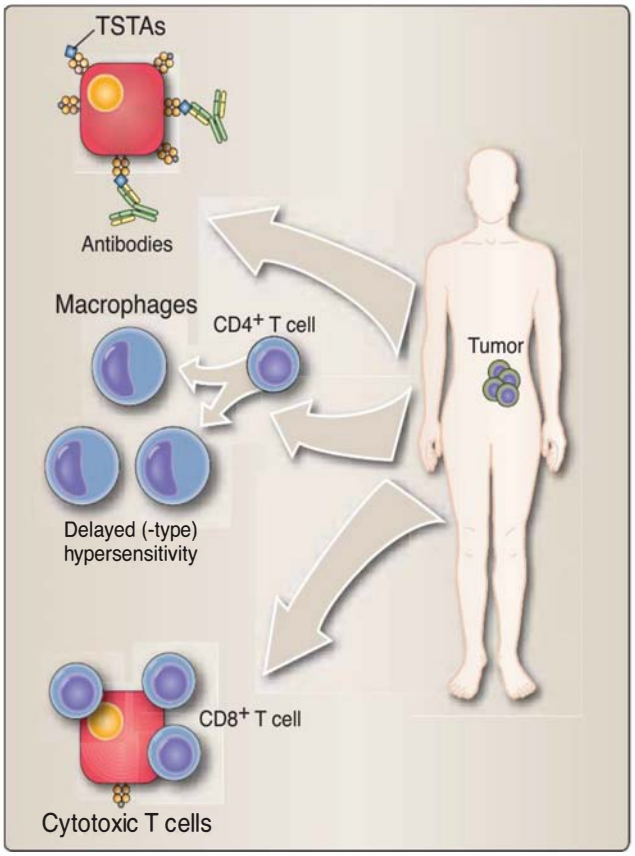

Figure 19.7
Adaptive immune responses against tumor cells. Humoral as well as cell-mediated immune responses are mounted against tumor cells.

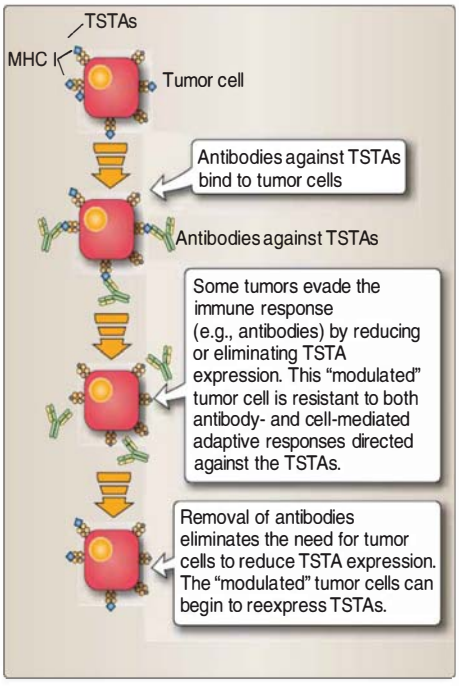

Figure 19.8
Antigenic modulation. Antibodies to tumor antigens may cause the tumor to downregulate antigen expression.

that facilitate evasion of the immune response by tumor cells have been identified.

A. Antibody enhancement of tumor growth

Because attempts to immunize cancer patients by injecting specific antibodies that were developed in culture against their tumor cells often resulted in enhanced tumor growth, studies have been initiated to explore the mechanisms of antibody-induced tumor cell growth. The antitumor antibodies may bind to the antigens on the tumor cells, masking the antigens and blocking the ability of CTL cells to bind and kill the tumor cell. Antibody bound to tumor antigen may inhibit binding of Fc receptors on macrophages, dendritic cells, and NK cells.

B. Antibody modulation of tumor antigens

In the presence of antibodies directed against tumor antigens, down-regulation of expression of certain tumor-specific antigens has been demonstrated. In a process known as antigenic modulation, the antigens disappear for a time and then reappear when the antibody is eliminated. Cells that do not express the antigen are no longer targets of other adaptive immune responses (Fig. 19.8).

