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

HYPERSENSITIVITY: ALLERGY, AUTOIMMUNITY, AND ALLOIMMUNITY

Hypersensitivity is an altered immunologic response to an antigen that results in disease or damage to the host. Hypersensitivity reactions can classified in two ways: by the source of the antigen that the immune system is attacking (allergy, autoimmunity, alloimmunity; Table 8-1) and by the mechanism that causes disease (types I, II, III, IV; see Table 8-3). The term allergy originally denoted both facets of the immune response: immunity, which is beneficial, and hypersensitivity, which is harmful. Allergy has now come to mean the deleterious effects of hypersensitivity to environmental (exogenous) antigens, and immunity means the protective responses to antigens expressed by disease-causing agents.

Autoimmunity is a disturbance in the immunologic tolerance of self-antigens. The immune system normally does not strongly recognize the individual’s own antigens. Healthy individuals of all ages, but particularly older adults, may produce low quantities of antibodies against their own antigens (autoantibodies), without development of overt autoimmune disease. Therefore, the presence of low quantities of autoantibodies does not necessarily indicate a disease state. Autoimmune diseases occur when the immune system reacts against self-antigens to such a degree that the person’s own tissues are damaged by autoantibodies or autoreactive T cells. Many clinical disorders are associated with autoimmune and are collectively referred to as autoimmune diseases (Table 8-2).

Alloimmunity (also termed isoimmunity) occurs when the immune system of one individual produces an immunologic reaction against tissues of another individual. Alloimmunity
Table 8-1  Relative Incidences and Examples of Hypersensitivity Reactions

<table>
<thead>
<tr>
<th>Target Antigen</th>
<th>Type I (Immunoglobulin E–[IgE] Mediated)</th>
<th>Type II (Tissue Specific)</th>
<th>Type III (Immune Complex)</th>
<th>Type IV (Cell Mediated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy</td>
<td>++++</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Environmental antigens</td>
<td>Hay fever</td>
<td>Hemolysis in drug allergies</td>
<td>Gluten (wheat) allergy</td>
<td>Poison ivy allergy</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>±</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Self-antigens</td>
<td>May contribute to some type III reactions</td>
<td>Autoimmune thrombocytopenia</td>
<td>Systemic lupus erythematosus</td>
<td>Hashimoto thyroiditis</td>
</tr>
<tr>
<td>Alloimmunity</td>
<td>±</td>
<td>+</td>
<td>Anaphylaxis to IgA in IV gamma globulin</td>
<td>Graft rejection</td>
</tr>
<tr>
<td>Another person’s antigens</td>
<td>May contribute to some type III reactions</td>
<td>Hemolytic disease of the newborn</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

*The frequency of each reaction is indicated in a range from rare (±) to very common (++++). An example of each reaction is given.

Table 8-2  Disorders Associated with Autoimmunity

<table>
<thead>
<tr>
<th>System Disease</th>
<th>Organ or Tissue</th>
<th>Probable Self-Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism (Graves disease)</td>
<td>Thyroid gland</td>
<td>Receptors for thyroid-stimulating hormone on plasma membrane of thyroid cells</td>
</tr>
<tr>
<td>Autoimmune thyroiditis</td>
<td>Thyroid gland</td>
<td>Thyroglobulin; microsomes</td>
</tr>
<tr>
<td>Primary myxedema</td>
<td>Thyroid gland</td>
<td>Microsomes</td>
</tr>
<tr>
<td>Insulin-dependent diabetes</td>
<td>Pancreas</td>
<td>Islet cells, insulin, insulin receptors on pancreatic cells</td>
</tr>
<tr>
<td>Addison disease</td>
<td>Adrenal gland</td>
<td>Surface antigens on steroid-producing cells; microsomes of adrenal cortex</td>
</tr>
<tr>
<td>Premature gonadal failure</td>
<td>Ovary</td>
<td>Interstitial cells; corpus luteum</td>
</tr>
<tr>
<td>Male infertility</td>
<td>Testis</td>
<td>Surface antigens on spermatozoa</td>
</tr>
<tr>
<td>Orchitis</td>
<td>Testis</td>
<td>Germinal epithelium</td>
</tr>
<tr>
<td>Female infertility</td>
<td>Ovary</td>
<td>Zona pellucida</td>
</tr>
<tr>
<td>Idiopathic hypoparathyroidism</td>
<td>Parathyroid gland</td>
<td>Surface antigens on chief cells (epithelial cells of gland)</td>
</tr>
<tr>
<td>Partial pituitary deficiency</td>
<td>Pituitary gland</td>
<td>Prolactin-producing cells; growth hormone–producing cells</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Skin</td>
<td>Intercellular substances in stratified squamous epithelium</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>Skin</td>
<td>Basement membrane</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Skin</td>
<td>Basement membrane (immunoglobulin A[IgA])</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>Skin</td>
<td>Surface antigens on melanocytes (melanin-producing cells)</td>
</tr>
<tr>
<td>Neuromuscular Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymyositis (dermatomyositis)</td>
<td>Muscle</td>
<td>Nuclear materials; myosin</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Neural tissue</td>
<td>Unknown</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Neuromuscular junction</td>
<td>Acetylcholine receptors; striations of skeletal and cardiac muscle</td>
</tr>
<tr>
<td>Polyneuritis</td>
<td>Nerve cell</td>
<td>Peripheral myelin</td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>Heart</td>
<td>Cardiac tissue (subsarcolemmal membrane); cross reaction with group A streptococcal antigen</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Heart</td>
<td>Cardiac muscle</td>
</tr>
<tr>
<td>Postvaccinal or postinfectious encephalitis</td>
<td>Central nervous system</td>
<td>Central nervous system myelin or basic protein</td>
</tr>
<tr>
<td>Gastrointestinal System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celiac disease (gluten-sensitive enteropathy)</td>
<td>Intestine</td>
<td>Gluten</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Colon</td>
<td>Mucosal cells</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>Ileum</td>
<td>Unknown</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>Stomach</td>
<td>Surface antigens of parietal cells; intrinsic factor</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
<td>Stomach</td>
<td>Parietal cells</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>Liver</td>
<td>Mitochondria; cells of bile duct</td>
</tr>
</tbody>
</table>

Continued
**Table 8-2  Disorders Associated with Autoimmunity—cont’d**

<table>
<thead>
<tr>
<th>System Disease</th>
<th>Organ or Tissue</th>
<th>Probable Self-Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic active hepatitis</td>
<td>Liver</td>
<td>Surface antigens, nuclei, microsomes, mitochondria or hepatocytes; smooth muscle</td>
</tr>
<tr>
<td>Eye</td>
<td>Lacrimal gland</td>
<td>Antigens of lacrimal gland, salivary gland, thyroid, and nuclei of cells; immunoglobulin G (IgG)</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>Uveal structures</td>
<td>Antigens of the iris, ciliary body, and choroid</td>
</tr>
<tr>
<td>Uveitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Connective Tissue</td>
<td>Joints</td>
<td>IgG, collagen</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Joints</td>
<td>Numerous antigens in nuclei, organelles, and extracellular matrix</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Multiple sites</td>
<td>Ribonucleoprotein and numerous other nucleoproteins</td>
</tr>
<tr>
<td>Scleroderma (progressive systemic sclerosis)</td>
<td>Multiple organs</td>
<td>Unknown</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>Joints</td>
<td>Nuclear antigens; IgG</td>
</tr>
<tr>
<td>Polymyositis nodosa (necrotizing vasculitis)</td>
<td>Arterioles (small arteries)</td>
<td>Ribonucleoprotein and numerous other nucleoproteins</td>
</tr>
<tr>
<td>Scleroderma (progressive systemic sclerosis)</td>
<td>Multiple organs</td>
<td>Unknown</td>
</tr>
<tr>
<td>Felty syndrome</td>
<td>Platelets, endothelial cells,</td>
<td>Membrane phospholipids, especially phosphatidylerine</td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome</td>
<td>trophoblast of placenta</td>
<td></td>
</tr>
<tr>
<td>Renal System</td>
<td>Kidney</td>
<td>Numerous immune complexes</td>
</tr>
<tr>
<td>Immune complex glomerulonephritis</td>
<td>Kidney</td>
<td>Glomerular basement membrane</td>
</tr>
<tr>
<td>Goodpasture disease</td>
<td>Neutrophil</td>
<td>Surface antigens on polymorphonuclear neutrophils</td>
</tr>
<tr>
<td>Hematologic System</td>
<td>Lymphocytes</td>
<td>Surface antigens on lymphocytes</td>
</tr>
<tr>
<td>Idiopathic neutropenia</td>
<td>Erythrocytes</td>
<td>Surface antigens on erythrocytes</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Platelets</td>
<td>Surface antigens on platelets</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenic purpura</td>
<td>Lung</td>
<td>Septal membrane of alveolus</td>
</tr>
</tbody>
</table>

**Mechanisms of Hypersensitivity**

Diseases caused by hypersensitivity reactions can be characterized also by the particular immune mechanism that results in the disease (see Table 8-1). These mechanisms are apparent in most hypersensitivity reactions and have been divided into four distinct types: type I (immunoglobulin E [IgE]–mediated) hypersensitivity reactions, type II (tissue-specific) hypersensitivity reactions, type III (immune complex–mediated) hypersensitivity reactions, and type IV (cell-mediated) hypersensitivity reactions (Table 8-3). This classification is artificial and seldom is a particular disease associated with only a single mechanism. The four mechanisms are interrelated, and in most hypersensitivity reactions, several mechanisms can be at work simultaneously or sequentially. Some of the mechanisms are secondary to the disease and not directly involved in the pathologic process, whereas others are the primary cause of tissue destruction.

Hypersensitivity reactions require sensitization against a particular antigen that results in primary and secondary immune responses. An individual is sensitized when an adequate amount of antibodies or T cells is available to cause a noticeable reaction on reexposure to the antigen. Some individuals become sensitized quite rapidly (after an apparent single exposure to the antigen), whereas others require multiple exposures that may occur over years. After sensitization has been achieved, hypersensitivity reactions can be immediate or delayed, depending on the time between exposure to the antigen and the onset of clinical symptoms. Reactions that occur within minutes to a few hours are termed immediate hypersensitivity reactions. Delayed hypersensitivity reactions may take several hours to appear and are at maximum severity days after reexposure to the antigen.
The most rapid and severe immediate hypersensitivity reaction is anaphylaxis. Anaphylaxis occurs within minutes of reexposure to the antigen and can be either systemic (generalized) or cutaneous (localized). Symptoms of systemic anaphylaxis include itching, erythema, headaches, vomiting, abdominal cramps, diarrhea, and breathing difficulties. In severe cases, contraction of bronchial smooth muscle, laryngeal edema, and vascular collapse may result in respiratory distress, decreased blood pressure, shock, and death. Examples of systemic anaphylaxis are allergic reactions to bee stings, peanuts, and fish. Cutaneous anaphylaxis causes the less severe symptoms of local inflammation.

**Type I: IgE-Mediated Hypersensitivity Reactions**

Type I reactions are mediated by antigen-specific IgE and the products of tissue mast cells (Figure 8-1). Most common allergies (e.g., pollen allergies) are type I reactions. In addition, most type I reactions occur against environmental antigens and are therefore allergic. Because of this strong association, many healthcare professionals use the term allergy to indicate only IgE-mediated reactions. However, IgE can contribute to a few autoimmune and alloimmune diseases, and many common allergies (e.g., poison ivy) are not mediated by IgE.