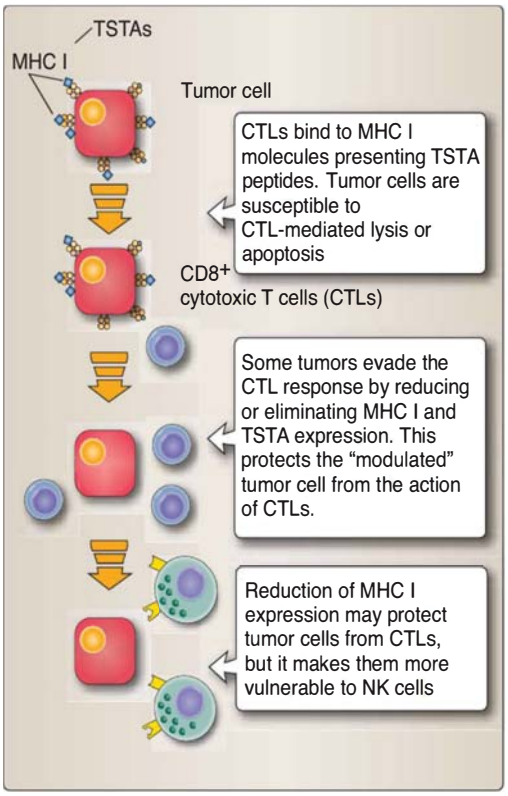

Figure 19.9
Decreased expression of tumor cell MHC I may impair CTL recognition, but increase recognition by and vulnerability to NK cells.

C. Modulation of MHC I expression

Tumor cells often express reduced levels of MHC I molecules. Malignant transformation may result in a reduction or total loss of MHC I molecules by the transformed cells. If tumor cells express decreased amounts of MHC I, NK cell responses to them may be enhanced, whereas CTL-mediated responses against those tumor cells are decreased (Fig. 19.9).

V. CANCER IMMUNOTHERAPY

Cancer immunotherapy is based on enhancement of the natural immune responses that the body mounts against malignant cells.

A. Cytokine therapy

Interleukins and interferons have been used to enhance the immune response to tumors. Because systemic administration of these cytokines can be dangerous, local application is required, complicating the treatment protocols. Although therapeutic benefit is sometimes obtained with cytokine therapy, more research and refinement of protocols are likely necessary before more widespread use and more benefit will be obtained from this approach (Fig. 19.10A).

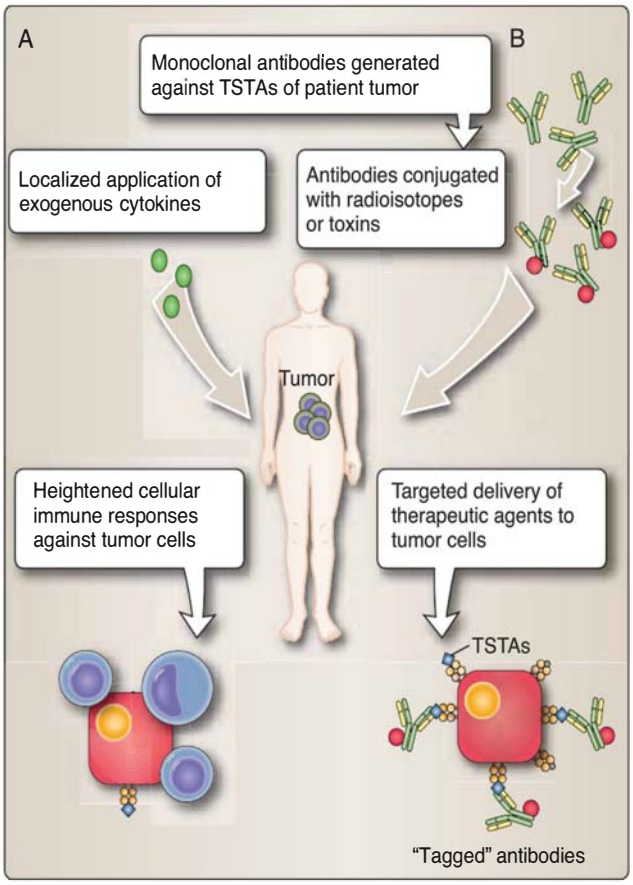

Figure 19.10
Cancer immunotherapies. **A.** Application of exogenous cytokines can heighten immune responses to tumor cells. **B.** Monoclonal antibodies generated against TSTAs of the patient's tumor cells can be "tagged" with toxins or radioactive materials to deliver a therapeutic "magic bullet" to a tumor.

B. Monoclonal antibodies

Anti-idiotypic monoclonal antibodies have been used to treat B-cell lymphomas (Fig. 19.10B), but the approach is complicated, requires custom antibodies for each patient's tumors, and is quite expensive; therefore it is not currently practical or efficacious for general use. More general approaches to produce monoclonal antibodies against determinants that are shared by all B-cell lymphomas are being investigated. Use of monoclonal antibodies to deliver a toxin or radioisotope directly to the tumor cells, sparing healthy cells, is another promising approach. Monoclonal antibodies are also being developed against certain growth factor receptors commonly expressed by certain tumors.