In some individuals, exposure to an environmental antigen causes primarily IgE production. Repeated exposure to the antigen usually is required to elicit enough IgE so that the person becomes “sensitized.” IgE has a relatively short life span in the blood because it rapidly binds to very-high-affinity Fc receptors on the plasma membranes of mast cells (Figure 8-1). The subclass IgG4 also has specific receptors on the mast cell and may contribute to the type I mechanism. Antibody that binds to mast cells is termed cytotoxic antibody (able to bind to cell surfaces) or reagin (skin-sensitizing antibody). Unlike Fc receptors on phagocytes, which bind IgG that has reacted with antigen, the Fc receptors on mast cells bind with IgE that has not previously interacted with antigen.

If further exposure of a sensitized individual to the antigen occurs, one molecule of antigen may bind simultaneously to two molecules of IgE-Fc receptor complexes on the mast cell’s surface (cross-link) resulting in activation of intracellular signaling pathways and mast cell degranulation (see Figure 7-1, B, and Chapter 6). The antigen that triggers cross-linking must have at least two antigenic determinants on the same molecule. Sometimes an IgE-mediated response is beneficial to the host, as is the case of some immune reactions against parasites. (This mechanism is described in Chapter 7 and illustrated in Figure 7-26.)

The products of mast cell degranulation can modulate almost all aspects of an acute inflammatory response. (The effects of biochemical mediators released by mast cells are illustrated in Figure 6-9). The most potent mediator is histamine, which affects several key target cells. Acting through the H1 receptors, histamine contracts bronchial smooth muscles, causing bronchial constriction; increases vascular permeability, causing edema; and causes vasodilation, increasing blood flow into the affected area (see Figures 6-3 and 6-10). The interaction of histamine with H2 receptors results in increased gastric acid secretion and a decrease of histamine released from mast cells and basophils. The action of histamine through H2 receptors suggests an important negative-feedback mechanism that stops degranulation. That is, the released histamine inhibits release of additional histamine by interacting with H2 receptors on the mast cells. Histamine also may affect control of the immune response through H2 receptors on most cells of the immune system. Another important activity of histamine is enhancement of the chemotactic activity of other factors, such as eosinophil chemotactic factor of anaphylaxis (ECF-A), which attracts eosinophils into sites of allergic inflammatory reactions and prevents them from migrating out of the inflammatory site. (The role of the eosinophil in inflammation is discussed in Chapter 6.)

**Type II: Tissue-Specific Hypersensitivity Reactions**

Type II hypersensitivity reactions are generally characterized by a specific cell or tissue being the target of an immune response. In addition to major histocompatibility locus antigens (HLAs; discussed in Chapter 7), most cells have other antigens on their surfaces. Some of these other antigens are called tissue-specific antigens because they are expressed on the plasma membranes of only certain cells in specific tissues. Platelets, for example, have groups of antigens that are found on no other cells of the body. The symptoms of many type II
diseases are determined by which tissue or organ expresses the particular antigen. Environmental antigens (e.g., drugs or their metabolites) may bind to the plasma membranes of specific cells (especially erythrocytes and platelets) and function as targets of type II reactions.

The five general mechanisms by which type II hypersensitivity reactions can affect cells are shown in Figure 8-2. All of these mechanisms begin with antibody binding to tissue-specific antigens or antigens that have attached to particular tissues. First, the cell can be destroyed by antibody (IgG or IgM) and activation of the complement cascade through the classical pathway. Formation of the membrane attack complex (C5-9) damages the membrane and may result in lysis of the cell (see Figure 8-2, A). For example, erythrocytes are destroyed by complement-mediated lysis in individuals with autoimmune hemolytic anemia (see Chapter 26) or as a result of an alloimmune reaction to ABO-mismatched transfused blood cells.

**Figure 8-1** Mechanism of type I IgE-mediated reactions. A. Th2 cells are activated by antigen-presenting dendritic cells to produce cytokines, including IL-3, IL-4, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF). IL-3, IL-5, and GM-CSF attract and promote the survival of eosinophils. Other cytokines (e.g., IL-4) induce B cells to class-switch to IgE-producing plasma cells. The IgE coats the surface of the mast cell by binding with IgE-specific Fc receptors on the mast cell’s plasma membrane (sensitization). Further exposure to the same allergen cross-links the surface-bound IgE and activates signals from the cytoplasmic portion of the IgE Fc receptors. These signals initiate two parallel and interdependent processes: mast cell degranulation and discharge of preformed mediators (e.g., histamine, eosinophil-chemotactic factor of anaphylaxis) and production of newly formed mediators such as arachidonic metabolites (leukotrienes, prostaglandins). Many local type I hypersensitivity reactions have two well-defined phases. The initial phase is characterized by vasodilation, vascular leakage, and depending on the location, smooth muscle spasm or glandular secretions. These changes usually become evident within 5 to 30 minutes after exposure to the antigen. The late phase occurs 2 to 8 hours later without additional exposure to the antigen. The late phase has more intense infiltration of tissues with eosinophils, neutrophils, basophils, monocytes, and Th cells and tissue destruction in the form of mucosal epithelial cell damage.
Second, antibody may cause cell destruction through phagocytosis by macrophages. IgG, as well as C3b of the complement system, are opsonins that bind to receptors on the macrophage (see Figure 6–2, B). Phagocytosis of the target cell follows. (Phagocytosis is illustrated in Figures 6–11 and 6–13.) For example, antibodies against platelet-specific antigens or against red blood cell antigens of the Rh system coat those cells at low density, resulting in their preferential removal by phagocytosis in the spleen, rather than by complement-mediated lysis.

Third, antibody and complement may attract neutrophils. Either antigen expressed normally on the vessel walls or soluble antigen in the circulation (e.g., released from cells within the body or from infectious agents or by way of drugs or medications) that has been deposited on the surface of endothelial cells may bind antibody (see Figure 8–2, C). The antibody initiates the complement cascade, resulting in the release of C3a and C5a, which are chemotactic for neutrophils, and deposition of complement component C3b. Neutrophils bind to the tissues through receptors for the Fc portion of antibody (Fc receptor) or for C3b and attempt to phagocytose the tissue. Because the tissue is large, phagocytosis cannot be completed; even so, neutrophils release their granules onto the healthy tissue. The components of neutrophil granules, as well as the several toxic oxygen products produced by these cells, will damage the tissue.

The fourth mechanism is antibody-dependent cell-mediated cytotoxicity (ADCC) (see Figure 8–2, D). This mechanism involves a subpopulation of cytotoxic cells that are not antigen specific (natural killer [NK] cells). Antibody on the target cell is recognized by Fc receptors on the NK cells, which release toxic substances that destroy the target cell.

The fifth mechanism does not destroy the target cell, but rather causes it to malfunction. In this mechanism of type II injury, the antibody is usually directed against antigenic determinants associated with specific cell-surface receptors, and the symptoms of the disease are a result of a direct effect of antibody binding alone (see Figure 8–2, E). The antibody reacts with the receptors on the target cell surface and modulates the function of the receptor by preventing interactions with their normal ligands, replacing the ligand and inappropriately stimulating the receptor, or destroying the receptor. For example, in the hyperthyroidism (excessive thyroid activity) of Graves’ disease, autoantibody binds to and activates receptors for thyroid-stimulating hormone (TSH) (a pituitary hormone that controls the production of the hormone thyroxine by the thyroid). In this way the antibody stimulates the thyroid cells to produce thyroxine. Under normal conditions, the increasing levels of thyroxine in the blood would signal the pituitary to decrease TSH production, which would result in less stimulation of the TSH receptor in the thyroid and a concomitant decrease in thyroxine production. Because the level of anti-TSH receptor antibody is not controlled by the pituitary, increasing amounts of thyroxine in the blood have no effect on antibody levels, and thyroxine production continues to increase despite decreasing amounts of TSH (see Chapter 21).

Type III: Immune Complex–Mediated Hypersensitivity Reactions

Mechanisms of Type III Hypersensitivity

Most type III hypersensitivity diseases are caused by antigen-antibody (immune) complexes that are formed in the circulation and deposited later in vessel walls or extravascular tissues (Figure 8–3). The primary difference between type II and type III mechanisms is that in type II hypersensitivity antibody binds to the antigen on the cell surface, whereas in type III the antibody binds to soluble antigen that was released into the blood or body fluids, and the complex is then deposited in the tissues. Type III reactions are not organ specific, and symptoms have little to do with the particular antigenic target of the antibody. The harmful effects of immune complex deposition are caused by complement activation, particularly through the generation of chemotactic factors for neutrophils. The neutrophils bind to antibody and C3b contained in the complexes and attempt to ingest the immune complexes.
Membrane attack complex

Complement-mediated lysis

IgM

C1

Erythrocyte antigen

Membrane attack complex

Osmotic lysis

Figure 8-2. Mechanisms of type II, tissue-specific, reactions. Antigens on the target cell bind with antibody and are destroyed or prevented from functioning by A, complement-mediated lysis (an erythrocyte target is illustrated here); B, clearance (phagocytosis) by macrophages in the tissue; C, neutrophil-mediated immune destruction; D, antibody-dependent cell-mediated cytotoxicity (ADCC) (apoptosis of target cells is induced by granzymes and perforin produced by natural killer [NK] cells and interactions of Fas ligand [FasL] on the surface of NK cells with Fas on the surface of target cells); or E, modulation or blocking the normal function of receptors by antireceptor antibody. This example of mechanism E depicts myasthenia gravis in which acetylcholine receptor antibodies block acetylcholine from attaching to its receptors on the motor end plates of skeletal muscle, thereby impairing neuromuscular transmission and causing muscle weakness. C1, Complement component C1; C3b, complement fragment produced from C3, which acts as an opsonin; C5a, complement fragment produced from C5, which acts as a chemotactic factor for neutrophils; Fcγ receptor, cellular receptor for the Fc portion of IgG; FcR, Fc receptor.
Alterations in Immunity and Inflammation

CHAPTER 8

They are often unsuccessful because the complexes are bound to large areas of tissue. During the attempted phagocytosis, large quantities of lysosomal enzymes are released into the inflammatory site instead of into phagolysosomes. The attraction of neutrophils and the subsequent release of lysosomal enzymes cause most of the resulting tissue damage.

Immune complexes can be of various sizes, depending on the relative amounts of antigen and antibody. Fairly large immune complexes are cleared rapidly from the circulation by tissue macrophages, whereas very large complexes eventually are filtered from blood through the kidneys, without any pathologic consequences. Intermediate-sized immune complexes (formed at a ratio of antigen to antibody that has a slight excess of antigen) are likely to be deposited in certain target tissues, where they have severe pathologic consequences, such as inflammation in the kidneys (glomerulonephritis), the vessels (vasculitis), or the joints (arthritis or degenerative joint disease).

**Immune Complex Disease**

The nature of the immune complexes may change during the progression of the disease, with resultant changes in the severity of the symptoms. Immune complex formation is dynamic as variations in the ratio of antigen to antibody, the class and subclass of antibody, and the quantity and quality of circulating antigen occur. Thus complexes formed early in a disease process may differ from those formed later, and several types of immune complexes may be present simultaneously. With the tremendous potential heterogeneity of immune complexes, it is not surprising that immune-complex diseases are characterized by a variety of symptoms and periods of remission or exacerbation of symptoms.

Because many immune complexes activate complement very effectively, complement levels in the blood may decrease during active disease. At times the individual’s blood may become hypocomplementemic (i.e., contains below normal amounts of complement activity). During type I, II, or IV hypersensitivity reactions, complement levels are unaffected, or some components of the complement cascade, such as C3, may even be increased.

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

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

A form of serum sickness is Raynaud phenomenon, a condition caused by the temperature-dependent deposition of immune complexes in the capillary beds of the peripheral circulation. Certain immune complexes precipitate at temperatures below normal body temperature, particularly in the tips of the fingers, toes, and nose and are called cryoglobulins. The precipitates block the circulation and cause localized pallor and numbness, followed by cyanosis (a bluish tinge resulting from oxygen deprivation) and eventually gangrene if the circulation is not restored.

Arthus Reaction. An Arthus reaction is the prototypic example of a localized immune complex–mediated inflammatory response. It is caused by repeated local exposure to an antigen that reacts with preformed antibody and forms immune complexes in the walls of the local blood vessels. Symptoms of an Arthus reaction begin within 1 hour of exposure and peak 6 to 12 hours later. The lesions are characterized by a typical inflammatory reaction, with increased vascular permeability, an accumulation of neutrophils, edema, hemorrhage, clotting, and tissue damage.

Type IV: Cell-Mediated Hypersensitivity Reactions
Whereas types I, II, and III hypersensitivity reactions are mediated by antibody, type IV reactions are mediated by T lymphocytes and do not involve antibody (Figure 8-4). Type IV mechanisms occur through either cytotoxic T lymphocytes (Tc cells) or lymphokine-producing Th1 cells. Tc cells attack and destroy cellular targets directly. Th1 cells produce cytokines that recruit and activate phagocytic cells, especially macrophages. Destruction of the tissue is usually caused by direct killing by toxins from Tc cells or the release of soluble factors, such as lysosomal enzymes and toxic reactive oxygen species (ROS), from activated macrophages.

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

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

Figure 8-4 Mechanism of type IV, cell-mediated, reactions. Antigens from target cells stimulate T cells to differentiate into cytotoxic T cells (Tc cells), which have direct cytotoxic activity, and helper T cells (Th1 cells) involved in delayed hypersensitivity. The Th1 cells produce lymphokines (especially interferon-γ [IFN-γ]) that activate the macrophage through specific receptors (e.g., IFN-γ receptor [IFNγR]). The macrophages can attach to targets and release enzymes and reactive oxygen species that are responsible for most of the tissue destruction.

Antigenic Targets of Hypersensitivity Reactions
Allergy
Allergy is a hypersensitivity response against an environmental antigen (allergen). Although the most common allergies are type I hypersensitivities, any of the other three mechanisms may cause allergic responses.

Typical allergens that induce type I hypersensitivity include pollens (e.g., ragweed), molds and fungi (e.g., Penicillium notatum), foods (e.g., milk, eggs, fish), animals (e.g., cat dander, dog dander), cigarette smoke, components of house dust (e.g., fecal pellets of house mites), and almost anything else we may encounter in our environment. Allergens that primarily elicit type I allergic hypersensitivities include plant resins (e.g., poison ivy, poison oak), metals (e.g., nickel, chromium), acetylates and chemicals in rubber, cosmetics, detergents, and topical antibiotics (e.g., neomycin). Type II and type III allergic hypersensitivities are relatively rare but may include antibiotics (e.g., penicillin, sulfonamides) and soluble antigens produced by infectious agents (e.g., hepatitis B).

Usually a sensitization process involving multiple exposures to the allergen occurs before adequate amounts of antibody or T cells are available to elicit a hypersensitivity response. In some instances, exposure to a particular allergen may not be apparent in the case of allergens that are drugs, additives, or preservatives in food. For example, milk may contain trace amounts of penicillin used for treating cows for mastitis. Thus, the first therapeutic exposure to penicillin may cause an unexpected hypersensitivity reaction. Additionally, penicillin
shares a β-lactam structure with cephalosporin, so that one antibiotic may be sensitive against another.  

**Genetic Predisposition**

Certain individuals are genetically predisposed to develop allergies, particularly type I allergies, and are called atopic.  

In families in which one parent has an allergy, allergies develop in about 40% of the offspring. If both parents have allergies, the incidence in the offspring may be as high as 80%.  

(Principles of genetic inheritance are discussed in Chapter 4.)

Atopic individuals tend to produce higher quantities of IgE and to have more Fc receptors for IgE on their mast cells. The airways and the skin of atopic individuals are also more responsive to a wide variety of both specific and nonspecific stimuli than are the airways and skin of individuals who are not atopic. Multiple genes have been associated with the atopic state, including polymorphisms in a large variety of cytokines that regulate IgE synthesis (e.g., interleukin [IL]-4, IL-5, IL-12, IL-13) and cellular receptors.

**Clinical Symptoms of Type I Allergies**

The clinical manifestations of type I reactions are attributable mostly to the biologic effects of histamine. These tissues are found in the gastrointestinal tract, the skin, and the respiratory tract (Figure 8-5 and Table 8-4). The particular symptoms frequently reflect the main portal of entry for the allergen. For instance, pollens and other airborne allergens usually cause respiratory symptoms.

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

Gastrointestinal allergies are caused primarily by allergens that enter through the mouth—usually foods or medicines. Symptoms include vomiting, diarrhea, or abdominal pain and may be severe enough to result in malabsorption or protein-losing enteropathy, if the reactions are prolonged or recurrent. Foods most often implicated in gastrointestinal allergies are milk, chocolate, citrus fruits, eggs, wheat, nuts, peanut butter, and fish. When food is the allergen, the active immunogen may be a product of food breakdown by digestive enzymes.

Urticaria, or hives, is a dermal (skin) manifestation of type I allergic reactions (see Figure 8-5). The underlying mechanism is the localized release of histamine and increased vascular permeability, resulting in limited areas of edema. Urticaria is characterized by white fluid-filled blisters (wheals) surrounded by areas of redness (flares). The **wheat and flare reaction** is usually accompanied by itching. Not all urticarial symptoms are caused by allergic (immunologic) reactions. Some, termed nonimmunologic urticaria, result from exposure to cold temperatures, emotional stress, medications, systemic diseases, hyperthyroidism, or malignancies (e.g., lymphomas).

If possible, avoidance of the allergen is the best method to limit allergic responses. Approximately 30% of laboratory animal handlers have allergies to animal dander and must use face masks or other devices to avoid contact.

Although some type I allergic responses can be controlled by blocking histamine receptors with antihistamines, the primary mechanism of control is the autonomic nervous system. The autonomic nervous system includes biochemical mediators (e.g., epinephrine, acetylcholine) that, like the mediators of the inflammatory response, have profound effects on cells. These mediators bind to appropriate receptors on mast cells and the target cells of inflammation (e.g., smooth muscle), thereby controlling (1) release of inflammatory mediators from mast cells and (2) the degree to which target cells respond to inflammatory mediators (see Chapter 6).

**Allergic Disease: Bee Sting Allergy**

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

If a child has had a previous anaphylactic reaction to bee stings, the chance of having another is about 60%. During the reaction the administration of antihistamines has little effect because histamine has already bound H1 receptors and initiated severe bronchial smooth muscle contraction. Most individuals carry self-injectable epinephrine. Autonomic nervous system mediators, such as epinephrine, bind to specific receptors on smooth muscle and reverse the effects of histamine and result in muscle relaxation. Similar anaphylactic reactions have been described against peanuts and other nuts, shellfish, fish, milk, eggs, and some medications.

**Tests of IgE-Mediated Allergy**

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

Reactivity to a particular food allergen may be tested by controlled administration of small doses of the suspected
allergen in order to evoke a mild allergic response. This approach can be dangerous if the individual has a history of anaphylactic responses. A safer approach is injection of an allergen into (intradermal) or onto (epicutaneous or prick test) the skin. If the individual is allergic to a particular allergen, a local wheal and flare reaction may occur within a few minutes at the site of injection. The diameter of the flare reaction is usually indicative of the individual’s degree of sensitivity to that allergen. In the most severely allergic individuals, even the extremely small amounts of allergen used for the

**Figure 8-5** Type I hypersensitivity reactions. Manifestations of allergic reactions as a result of type I hypersensitivity include itching, angioedema (swelling caused by exudation), edema of the larynx, urticaria (hives), bronchospasm (constriction of airways in the lungs), hypotension (low blood pressure) and dysrhythmias (irregular heartbeat) because of anaphylactic shock, and gastrointestinal cramping caused by inflammation of the gastrointestinal mucosa. Photographic inserts show a diffuse allergic-like eye and skin reaction on an individual. The skin lesions have raised edges and develop within minutes or hours, with resolution occurring after about 12 hours. (From Roitt I, Brostoff J, Male D: Immunology, ed 6, St. Louis, 2001, Mosby.)

<table>
<thead>
<tr>
<th>Typical Allergen</th>
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<td>Injectants</td>
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<td>Drugs</td>
<td>Types I, II, III</td>
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<td>Bee venom</td>
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<td>Vaccines</td>
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<tr>
<td>Poison ivy, metals</td>
<td>Type IV</td>
<td>Contact dermatitis</td>
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*An order of fungi that is stimulated by warmth to grow and proliferate. Modified from Bellanti JA: Immunology III, Philadelphia, 1985, Saunders.
skin test may evoke a systemic anaphylaxis. Skin test is also contraindicated if the patient is using medications that may affect the test or has diffuse dermatitis, which would make the reaction difficult to interpret.\textsuperscript{28}

A variety of laboratory tests can detect IgE antibodies in serum. These assays have various commercial acronyms, depending on whether they are radioimmunoassays (RIAs; reactivity detected by measuring a radioactive reagent) or enzyme immunoassays (EIAs or ELISA [enzyme-linked immunosorbent assay]; reactivity detected by measuring a color change caused by an enzyme-labeled reagent). One set of assays measures circulating levels of total IgE, with atopic individuals usually having elevated levels. Other assays are capable of measuring circulating levels of specific IgE antibodies against selected allergens. The amount of IgE against a specific allergen correlates well with the degree of skin test reactivity and the severity of clinical symptoms related to the same allergen, although the laboratory test is less sensitive.

**Desensitization**

Clinical desensitization to allergens can be achieved in some individuals.\textsuperscript{29} Minute quantities of the allergen are injected in increasing doses over a prolonged period. The procedure may reduce the severity of the allergic reaction in the treated individual. However, this form of therapy is associated with a risk of systemic anaphylaxis, which can be severe and life threatening. This approach works best for allergies against some food allergens and with biting insect allergies (80% to 90% rate of desensitization over 5 years of treatment).\textsuperscript{30}

The mechanisms by which desensitization occurs may be several, one of which is the production of large amounts of so-called blocking antibodies, usually circulating IgG. A blocking antibody presumably competes in the tissues or in the circulation for binding with antigenic determinants on the allergen so that the allergen is “neutralized” and is unable to bind with IgE on mast cells. Sublingual desensitization (another approach that works best with some food allergies) produces slgA and circulating IgG that may prevent the allergen from accessing mast cells. Desensitization injections also may stimulate the generation of clones of regulatory T lymphocytes, which inhibit hypersensitivity by suppressing the production of IgE or modifying the Th1/Th2 interactions in favor of production of anti-inflammatory cytokines.

Other approaches to suppressing type I allergic reactions have been tested, with some preliminary success. An example is injection of anti-IgE antibody directed against the Fc portion of the IgG in order to decrease binding of IgE to mast cells.

**Type IV Allergic Hypersensitivities**

The allergens that induce a type IV allergic reaction are mostly haptenst that react with normal self-proteins in the skin. When presented in this fashion, these antigens induce a cell-mediated response. The primary result is an allergic contact dermatitis that is confined to the area of contact with the allergen. The best-known example is poison ivy (Figure 8-6). The antigen in that instance is a plant catechol, urushiol, that reacts with normal skin proteins and evokes a cell-mediated immune response.