C. Cancer vaccines

Development of vaccines to protect against the future development of cancer has many obvious benefits. Identification of the viruses responsible for malignant transformation, such as human papillomavirus in cervical cancer, has facilitated development of an immunization protocol to prevent infection by the virus, thus preventing development of cervical cancer. Vaccines are also being developed in attempt

CLINICAL APPLICATION
Herceptin and HER2 positive breast cancer

Trastuzumab (Herceptin) is a drug therapy used to treat HER2+ breast cancer. Herceptin blocks binding to the *HER2/neu* receptor that is overexpressed on the tumor cells. The HER2 protein is a single chain growth factor receptor that normally functions by dimerizing with other receptor chains and signaling via phosphorylation of tyrosine residues. The normal biological response to HER signaling is stimulation of cell division. Tumors that express HER2 are overstimulated to divide. When binding and signaling via HER2 is blocked by the monoclonal antibody drug therapy, the cells expressing HER2 are arrested in the G1 phase of the cell cycle and their division is halted.

to prevent cancers from recurring in individuals who have been diagnosed with conditions including melanoma, a life-threatening skin cancer, and renal carcinoma. For melanoma, TSTAs have been shown to be quite similar from person to person, and vaccines now being developed are based on the common TSTAs.

Customized vaccines are also being made using a patient's own tumor cells and are given to patients after surgical removal of their tumors. Such vaccines are designed to stimulate an immune response against any malignant cells remaining in their bodies. Promising results have been obtained in some clinical trials.

Chapter Summary

- Cancer cells have unregulated rates of cell growth and invade healthy tissue.
- **Metastasis** is a characteristic of many malignant cells as they become dislodged from the main tumor and travel to distant sites in the body.
- **Lymphomas** and **leukemias** are tumors of immune cells that are derived from hematopoietic cells. Lymphomas are solid tumors, whereas leukemias grow as dispersed, single malignant cells.
- **Malignant transformation** is the process by which a normal cell becomes a cancerous cell.
- **Oncogenes** are sometimes linked to malignant transformation. Mutations of cellular oncogenes often results in a change in cellular growth.
- Tumor antigens include tumor-specific transplantation antigens (TSTAs) that result from altered proteins expressed as a consequence of gene mutations within tumor cells and tumor-associated transplantation antigens (TATAs) that are not unique to tumor cells but have unusual expression on tumor cells.
- The immune surveillance theory suggests that cancer cells frequently arise within the body but are normally eliminated by the immune system before a tumor develops.

- Innate immune responses against tumors include NK cell killing of tumors and macrophage production of antitumor cytokines, including tumor necrosis factor and the interferons.
- Adaptive immune responses against tumors include generation of antitumor antibodies, CTL killing of tumor cells, and DTH reactions.
- Immune evasion by tumor cells facilitates survival of malignant cells. Antitumor antibodies may actually enhance the growth of some tumors and may result in decreased detection of some tumor antigens. In addition, tumor cells often have lower than normal levels of MHC I molecules, helping the tumors to evade immune detection.
- Cancer immunotherapy is designed to increase the immune response against cancer cells. Cytokines and monoclonal antibodies have proven to have some limited effects in treating certain cancers. Vaccination, either to prevent development of a type of cancer or to inhibit recurrence of a tumor within a patient, continues to be explored.

Study Questions

19.1. Which of the following may be expected in cells over expressing *Src*?

A. Enhanced rate of apoptosis
B. Death by necrosis
C. Increased expression of MHC I molecules
D. Senescence (loss of ability to divide)
E. Unregulated cell division

The correct answer is E. A mutation in the oncogene *Src* results in loss of regulatory function of a tyrosine kinase that normally regulates cell division. *Src* does not regulate cell death by apoptosis or by necrosis nor would a mutant *Src* induce senescence. Increased MHC I expression would not be linked to a tumor cell with a mutated *Src*; tumor cells often have decreased levels of MHC I expression.

19.2. A bone marrow biopsy from a patient with acute lymphocytic leukemia reveals the presence of a mutated form of p53 within leukemic cells. This mutation is likely responsible for which of the following?

A. An increase in the *Bax-to-Bcl-2* ratio
B. Decreased activity of NK cell KIR function
C. Excess activity of a GTP-binding protein
D. Growth of malignant cells as a solid tumor
E. Loss of suppression of cell growth

The correct answer is E. *P53* is a tumor suppressor gene. When it is mutated, the suppressor action is lost, resulting in unregulated cell growth. An increase in the *Bax-to-Bcl-2* ratio would favor apoptosis and not tumor growth that is seen with mutant *p53*. *P53* mutants do not mediate NK cell KIR function. *P53* is a tumor suppressor gene and not a GTP-binding protein such as *ras*. Leukemias grow not as solid tumors but as dispersed, single malignant cells.

19.3. Which of the following is correct regarding tumor-specific transplantation antigens (TSTAs)?

A. Also present in high concentration on normal somatic cells
B. Often found on normal fetal cells as well as on tumor cells
C. Readily identified on most naturally occurring tumors
D. Result from mutant proteins expressed by tumor cells
E. Stimulate apoptosis on cells that express them

The correct answer is D. TSTAs result from mutant proteins expressed by tumor cells. Mutations of genes within the tumor cells lead to altered proteins on the surfaces of the tumor cells. TSTAs are not found on normal somatic cells or on normal fetal cells but are unique to tumors. Although they have been demonstrated on experimentally induced tumors, identification of TSTAs on naturally occurring tumors has proved to be very difficult. Stimulation of apoptosis of tumor cells would result in elimination of tumor cells and would be beneficial to the patient with the tumor. Expression of TSTAs does not appear to stimulate apoptosis.

19.4. According to the immune surveillance theory,

A. antibodies arise during fetal development that can destroy tumors.
B. cancer cells rarely arise within a normal individual.
C. innate immune responses eliminate specific tumor cell antigens.
D. tumors arise only if malignant cells escape immune detection.
E. tumor-infiltrating lymphocytes prevent malignant transformations.

The correct answer is D. According to the immune surveillance theory, tumors arise only if malignant cells escape detection by the immune system. This theory suggests that cancer cells frequently arise within the body but are normally eliminated before becoming clinically detectable. This theory does not suggest that germline-encoded antibodies develop to destroy tumors. Innate immune responses against tumors are based on broad characteristics of tumors, not on specific tumor cell antigens. Tumor-infiltrating lymphocytes may induce tumor regression and do not induce a normal cell to become transformed into a cancer cell.

19.5. Which of the following is a cytokine known to have antitumor activity?

A. Epidermal growth factor
B. Interferon-γ
C. Interleukin-2
D. Interleukin-12
E. Platelet-derived growth factor

The correct answer is B. Interferons-α, -β, and -γ have all been shown to increase MHC I expression on tumor cells, and IFN-γ also appears to inhibit tumor cell proliferation. The growth factors and other cytokines listed have growth stimulatory actions.

19.6. Lymphokine-activated killer (LAK) cells are indistinguishable from

A. B lymphocytes.
B. macrophages.
C. malignant somatic cells.
D. NK cells.
E. T lymphocytes.

The correct answer is D. LAK cells are NK cells that are generated in the presence of high concentrations of interleukin-2 and are able to kill fresh tumor cells. LAK cells are not B or T lymphocytes nor are they macrophages. LAK cells can kill tumor cells and are not themselves malignant somatic cells.

19.7. Which of the following provides evidence of immune evasion by tumor cells?

A. Downregulation of MHC I molecules by tumor cells
B. Enhanced production of tumor necrosis factor by macrophages
C. IFN-γ-mediated inhibition of tumor cell proliferation
D. Generation of antibodies against tumor-specific antigens
E. Stimulation of tumor cell apoptosis by increased Bax expression

The correct answer is A. Downregulation of MHC I molecules is a defense mechanism used by many tumor cells to evade recognition by the immune system. The other mechanisms listed all describe immune responses initiated against tumor cells that have the potential to stop tumor growth. TNF and IFN-γ are produced by macrophages and inhibit tumor cell proliferation. Antibodies directed against tumor-specific antigens are part of the humoral immune response aimed at halting tumor progression. Stimulation of apoptosis by increased Bax expression would serve to eliminate tumor cells and is therefore not a mechanism to evade the immune response.

19.8. A new method to reduce the incidence of cervical cancer involves

A. administration of tumor necrosis factor to the cervix.
B. injection of antibodies against other patients' cervical tumors.
C. stimulation of antibody-mediated cell lysis of cervical tumor cells.
D. use of patient's tumor cells to develop an individualized vaccine.
E. vaccination against human papillomavirus.

The correct answer is E. Vaccination against human papillomavirus, the causative agent in cervical cancer, may reduce the future incidence of cervical cancer. Neither administration of TNF nor injection of antibodies against other patients' cervical tumors is being done to prevent occurrence of cervical cancer. For certain other cancers, individualized vaccines are being used in clinical trials. However, such a vaccine requires that the patient have a tumor and would therefore not reduce the incidence of a type of cancer.