As noted, type I hypersensitivity reactions may result in a skin reaction (e.g., hives formed during an allergic reaction to a particular food).\textsuperscript{31} The distribution of the lesions may suggest whether the reaction is caused by immediate (type I) or delayed (type IV) hypersensitivity mechanisms. Immediate hypersensitivity reactions, termed atopic dermatitis, are usually characterized by widely distributed lesions, whereas contact dermatitis (delayed hypersensitivity) consists of lesions only at the site of contact with the allergen, such as a metal allergy to jewelry (see Figure 8-6).

**Types II and III Allergic Hypersensitivities**

Type II allergic hypersensitivities are usually against allergens that bind to the surface of cells and elicit an IgG or IgM response. For instance, allergic reactions against many drugs (e.g., penicillin, sulfonamides) occur after the drug binds to proteins on the plasma membranes of a person’s cells and becomes immunogenic.\textsuperscript{32} The immune system attacks the allergen on the cell membrane and destroys the cell as well. In allergic reactions to penicillin, the immunogenic antigen is a metabolite of penicillin catabolism that binds to the plasma membranes of erythrocytes or platelets and induces an antibody response that destroys the cells (type II hypersensitivity), causing anemia or thrombocytopenia. Type II allergic reactions also can occur against antigens of infectious diseases. For instance, encephalitis secondary to a rubella infection may result from damage to cells of the nervous system by an immune response against rubella virus antigen on the cell’s plasma membrane.

Type III allergic reactions occur after the formation of immune complexes containing soluble allergens. For instance, Arthus reactions may be observed after injection, ingestion, or inhalation of allergens. Skin reactions can follow subcutaneous or intradermal inoculation with drugs, fungal extracts, or antigens used in skin tests. Gastrointestinal reactions, such as gluten-sensitive enteropathy (celiac disease), follow ingestion of antigen, usually gluten from wheat products (see Chapter 39). Allergic alveolitis is a type III acute hemorrhagic inflammation of the air sacs (alveoli) of the lungs resulting from inhalation of fungal antigens, usually particles from moldy hay (farmer’s lung) or pigeon feces (pigeon breeder’s disease) (see Chapter 33). Circulating drugs (e.g., penicillin) or antigens produced from infectious diseases (e.g., hepatitis B, streptococcal infection) may form circulating immune complexes that are deposited in the circulation (vasculitis) or the kidneys (glomerulonephritis).

**Autoimmunity**

**Breakdown of Tolerance**

Self-antigens are usually in a state of tolerance, or immunologic homeostasis, with the host’s own immune system.\textsuperscript{33} Central tolerance develops in humans during the embryonic period as autoreactive lymphocytes are either eliminated or suppressed in the primary lymphoid organs during differentiation and proliferation of immature T or B lymphocytes.
Clones of cells with antigen receptors for self-antigens are deleted. Peripheral tolerance is maintained in the secondary lymphoid organs through the action of regulatory T lymphocytes or antigen-presenting dendritic cells. Autoimmunity is a breakdown of tolerance in which the body’s immune system begins to recognize self-antigens as foreign. In most autoimmune conditions the mechanism of tolerance breakdown is unknown, although several potential mechanisms have been suggested.

Sequestered Antigen. The induction of central tolerance requires that the self-antigen be present in the fetus and exposed to the developing fetal immune system. Some self-antigens may not normally encounter the immune system in either fetal or adult life, but are sequestered or hidden from the immune system in immunologically privileged sites, so named because foreign tissues can be transplanted into these sites with less chance of immunologic rejection. For example, several sites (e.g., anterior chamber of the eye, the brain) are separated from the circulation by barriers (blood-ocular and blood-brain barriers) that offer protection against many immune cells and to lead to relatively poor lymphatic drainage. Lymphocytes that enter these sites encounter tissue that expresses Fas ligand (FasL) and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL). These molecules induce the lymphocytes to undergo apoptosis, thus protecting the tissue. Self-antigens in these sites are not normally seen

Figure 8-6 Development of allergic contact dermatitis, a delayed hypersensitivity reaction. A, Shown here is the development of allergy to catechols from poison ivy. No dermatitis results from the primary contact because the antigens (catechols) are sensitizing the immune response and producing memory T cells. Secondary contact, however, quickly activates a type IV, cell-mediated reaction that causes dermatitis. B, This contact dermatitis was caused by a delayed hypersensitivity reaction that lead to vesicles and scaling at the sites of contact. (From Damjanov I, Linder J: Anderson’s pathology, ed 10, St. Louis, 1996, Mosby.)
by the immune system and are therefore not immunogenic. However, if the barriers are damaged, antigenic sensitization can occur, and the resultant antibodies and lymphocytes can enter the site and cause additional damage to the tissue. For instance, physical trauma to one eye may result in release of sequestered antigen into the blood or lymphatics, resulting in immunologic injury to the other eye (sympathetic uveitis).

**Infectious Disease.** A long-standing hypothesis is that foreign antigens from infectious microorganisms can initiate autoimmune disease through a process of **molecular mimicry**. Some antigens of infectious agents so closely resemble (mimic) a particular self-antigen that antibodies or T cells produced to protect against the infection also recognize the self-antigen as foreign (**cross-reactive antibody** or **T cell**). Although the relationship between many autoimmune diseases and predisposing infections is being investigated, the only clearly defined example so far is acute rheumatic fever (38). In a small number of individuals with group A streptococcal sore throats, the M proteins in the bacterial capsule induce antibodies that also react with proteins in the heart valve, damaging the valve.

**Neoantigen.** In certain situations a neoantigen that induces an allergic reaction may lead also to autoimmunity. Many **neoantigens** (new antigens) are haptened, which become immunogenic after binding to self-proteins. The immune reaction against the neoantigen may lead to an immunologic reaction against normal antigenic determinants on the protein. Many experimental autoimmune diseases (e.g., experimental autoimmune thyroiditis) can be initiated by this mechanism.

**Forbidden Clone.** During differentiation and proliferation of lymphoid stem cells into immature T and B lymphocytes (see Figures 7-10 and 7-12), some lymphocytes produce receptors that react with self-antigens. Many autoreactive lymphocytes interact with self-antigens and other co-stimulatory molecules on the surface of thymic epithelial cells and are induced to undergo clonal deletion by a process of apoptosis. Thus lymphocytes reactive against self-antigen are prevented, or “forbidden,” from maturing. Autoimmunity may result from the survival of a **forbidden clone** and its proliferation later in life.

**Defective Peripheral Tolerance.** Tolerance to some self-antigens is controlled in the secondary lymphoid organs. This process is controlled by a variety of cells, including antigen-presenting dendritic cells and members of a family of regulatory T lymphocytes (Treg cells) that normally suppress immune responses against self. Defects in particular regulatory cells may result in expansion of clones of autoreactive cells and the development of autoimmune disease. Systemic lupus erythematosus, which is characterized by the production of a large array of autoantibodies, may be caused by a general breakdown in the regulatory network.

**Original Insult**

Although many theories exist, the initial cause of most autoimmune diseases is unknown (see What’s New? Maternal Microchimerism and Autoimmune Disease). It is suspected that some autoimmune diseases are initiated by infections that have resolved without leaving evidence that would lead to identification of the particular infectious agent. The evidence for an infectious causation is clear for only one autoimmune disease: acute rheumatic fever. In a small number of individuals with group A streptococcal sore throats, the M proteins in the bacterial capsule induce antibodies that also react with proteins in the heart valve, damaging the valve.

Additionally, some streptococcal skin or throat infections result in the release of bacterial antigens into the blood and the formation of circulating immune complexes. The complexes...
may deposit in the kidneys and initiate an immune complex glomerulonephritis (inflammation of the kidney). Thus capsular antigens of the group A Streptococcus may mimic (antigenic mimicry) normal heart antigens resulting in a type II autoimmune hypersensitivity (rheumatic fever), whereas in another person this infection may release bacterial antigen (an environmental antigen) into the blood, resulting in a type III allergic hypersensitivity (poststreptococcal glomerulonephritis).

**Genetic Factors**

Genetic factors that contribute to autoimmunity are easier to identify than the original insult that initiates the disease.** It is fairly well established that autoimmune diseases can be familial. Affected family members may not all develop the same disease, but several members may have different disorders characterized by a variety of hypersensitivity reactions, including autoimmune and allergic.

Associations with particular autoimmune diseases have been identified for a variety of major histocompatibility complex (MHC) alleles (see Chapter 7) or non-MHC genes. The specific HLA alleles of susceptible and resistant individuals have been analyzed for almost every known disease, and almost universally individuals with certain diseases are more likely than the general population to have a specific HLA allele or set of alleles. Some associations are strong; others are more tenuous (Table 8-5). The reason some HLA alleles are associated with autoimmune diseases in which the mother produces an autoantibody may be present against the use of particular HLAs as receptors for disease-causing microorganisms. These genes may determine an individual’s susceptibility to specific infectious agents or the capacity of that individual to mount an immune response against specific antigens. Therefore, an individual of a specific HLA type may have inappropriate or exaggerated immune responses against a microorganism, resulting in a hypersensitivity reaction.

A large variety of non-MHC genes also have been identified as risk factors for the development of specific autoimmune diseases. Most of these genes encode for inflammatory cytokines or co-stimulatory molecules found on the cell surface.

**Alloimmunity**

Alloimmunity occurs when an individual’s immune system reacts against antigens on the tissues of other members of the same species. The two clinically relevant examples of this reactivity are (1) several transient neonatal diseases (in which the maternal immune system becomes sensitized against antigens expressed by the fetus) and (2) transplant rejection and transfusion reactions (in which the immune system of a recipient of an organ transplant or blood transfusion reacts against antigens on the donor cells).

**Transient Neonatal Alloimmunity**

Because the fetus is a hybrid between the mother and father, it expresses paternal antigens that are not found in the mother. Occasionally these fetal antigens cross the placenta and elicit an immune response in the mother (e.g., production of alloantibodies against the fetal antigens). The maternal alloantibody may be transported across the placenta into the fetal circulation, bind to the fetal cells, and produce alloimmune disease in the fetus and neonate. The mother’s immune system produces the antibody, but because her cells do not express the target antigen, she has no symptoms of the disease.

Neonatal alloimmune disease may be secondary to maternal autoimmune diseases in which the mother produces an IgG autoantibody specific for maternal self-antigens that are found on fetal cells as well. Therefore, symptoms of the same autoimmune disease may affect mother and child, even though the autoantibody is being produced only by the mother’s immune system. This form of disease usually occurs only in association with type II (tissue-specific) hypersensitivity reactions. It does not occur in association with IgE-mediated (type I) reactions, immune complex-mediated (type III) reactions, or cell-mediated (type IV) reactions because the immunologic factors (IgE, immune complexes, T cells) that cause these reactions do not readily cross the placenta and enter the fetal circulation in sufficient quantity.

Symptoms of the alloimmune disease may be present in utero or immediately after birth and may be fatal to the fetus or neonate. At birth, maternal circulating antibody can no longer enter the child, and if symptoms are successfully treated, the disease will disappear as the maternal antibody is catabolized.
Examples of maternal immunologic hypersensitivity diseases in which the child can be affected include the following antibody-mediated diseases:

1. **Graves disease**—an autoimmune disease in which maternal antibody against the receptor for TSH causes neonatal hyperthyroidism
2. **Myasthenia gravis**—an autoimmune disease in which maternal antibody binds with receptors for neural transmitters on muscle cells (acetylcholine receptors), causing neonatal muscular weakness (see Chapter 17)
3. **Immune thrombocytopenic purpura**—both autoimmune and alloimmune variants in which maternal antiplatelet antibody destroys platelets in the fetus and neonate (see Chapter 27)
4. **Alloimmune neutropenia**—in which maternal antibody against neutrophils destroys neutrophils in the neonate
5. **Systemic lupus erythematosus**—autoimmune disease in which diverse maternal autoantibodies induce anomalies (e.g., congenital heart defects) in the fetus or cause pregnancy loss
6. **Rh and ABO alloimmunization** (e.g., erythroblastosis fetalis)—in which maternal antibody against erythrocyte antigens induces anemia in the child (see Chapter 28)

### Autoimmune and Alloimmune Diseases

Many examples of autoimmune or alloimmune diseases have been described. Several basic principles are exemplified by two examples, systemic lupus erythematosus (an autoimmune disease) and tissue rejection (i.e., transplant rejection or transfusion reaction) (an alloimmune phenomenon).

Most of the classic autoimmune diseases, including disorders of the endocrine system (autoimmune thyroiditis and Graves disease), hematologic system (the hemolytic and pernicious anemias), nervous system (myasthenia gravis), and connective tissue in joints (rheumatoid arthritis), are discussed in Unit II of this book.

### Systemic Lupus Erythematosus

**Systemic lupus erythematosus (SLE)** is a chronic, multisystem, inflammatory disease and is one of the most common, complex, and serious of the autoimmune disorders. SLE is characterized by the production of a large variety of autoantibodies against nucleic acids, erythrocytes, coagulation proteins, phospholipids, lymphocytes, platelets, and many other self-components. The most characteristic autoantibodies produced in SLE are against nucleic acids (e.g., single-stranded deoxyribonucleic acid [DNA], double-stranded DNA), histones, ribonucleoproteins, and other nuclear materials.

Deposition of circulating immune complexes containing antibody against DNA produces tissue damage in individuals with SLE. DNA and DNA-containing immune complexes have a high affinity for glomerular basement membranes and therefore may be selectively deposited in the glomerulus (Figure 8-7). (Kidney structures are described in Chapter 35.) The presence of DNA in the circulation increases from cellular damage in response to trauma, drugs, or infections and is usually removed in the liver. Removal of circulating DNA is slowed in the presence of immune complexes, thereby increasing the potential for deposition in the kidney. (The liver’s role in removing waste products from the blood is discussed in Chapter 35.) Deposition of immune complexes composed of DNA and antibody also causes inflammatory lesions in the renal tubular basement membranes, brain (choroid plexus), heart, spleen, lung, gastrointestinal tract, skin (see Figure 8-7), and peritoneum.

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

A transient lupus-like syndrome that is indistinguishable both clinically and in the laboratory from spontaneously occurring SLE can develop from the prolonged use of drugs. The drugs most often implicated are hydralazine...
(an antihypertensive agent) and procainamide (an antidysrhythmic drug). In genetically susceptible individuals, certain environmental agents, such as ultraviolet light, and several infectious agents may trigger lupus-like immune reactions.

Clinical manifestations of SLE include arthralgias or arthritis (90% of individuals), vasculitis and rash (70% to 80% of individuals), renal disease (40% to 50% of individuals), hematologic abnormalities (50% of individuals, with anemia being the most common complication), and cardiovascular diseases (30% to 50% of individuals). As with most autoimmune diseases, the disease process develops slowly (up to 10 years from occurrence of the first autoantibody until diagnosis) and is characterized by frequent remissions and exacerbations. Because the signs and symptoms affect almost every body system and tend to come and go, SLE is extremely difficult to diagnose. This has led to the development of a list of 11 common clinical findings. The serial or simultaneous presence of at least four of them indicates that the individual has SLE.

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

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

Transfusion Reactions

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

ABO System

Human blood transfusions were carried out as early as 1818, but they were often unsuccessful. Sometimes after a transfusion, the recipient’s red blood cells would clump together, thereby blocking the capillaries and causing death in some instances. In 1901, Karl Landsteiner reported that this reaction was related to the ABO antigens located on the surface of erythrocytes.

The ABO blood group consists of two major carbohydrate antigens, labeled A and B (Figure 8-8). These two carbohydrate antigens are codominant, which means that both A and B can be simultaneously expressed, resulting in an individual having any one of four different blood types. The erythrocytes of persons with blood type A have the type A carbohydrate antigen (i.e., carry the A antigen), those with blood type B carry the B antigen, those with blood type AB carry both A and B antigens, and those of blood type O carry neither the A nor the B antigen. A person with type A blood also has circulating antibodies to the B carbohydrate antigen. If this person receives blood containing B antigens (i.e., blood from a type AB or B individual), a severe transfusion reaction occurs and the transfused erythrocytes are destroyed by agglutination (Figure 8-9) or complement-mediated lysis. Similarly, a type B individual (whose blood contains anti-A antibodies) cannot receive blood from a type A or AB donor. Type O individuals, who have neither A or B antigen but have both anti-A and anti-B antibodies, cannot accept blood from any of the other three types. These naturally occurring antibodies, called isohemagglutinins, are immunoglobulins of the IgM class and are induced by similar antigens expressed on naturally occurring bacteria in the intestinal tract.

Because individuals with type O blood lack both types of antigens, they are considered universal donors, meaning that anyone can accept their red blood cells. Similarly, type AB individuals are considered universal recipients because they lack both anti-A and anti-B antibodies and can be transfused with any ABO blood type. When large volumes of whole blood (i.e., cells plus plasma) are transfused, however, antibodies in the donor’s blood can bind to antigenic determinants on the recipient’s erythrocytes, causing agglutination of the recipient’s own cells. Agglutination and lysis cause harmful transfusion reactions that can be prevented only by complete and careful ABO matching between donor and recipient.

Rh System

The Rh blood group is the most polymorphic system of red cell antigens, consisting of at least 50 separate antigens. At least five major antigens and a large number of rare variants have been identified and are expressed primarily on erythrocytes. The major antigens are contained on two proteins encoded from two closely linked genes, RHCE and RHCE. The RhD protein expresses the dominant antigen,
which determines whether an individual is Rh-positive or Rh-negative. Individuals who express the D antigen on the RhD protein are Rh-positive, whereas individuals who do not express the D antigen are Rh-negative. The letter \( d \) is used to indicate lack of D. Rh-positive individuals can have either a \( DD \) or \( Dd \) genotype, whereas Rh-negative individuals have the \( dd \) genotype. About 15% of North American whites are Rh-negative, whereas the Rh-negative genotype is much less common among members of other ethnic groups. Rh-negative individuals can make anti-D if exposed to Rh-positive erythrocytes, but because the letter \( d \) is used to indicate the lack of the D antigen and does not represent a different antigen, Rh-positive individuals do not produce an antibody against \( d \). The second protein, RhCE, expresses two different antigens, C and E, each of which has two different alleles (\( C \) or \( c \), \( E \) or \( e \)). Therefore, four potential haplotypes of \( C \) and \( E \) antigens are commonly observed: \( CE, Ce, cE, \) and \( ce \). IgG anti-D alloantibody produced by Rh-negative mothers against erythrocytes of their Rh-positive fetuses was the primary cause of Rh maternal-fetal incompatibility and the resulting hemolytic disease of the newborn (see Chapter 28). However, over the past several decades, the incidence of mothers with high titers of anti-D antibody has decreased dramatically because of the use of prophylactic anti-D immunoglobulin. By mechanisms that are still not completely understood, administration of anti-D antibody within a few days of exposure to RhD-positive erythrocytes completely prevents sensitization against the D antigen. Because
Graft Rejection

Transplantation of organs commonly is complicated by an immune response against antigens—primarily HLA—on the donated tissue. Most of our knowledge on the transplantation of organs is based on renal transplant studies. The primary mechanism of the rejection of transplanted organs is a type IV cell-mediated reaction. Two randomly chosen individuals are almost certainly antigenically different to some degree. Organ transplants between them could be rejected in approximately 2 weeks without the extensive use of immunosuppressive drugs.

After the donor and recipient are matched for ABO antigens, HLAs are the principal targets of the rejection reaction; HLA matching of donor and recipient enhances the probability of acceptance of the graft. Not all HLA loci are equally important; matching at the HLA-DR locus appears to be the most critical for graft acceptance, and matching at HLA-A and HLA-B of slightly lesser importance. (These loci are discussed in Chapter 7.)

Transplant rejection may be classified as hyperacute, acute, or chronic, depending on the amount of time that elapses between transplantation and rejection. Hyperacute rejection is immediate and rare. When the circulation is reestablished to the grafted area, the graft may immediately turn white (the so-called white graft) instead of a normal pink. Hyperacute rejection usually occurs in recipients with preexisting antibody to antigens in the graft. The antibodies may have resulted from rejection of a previous graft or from prior blood transfusions that contained platelets and white blood cells with foreign HLA. Additionally, about half of women who have had multiple pregnancies have circulating antibodies against their husband’s HLA antigens. As the circulation to the graft is established, antibodies bind to the vascular endothelial cells in the grafted tissue and activate the inflammatory response, including the coagulation cascade, which results in stasis of blood flow into the tissue (Figure 8-10). (Coagulation is described in Chapters 6 and 25.) Biopsies of the graft often show deposits of antibody (IgG and IgM), complement, and neutrophils. This condition is rare because of effective pretransplantation cross-matching during which a recipient is tested for antibodies against the HLA antigens of the potential donor.

Acute rejection is primarily a cell-mediated immune response that occurs within days to months after transplantation. This type of rejection occurs when the recipient develops an immune response against unmatched HLAs after transplantation. Sensitization is usually initiated by the recipient’s lymphocytes interacting with the donor’s dendritic cells within the transplanted tissue, resulting in induction of recipient Th1 and Tc cells against the donor’s antigens. The Th1 cells release cytokines that activate infiltrating macrophages, and the Tc cells directly attack the endothelial cells in the transplanted tissue. A biopsy of the rejected organ usually shows an infiltration of lymphocytes and macrophages characteristic of a type IV reaction. Immunosuppressive drugs may delay or lessen the intensity of acute rejection.

A form of autoimmune hemolytic anemia is often caused by autoantibodies against Rh antigens, especially e. This variant is caused by IgG antibodies that react with erythrocytes at normal body temperature (thus called warm autoimmune hemolytic anemia) and increase phagocytic destruction of the red cell. This characteristic differentiates the warm variant from another form of autoimmune hemolytic anemia, which is caused by IgM autoantibodies that react optimally with erythrocytes in the cooler portions of the body (e.g., fingers, toes) and is referred to as cold autoimmune hemolytic anemia.

Hemolytic disease of the newborn related to the D antigen has been controlled, alloantibodies against the other Rh antigens (usually C, c, or E) have become more important. In general, these alloantibodies are associated with a less severe hemolytic disease.

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Hemolytic disease of the newborn related to the D antigen has been controlled, alloantibodies against the other Rh antigens (usually C, c, or E) have become more important. In general, these alloantibodies are associated with a less severe hemolytic disease.
Another form of acute rejection, acute antibody-mediated rejection, has recently been recognized and accounts for about 10% of acute rejections. This form of rejection is mediated by antibody and complement. The predominant antibodies are against HLA antigens or, on occasion, autoantigens in the graft (e.g., vimentin, angiotensin receptor), but, unlike those antibodies that cause hyperacute rejection, are not present at the time of transplantation. Sensitization takes 2 weeks or longer and results in the accumulation of antibody, complement, neutrophils, and thrombi in the vasculature of the graft (a type II hypersensitivity reaction).

Chronic rejection may occur after a period of months or years of normal function. It is characterized by slow, progressive organ failure. Chronic rejection may be caused by inflammatory damage to endothelial cells lining blood vessels as a result of a weak cell-mediated immunologic reaction against minor histocompatibility antigens on the grafted tissue.

**DEFICIENCIES IN IMMUNITY**

Disorders resulting from immune deficiency are the clinical sequela (results) of impaired function of one or more components of the immune or inflammatory response, including B cells, T cells, phagocytes, and complement (Table 8-6). An immune deficiency is the failure of these mechanisms of self-defense to function at their normal capacity, resulting in increased susceptibility to infections. Primary (congenital) immune deficiency is caused by a genetic anomaly, whereas secondary (acquired) immune deficiency is caused by another illness, such as cancer or viral infection, or by normal physiologic changes, such as aging. Acquired forms of immune deficiency are far more common than the congenital forms.

**Initial Clinical Presentation**

The clinical hallmark of immune deficiency is a tendency to develop unusual or recurrent, severe infections. Preschool and school-age children normally may have 6 to 12 infections per year, of which 3 or 4 are ear infections, and adults may have 2 to 4 infections per year. Most of these are not severe and are limited to viral infections of the upper respiratory tract, recurrent streptococcal pharyngitis, or mild otitis media.

Potential immune deficiencies are considered if the individual has had severe, documented bouts of pneumonia, otitis media, sinusitis, bronchitis, septicemia, or meningitis or infections with opportunistic microorganisms that normally are not pathogenic or usually confined to one site (e.g., Pneumocystis jirovecii, disseminated Candida infection, cytomegalovirus [CMV]). Infections are generally recurrent with only short intervals of relative health, and multiple simultaneous infections are common. Individuals with primary immune deficiencies often have eight or more ear infections, two or more serious sinus infections, and two or more pneumonias, recurrent abscesses or infections in unusual sites, or persistent fungal infections (particularly thrush in an individual at least 1 year old) within a year. Recurrent internal infections, such as meningitis, otosynomyelitis, or sepsis, are common. Prolonged antibiotic use is commonly ineffective by oral or injected routes and may necessitate intravenous administration. Additional symptoms may include failure to thrive and chronic diarrhea. A familial history of immune deficiency may be found in some types of primary deficiency.

The type of recurrent infections that manifest may indicate the type of immune defect. Deficiencies in T-cell immune responses are suggested when recurrent infections are caused by certain viruses (e.g., varicella, vaccinia, herpes, cytomegalovirus), fungi and yeasts (e.g., Candida, Histoplasma), or certain atypical microorganisms (e.g., P. jirovecii). B-cell deficiencies and phagocyte deficiencies, however, are suggested if the individual has documented, recurrent infections with microorganisms that require opsonization (e.g., encapsulated bacteria) or viruses against which humoral immunity is normally effective (e.g., rubella). Some complement deficiencies resemble defects in antibody or phagocyte function, but others are commonly associated with disseminated infections with bacteria of the genus Neisseria (Neisseria meningitidis and Neisseria gonorrhoeae).

Much of our current understanding of the development of the immune system and the interactions of the cells in the immune response was developed by studying congenital and acquired immune deficiencies or, as they have been called, “experiments of nature.” Many immune deficiencies result from selective altering or removal of one component of the immune system. We can understand the importance of that component by observing the effect of its removal on the remainder of the immune response.

**Primary Immune Deficiencies**

Most primary immune deficiencies are the result of a single gene defect (Figure 8-11). Generally, the mutations are sporadic and not inherited: a family history exists in only about 25% of individuals. The sporadic mutations occur before birth, but the onset of symptoms may be early or later, depending on the particular syndrome. In approximately 60% of the cases symptoms of immune deficiency appear within the first 2 years of life, whereas other immune deficiencies are progressive, with the onset of symptoms appearing in the second or third decade of life. The most common symptoms include sinusitis (68% of individuals), pneumonia (51%), ear infections (51%), diarrhea (30%), and bronchitis (55%), with the incidence varying depending on the specific syndrome.

Many immune deficiencies also are associated with other characteristic defects; some of which appear to be unrelated to the immune system yet may be life threatening in themselves. Examples include eczema and thrombocytopenia (in Wiskott-Aldrich syndrome); cardiac anomalies, low levels of calcium in the blood, and structural anomalies of the face (in DiGeorge syndrome); or a severe lack of muscular coordination and dilation of the small blood vessels (in ataxia-telangiectasia). These associated symptoms can be useful diagnostically. For instance, the principal immunologic defect in DiGeorge syndrome is the partial or complete absence of T-cell immunity.
<table>
<thead>
<tr>
<th>Classification*</th>
<th>Example</th>
<th>Mutation</th>
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<td><strong>B-Cell Defects</strong></td>
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<td>B-cell receptor signaling</td>
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<td>Btk</td>
<td>Little or no B-cell maturation or antibody</td>
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<td>IgMγ chain</td>
<td>Little or no class-switch to IgG or IgA, with overproduction of IgM</td>
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<td>Class-switch: selective</td>
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<td>Little or no class-switch to IgG or IgA, with overproduction of IgM</td>
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<td>IG subscript deficiency</td>
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<td></td>
<td>Selective IgA deficiency</td>
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<tr>
<td></td>
<td>Common variable immune deficiency</td>
<td>Multiple</td>
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<td><strong>T-Cell Defects</strong></td>
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<td>Defective primary lymphoid organ for T-cell development</td>
<td>Chronic mucocutaneous candidiasis</td>
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<td>Little or no response to <em>Candida</em></td>
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<td>Antigen specific response</td>
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<td>Unknown</td>
<td>Complete; lack of white blood cells</td>
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<tr>
<td>Combined T- and B-Cell Defects</td>
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<td>ADA</td>
<td>Complete; few or no T, B, or NK cells</td>
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<tr>
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<td>SCID: cytokine receptor defects</td>
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<tr>
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<td>RAG-1 or RAG-2 deficiency</td>
<td>RAG-1/RAG-2</td>
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<td>Complement Defects</td>
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<td>Alternative pathway</td>
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<td>Properdin, factor D or B</td>
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<td></td>
<td>C3 deficiency</td>
<td>Factor H, factor I</td>
<td>Factor H, factor I</td>
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<td>Terminal pathway</td>
<td>C3 deficiency</td>
<td>C3</td>
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<td>C5, C6, C7, C8, or C9 deficiency</td>
<td>C5, C6, C7, C8, or C9</td>
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<tr>
<td><strong>Phagocyte Defects</strong></td>
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<td>ELA2, WASP</td>
<td>Inadequate numbers of neutrophils</td>
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<td>ELA2</td>
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<td>Adhesion defects</td>
<td>Leukocyte adhesion defect (LAD)−1</td>
<td>CD18</td>
<td>Decreased phagocyte adhesion to endothelium</td>
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<td>LAD-2</td>
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<td>Phagocytosis defects</td>
<td>C3 receptor deficiency</td>
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<td>Myeloperoxidase deficiency</td>
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<td></td>
<td>Chronic granulomatous disease</td>
<td>NADPH oxidase</td>
<td>Defective production of H₂O₂</td>
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</table>

*AICD, Activation-induced cytidine deaminase; SCID, severe combined immune deficiency; TCR/BCR, T-cell receptor/B-cell receptor; MHC, major histocompatibility complex; NADPH, nicotinamide adenine dinucleotide phosphate; NK, natural killer.*
Figure 8-11 Lymphocyte development defects. This diagram shows defects in lymphocyte development that may account for congenital (primary) immune deficiencies. See the text and refer to Figures 7-10 through 7-12 for more detailed information. Pluripotent stem cell indicates the common stem cells for lymphocytic, granulocytic, and monocytic lineages. Cytokine receptor defects include X-linked severe combined immunodeficiency (SCID) (IL-2 receptor defect), JAK3 defects, and IL-7 receptor defects. T-cell receptor (TCR) defects include defects in CD3, CD45, and ZAP-70. Neither common variable immune deficiency nor chronic mucocutaneous candidiasis is included in this figure because the cause of these defects remains unknown. See Table 8-6 for further information on each defect. ADA, Adenosine deaminase deficiency; Agamma, Agammaglobulinemia; AICD deficiency, activation-induced cytidine deaminase deficiency; AT, ataxia-telangiectasia; PNP, purine nucleoside phosphorylase deficiency; slgM and slgD, Surface IgM and IgD. WAS, Wiskott-Aldrich syndrome.
Primary immunodeficiencies are classified into five groups, based on which principal component of the immune or inflammatory systems is defective. This chapter uses the five classifications proposed by the National Institutes of Health. B-lymphocyte deficiencies result from defects in B-cell immune responses. T-cell immunity rarely depends on competent B-cell responses, thus T-cell immune responses are not affected in pure B-lymphocyte deficiencies. T-lymphocyte deficiencies are defects in the development and function of T lymphocytes. Because helper T cells are obligatory in the development of many B-lymphocyte responses, antibody production is often diminished in these conditions, although the B cells are fully capable of producing an adequate antibody response. Many textbooks disagree on the classification of several specific immune deficiencies because of the difficulty in distinguishing between primary B-cell defects and those that are secondary to a primary T-cell defect. The classifications described below define T-cell defects as those with a clear defect in T-cell immunity, with normal B-cell immune responses. Combined T- and B-lymphocyte deficiencies result from inherent defects that directly affect the development of both T and B lymphocytes. Some combined deficiencies result in major defects in both the T- and B-cell immune responses, whereas others are “partial” and more adversely affect T cells than B cells. The partial combined deficiencies include many conditions that may be classified as T-cell defects in other textbooks. Complement deficiencies and phagocytic deficiencies frequently present like antibody deficiencies because of the close interactions among antibody, complement, and phagocytes.

**B-Lymphocyte Deficiencies**

A defect in B-cell development results in lower levels of circulating immunoglobulins and increased susceptibility to infections in which antibodies are the primary protective mechanism. The condition in which immunoglobulin levels are lower than normal is termed hypogammaglobulinemia. The condition in which they are totally or nearly totally absent is termed agammaglobulinemia. Normal lymphocyte development is discussed in Chapter 7.) Recurrent infections range from life threatening to mild, depending on the severity of the deficiency. Characteristic infections include encapsulated bacteria (e.g., *Streptococcus pneumoniae* or *Haemophilus influenzae*) that may cause pneumonia or sepsis and other microorganisms that cause infections of the sinuses, ears, and gastrointestinal tract.

The most severe B-lymphocyte deficiency is Bruton’s agammaglobulinemia, also referred to as X-linked agammaglobulinemia. Somewhat less than a third of the mutations are sporadic. This condition results from mutations in the gene for Bruton’s tyrosine kinase (Btk); an enzyme involved in intracellular signaling from several B-cell receptors, including the IgM B-cell antigen receptor, the IL-5 receptor, and the IL-6 receptor. Ineffective signaling results in the arrest of the development in the bursal-equivalent tissue (bone marrow) of early cells in the B-cell lineage into mature B cells (see Figure 8-11). Few or no circulating mature B cells are present, although T-cell number and function are normal. At 6 months of life the approximate normal serum concentrations of immunoglobulins are IgG, 400 mg/dl; IgM, 40 mg/dl; and IgA, 30 mg/dl. In 6-month-old children with Bruton’s agammaglobulinemia, serum IgG levels are well below 100 mg/dl and IgM and IgA are almost absent.

An autosomal recessive form of agammaglobulinemia (autosomal agammaglobulinemia) results from other mutations in the B-cell receptor. The most common is a mutation of the mu (μ) chain of the IgM portion of the receptor. This mutation prevents intracellular signaling after antigen binds to the receptor, leading to blocked maturation, no antibody production, and very severe infections.

Several defects in antibody class-switch have been identified (see Figure 7-11). X-linked hyper-IgM syndrome results from a mutation in CD40 ligand, which is expressed on the surface of helper T (Th) cells. Th cells stimulate B cells to undergo a switch in the class of antibody they produce through multiple Th–B cell interactions involving ligands expressed on one cell binding to specific receptors on the other cell. The ligand–receptor interaction results in an intracellular signal facilitating rearrangement of the genes for the antibody variable region from a site near the constant region gene for the μ chain to the constant region for a different antibody H chain (see Figure 7-20). A critical ligand–receptor interaction occurs between the receptor CD40 on the B cell and its ligand (CD154 or CD40L) on the Th cell. A mutation in CD40L results in defective class-switch, decreased or absent production of IgG and IgA, poor development of memory B cells, and overproduction of IgM, which does not require class-switch. T-cell immunity is not affected.

Defects in other components of Th–B-cell interaction result in autosomal hyper-IgM syndrome. Mutations in CD40 on B cells result in a similar effect to that described above. A defect in a DNA editing enzyme (activation-induced...
monly diagnosed immune deficiency. As the name implies, it may or not be accompanied by decreased levels of IgA. The presentation is very heterogeneous. It is characterized by anaphylactic reactions that can follow administration of blood products that contain IgA. Serious complications of IgA deficiency include severe atopic diseases and autoimmune diseases; selective IgA deficiency is two or three times more common in atopic individuals than in others. Secretory IgA normally may prevent the uptake of allergens from the environment so that IgA deficiency may lead to increased allergen uptake and a more intense challenge to the immune system because of prolonged exposure to environmental antigens. One of the most severe complications of IgA deficiency is an anaphylactic reaction that can follow administration of blood products that contain IgA. Serious anaphylactic reactions can occur in individuals totally lacking IgA because the immune system recognizes donor IgA as a foreign antigen. Initial sensitization can occur in fetal life through exposure to maternal IgA that leaks across the placenta or later through the ingestion of maternal IgA in breast milk or bovine IgA in cow’s milk. Sensitization also can occur with initial administration of blood products containing IgA. The individual’s primed immune system then acts against donor IgA on subsequent exposure.

**Common variable immune deficiency** is the most commonly diagnosed immune deficiency. As the name implies, the presentation is very heterogeneous. It is characterized by hypogammaglobulinemia, but the particular class of antibody that is decreased varies: most have low amounts of IgG, which may or may not be accompanied by decreased levels of IgA or IgM, or both, with normal numbers of B cells. Some may have accompanying T-cell defects. Multiple genetic defects in terminal differentiation account for this condition, although the specific defects have not been identified in most patients. The age of onset of symptoms, such as recurrent bacterial respiratory tract infections, is generally later than most primary immune deficiencies (late 20s). Secondary complications include arthritis (infectious and noninfectious), gastrointestinal symptoms (malabsorption, chronic diarrhea) autoimmune disease (anemia, thrombocytopenia, endocrine diseases), and cancer (of the lymphoid system, skin, and gastrointestinal tract).

**T-Lymphocyte Deficiencies**

Two well-studied examples of T-lymphocyte defects that represent different ends of the T-cell differentiation process include DiGeorge syndrome and chronic mucocutaneous candidiasis. Lymphoid stem cells begin maturing into functional T lymphocytes in the thymus. DiGeorge syndrome (congenital thymic aplasia or hypoplasia) is caused by the lack, or more commonly partial lack, of the thymus, resulting in greatly decreased T-cell numbers and function and in life-threatening viral, fungal, and intracellular bacterial infections (see Figure 8-11). The defect is attributed usually to deletions on chromosome 22 (some deletions also have been identified on chromosome 10); about 25% of which are inherited. The deleted region encodes information for formation of organs that originate from the third and fourth pharyngeal pouches during the twelfth week of gestation. In addition to the lack of thymus development, the individual may present with a partial or complete absence of the parathyroid gland (resulting in decreased blood calcium levels), major structural defects in the heart and the aorta (resulting in inadequate blood flow and inadequate oxygenation of the tissues), and abnormal facial characteristics (e.g., underdeveloped chin, low-set ears, shortened structure of the upper lip) (Figure 8-12).

**Chronic mucocutaneous candidiasis** is a primary defect of T lymphocytes in response to a specific infectious agent, the yeast *C. albicans*. At least seven variants of this condition have been described. All are characterized by mild to extremely severe chronic mucocutaneous candidiasis: *Candida* infections that involve the mucous membranes, nails, and skin. Invasive candidiasis is extremely rare. Although most B- and T-cell immune responses may be normal, most individuals with this defect cannot react to antigens from *Candida*. The cause of this defect is unknown.

**Combined T- and B-Lymphocyte Deficiencies**

The most severe deficiencies usually occur when both the B- and T-cell immune responses are affected. A great deal of knowledge about the evolution of bone marrow stem cells into functional B- and T-cell effectors came from studying children with the most severe immune deficiency, severe combined immune deficiency (SCID). The most severe form of SCID is reticulogenesis (failure of blood cells to develop), in which a common stem cell for all white blood cells is
absent; therefore T cells, B cells, and phagocytic cells never develop (see Figure 8-11). Most children with reticular dysgenesis die in utero or very soon after birth. More typically, a defect occurs after some stem cells become committed to developing into lymphocytes (lymphoid stem cells); therefore, most individuals with SCID are deficient in lymphocyte development, but have normal numbers of all other white blood cells. SCID often results in few or absent T and B lymphocytes in the circulation and secondary lymphoid organs (spleen, lymph nodes). The thymus is usually hypoplastic (underdeveloped) because of the absence of T cells. Immunoglobulin levels, especially of IgM and IgA, are absent or greatly reduced, although IgG levels may be almost normal in the first months of life because of the presence of maternal antibodies. In the most severe defects, death occurs at about 1 year of life.

At least 20 different forms of SCID have been identified. Depending on the specific genetic mutation, the defect may involve T cells, B cells, and NK cells or may suppress more severely the function of one cell type, with relatively minor effects on the others. All three cells are adversely affected (T–, B–, NK–) in SCID resulting from a deficiency of adenosine deaminase (adenosine deaminase [ADA] deficiency), which is an enzyme involved in purine metabolism (see Figure 8-11). This defect is autosomal recessive and results in the accumulation of toxic purine metabolites to which rapidly dividing cells, such as lymphocytes, are especially sensitive. ADA deficiency accounts for about 16% of all persons with SCID. The development of T cells, B cells, and NK cells is arrested very early, and very few lymphocytic cells are found in the blood. In some forms of SCID, the defect resides in receptors for cytokines that are necessary for maturation of lymphocytes (see Figure 8-11). T cells and NK cells are preferentially affected (T–, B+, NK–) in SCID resulting from a deficiency of adenosine deaminase (ADA deficiency), which is an enzyme (a tyrosine kinase) that associates with IL-2Rγ in normal cells and communicates information from the receptor to the nucleus. Thus cells with defects in JAK3 cannot respond to cytokines that bind to these receptors on the cell surface. An autosomal form results from mutations of one of the protein chains (α-chain) of the IL-7 receptor (IL-7 receptor deficiency). IL-7 appears to be necessary for the maturation of T cells, so that this deficiency has relatively normal levels of B cells and NK cells.

Mutations in another purine metabolism enzyme, purine nucleoside phosphorylase (purine nucleoside phosphorylase [PNP] deficiency) are less severe than ADA deficiency (see Figure 8-11). T cells and NK cells appear to be more susceptible to mutations in PNP so that B-cell function can be relatively normal.

Another form of SCID preferentially affects T cells and B cells (T–, B–, NK+). T and B lymphocytes possess receptors for antigen, whereas NK cells do not. Those receptors result from a process of genetic rearrangement of V and J genes to form the variable regions of the L chain (B-cell receptor [BCR]) and the γ-chain (T-cell receptor [TCR]) and the CD4– and CD8– genes to form the variable regions of the H chain (BCR) and β-chain (TCR). Successful rearrangement is controlled by two recombination activating enzymes (RAG-1 and RAG-2). RAG enzymes cut and repair double-stranded breaks in DNA that are necessary for genetic rearrangement. RAG-1 or RAG-2 deficiencies are autosomal recessive and result in arrested lymphocyte development from blocked recombination of variable regions of B-cell and T-cell receptors (see Figure 8-11).

Forms of partial SCID, with the defect being primarily of T cells, arise from mutations in several components of the TCR complex (see Figure 8-11). Defects in the TCR result in inadequate maturation of T cells, with normal B and NK cells. Antibody production may be depressed because of the lack of Th cells. The TCR is a complex organization of proteins that react with antigen (α- and β-chains), then provide an intracellular signal to the nucleus (γ-, δ-, and ε-chains [collectively called CD3]) and the associated molecules CD45 and ZAP-70). Examples of these deficiencies include mutations in CD3, CD45, or ZAP-70. The T-cell defect in each can range from mild to severe in nature, with normal B lymphocytes.

Even if nearly adequate numbers of B and T cells are produced, their ability to process and present antigen may be defective. The bare lymphocyte syndrome is a group of immune deficiencies characterized by an inability of lymphocytes and macrophages to present antigen because of defects in class I or class II MHC antigen expression (see Figure 8-11). MHC class I deficiency results from mutations in the genes for TAP1 or TAP2, which control the transport of antigenic protein fragments across the endoplasmic reticulum and the
formation of MHC class I/antigen complexes for transporta-
tion to the cell surface (see Figure 7-16). Because MHC class I
molecules preferentially present antigen to CD8+ Tc cells, the
resultant deficiency is of CD8+ cytotoxic cells, with normal
levels of CD4+ helper cells and normal antibody production.

MHC class II deficiency is more severe. A variety of muta-
tions prevent normal production of MHC class II molecules,
which present antigen to CD4+ helper cells. Because of defec-
tive recruitment of helper T cells, normal antibody responses
are greatly suppressed. Children with this deficiency develop
life-threatening infections and usually die before age 5 years.

Some combined immune deficiencies are secondary to
mutations that affect a variety of cells other than immuno-
cytes. For instance, Wiskott-Aldrich syndrome (WAS; an X-
linked recessive disorder) results from sporadic mutations in
the WAS protein (WASP), which is involved in intracellular
signaling and regulation of the organization of the cell’s actin
cytoskeleton \(^{70}\) (see Figure 8-11). The defects in the cytoskel-
on lead to the classic symptoms of thrombocytopenia (with
resultant bleeding disorders), scaly eczema, and defective T
and B cells. IgA and IgG levels are usually normal, but IgM
responses are highly depressed. Antibody responses against
antigens that elicit primarily an IgM response, such as poly-
saccharide antigens from bacterial cell walls (e.g., of Pseudo-
monas aeruginosa, S. pneumoniae, H. influenzae, and other
microorganisms with polysaccharide outer capsules), are de-
cicient. Persons with WAS have a very high risk of lymphoid
malignancies (leukemias and lymphomas).

Ataxia-telangiectasia (AT) is an autosomal recessive dis-
order resulting from a large variety of sporadic mutations in
the ATM gene, which encodes a protein involved in repair of
double-stranded breaks in DNA. Affected infants often de-
velop ataxia (unsteady gait), which usually becomes apparent
when the child is learning to walk. The neurologic defect may
eventually lead to confinement in a wheelchair. Telangiectasia
(dilation of capillaries) can occur in the eyes and skin, espe-
cially on the ears, neck, and extremities. Both B and T cells
are variably affected and unrepai red double-stranded DNA
breaks are commonly observed in the regions encoding the
T-cell and B-cell receptors. About 70% of those with AT are
IgA deficient, occasionally accompanied by deficiencies in
IgG (see Figure 8-11). Individuals with AT are at high risk for
developing leukemias and lymphomas.

**Complement Deficiencies**

Complement activation is a necessary component of protec-
tion against many infectious agents. As a result, some defects
in the complement cascade often resemble antibody deficien-
cies, with recurrent infections with encapsulated bacteria
(e.g., H. influenzae and S. pneumoniae). \(^{71}\) Additionally, the Fc
portion of IgG and some activated complement components,
such as C3b, function as opsonins and facilitate phagocytosis
by neutrophils and macrophages. In addition to recurrent in-
fec tions, deficiencies in the classical pathway commonly lead
to a SLE-like syndrome. As noted, excessive levels of circu-
lating complexes of antibody, antigen, and complement may
lead to type III hypersensitivity diseases (immune complex
diseases). However, healthy individuals release small amounts
of soluble intracellular antigens into the blood during normal
cell turnover. Low levels of naturally occurring autoantibodies
and limited activation of the classical pathway of the comple-
ment system through C3 facilitate the removal of this debris
by phagocytes. Thus some complement defects may slow the
clearance from the blood of natural immune complexes, lead-
ing to SLE-like symptoms.

**C3 deficiency** is the most severe complement defect (Figure
8-13). C3 is the component that unites all pathways of comple-
ment activation, and complement component C3b is a major
opsonin. Persons with C3 deficiency are at risk for recurrent
life-threatening infections with encapsulated bacteria at an
early age, as well as a SLE-like syndrome that may be compi-
licated by kidney disease (glomerulonephritis). \(^{72}\) C2 deficiency,
more so than C1 or C4 deficiencies, also has an increased risk
for recurrent respiratory infections with encapsulated bacteria
(e.g., S. pneumoniae, H. influenzae).

Mannose-binding lectin (MBL) deficiency is the primary
defect of the lectin pathway of complement activation. The
defect results in increased risk of infection with microor-
organisms that have polysaccharide capsules rich in mannose, par-
ticularly the yeast Saccharomyces cerevisiae and encapsulated
bacteria such as N. meningitidis and S. pneumoniae.

Deficiencies in the alternative pathway also result in recur-
fent infections with encapsulated bacteria. Properdin defi-
ciency is associated with recurrent meningococcal infections
and is X-linked, whereas all other complement deficiencies
are autosomal recessive. Symptoms generally appear in the
second decade of life. Factor I and factor H are major regula-
tors of the complement cascade and control the level of spon-
taneous activation of C3. Factor I deficiency and factor H
deficiency can be severe because they lead to increased spon-
taneous destruction of C3 and a secondary C3 deficiency.

Deficiencies of components of the terminal portion of the
complement cascade (C5, C6, C7, C8, or C9 deficiencies)
are associated with increased infections with only one group
of bacteria; those of the genus Neisseria (N. meningitidis or
N. gonorrhoeae). Neisseria usually cause localized infections
(meningitis or gonorrhea), but those individuals with termi-
nal pathway defects have more than an 8000-fold increased
risk for systemic infections with atypical strains of these mi-
croorganisms. C9 deficiency is the most common terminal
pathway defect, appears primarily in Japanese populations,
and is generally asymptomatic. The other deficiencies of the
terminal pathway are extremely rare, but are characterized by
more aggressive infections. The risk for systemic infections
with Neisseria is also increased in those with deficiencies of
C2, factor D, factor B, and properdin.

**Phagocytic Deficiencies**

Phagocytosis is generally aided by bacterial opsonization with
IgG or C3b; therefore, defects in phagocytic killing usually re-
result in recurrent infections with the same group of microor-
organisms (encapsulated bacteria) associated with antibody and
complement deficiencies. Phagocytosis is a multistep process that involves initial adhesion between circulating phagocytes and the endothelial cells lining the circulation (see Figure 6-11). The phagocytes exit the circulation and move to a site of infection by a chemotactic process in response to soluble chemotactic factors released by the infection. The process of phagocytosis itself begins with attachment of the phagocyte to the targeted bacteria through the interaction of opsonins on the microorganism and matched receptors on the phagocyte’s surface. Phagocytic engulfment results in internalization of the infectious agent and activation of a variety of oxygen-dependent and oxygen-independent killing mechanisms. Deficiencies can arise from mutations that affect one or more of these steps (Figure 8-14).

Inadequate numbers of phagocytes, particularly neutrophils (severe congenital neutropenias), result in a variety of recurrent and severe bacterial infections beginning early in life. Approximately 50% of these patients have a mutation in the neutrophil elastase gene (ELA2). Other mutations have been identified (e.g., WAS gene) in the other 50%. A milder form, cyclic neutropenia, is autosomal dominant with almost 100% of affected individuals having a mutation in the ELA2 gene. Changes in neutrophil levels are cyclic and may remain at or near normal for 2 to 3 weeks, followed by periods of neutropenia lasting a few days to weeks. During the neutropenia, the individual has increased susceptibility to recurrent bacterial infections.

Near sites of inflammation, soluble mediators diffuse into the circulation and induce expression of a variety of adhesion molecules on the phagocyte surface, which interact with complementary molecules on the endothelial cells to increase adherence between the phagocyte and the vessel wall and allow for margination and diapedesis to occur. Leukocyte adhesion deficiencies (LAD) result from mutations in various phagocyte adhesion molecules (see Table 6-3). Leukocyte adhesion deficiency, type 1 (LAD-1) results from an autosomal recessive mutation in CD18, which is a β2 integrin chain that is shared by several different receptors. LAD-2 results from a defect in adding the monosaccharide fucose to carbohydrates on the phagocyte surface. Surface carbohydrates with fucose are ligands for selectins on the endothelial and leukocyte. These and other defects in leukocyte adhesion molecules usually result in increased levels of neutrophils in the blood (leukocytosis) because they cannot leave the circulation and in increased recurrent bacterial and fungal infections.

Additional deficiencies diminish the leukocyte’s recognition of opsonins of the complement cascade (e.g., C3b). Deficiencies in the complement receptor for C3 (C3 receptor deficiency) result in recurrent bacterial infections, particularly of the skin.
A variety of defects in killing of microorganisms have been described. **Chédiak-Higashi syndrome** results from a defect in cytoplasmic granules from an autosomal recessive mutation in the lysosomal trafficking regulator gene (CHS1). The CHS1 protein helps control movement of granules to cellular membranes in preparation for degranulation. As a result of these mutations, the granules remain in the cytoplasm and form large aggregates that are readily apparent microscopically. Leukocytes from individuals with Chédiak-Higashi syndrome have decreased chemotaxis, granular fusion, and bacterial killing. Platelet granules also may be affected, resulting in prolonged bleeding, and partial albinism can occur because of defects in melanocyte granules. Affected children develop recurrent infections of the skin, respiratory tract, and mucous membranes, especially with gram-positive bacteria.

The enzyme myeloperoxidase participates in a major mechanism of bacterial killing in phagocytes. Myeloperoxidase is found in primary granules and catalyzes the formation of acids from halides (e.g., chloride ion) and hydrogen peroxide (H₂O₂). As a result of phagocytosis, neutrophils and other phagocytes switch much of their glucose metabolism to the hexose-monophosphate shunt. A byproduct of this pathway is the conversion of molecular oxygen by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and other enzymes into highly reactive and toxic oxygen derivatives, including hydrogen peroxide. Two deficiencies in the myeloperoxidase–hydrogen peroxide killing process have been extensively studied. **Myeloperoxidase deficiency** is a relatively mild disorder characterized by a complete or partial deficiency in myeloperoxidase. Individuals do not have severe recurrent infections because most infectious bacteria are sensitive to direct killing by many of the toxic oxygen molecules produced by NADPH oxidase. The exception is the person with concurrent diabetes, who may have recurrent disseminated candidiasis.

**Chronic granulomatous disease** (CGD) is a more severe defect in the myeloperoxidase–hydrogen peroxide system. Several forms of the disease have been characterized, both X-linked (about 70% of the individuals) and autosomal recessive, with the X-linked being more severe. CGD results from a variety of mutations (at least four have been identified) in portions of the NADPH oxidase complex, resulting in deficiencies in the production of hydrogen peroxide and other oxygen products. Thus individuals have adequate myeloperoxidase and chloride but lack the necessary hydrogen peroxide.
peroxide. Individuals with CGD have recurrent severe pneumonias; tumor-like granulomas in lungs, skin, and bones; and other infections with some normally relative innocuous microorganisms, such as *Staphylococcus aureus*, *Serratia marcescens*, *Aspergillus* spp., and others. These are catalase-positive microorganisms. Infections with more virulent, but catalase-negative, microorganisms (e.g., *S. pneumoniae*) are rare. Most microorganisms produce their own hydrogen peroxide as a byproduct, which accumulates in the phagocytic vacuole and can be used by the phagocyte’s myeloperoxidase to kill the microorganism. Some microorganisms also produce the enzyme catalase, which breaks down hydrogen peroxide to the phagocyte’s myeloperoxidase, leading to their own death. Catalase-positive microorganisms, however, destroy the bacterial hydrogen peroxide and survive and cause infection.

**Secondary Immune Deficiencies**

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

- Normal physiologic conditions
  - Pregnancy
  - Infancy
  - Aging
- Psychologic stress
- Emotional trauma
- Eating disorders
- Dietary insufficiencies
  - Malnutrition caused by insufficient intake of large categories of nutrients, such as protein or calories
  - Insufficient intake of specific nutrients, such as vitamins, iron, or zinc
- Malignancies
  - Malignancies of lymphoid tissues, such as Hodgkin disease, acute or chronic leukemia, or myeloma
  - Malignancies of nonlymphoid tissues, such as sarcomas and carcinomas
- Metabolic diseases or genetic syndromes
  - Diabetes
  - Cystic fibrosis
  - Alcoholic cirrhosis
  - Sickle cell disease
  - SLE
  - Chromosome abnormalities, such as trisomy 21 (Down syndrome)
- Environmental
  - Ultraviolet (UV) light
  - Ionizing radiation
  - Chronic hypoxia
- Physical trauma
  - Burns

Medical treatments
- Stress caused by surgery
- Anesthesia
- Immunosuppressive treatment with corticosteroids or antilymphocyte antibodies
- Splenectomy
- Cancer treatment with cytotoxic drugs or ionizing radiation
- Infections
  - Congenital infections, such as rubella, cytomegalovirus, hepatitis B
  - Acquired infections, such as acquired immunodeficiency syndrome (AIDS)

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

**Normal Physiologic Conditions**

The competence of an individual’s immune system varies throughout life. Pregnancy itself is considered by many to be an immunocompromised condition. Pregnant women may have decreased reactivity or altered results in several tests of the immune system, including skin tests against various antigens, circulating numbers of T lymphocytes, and other very general tests. Pregnancy itself, however, is not associated with a marked change in infections, suggesting that the mother’s immune system is not severely altered.

The newborn child is immunologically immature. Although T-cell immune responses may be normal or near normal, other components of the immune system (especially antibody production) are just beginning to mature. Beginning at about 32 weeks of pregnancy, the placenta transports maternal antibodies into the fetal blood to protect the child during the first months of life (see Figure 7-30). After the delivery, the level of the mother’s antibodies slowly decreases in the newborn so that maternal antibodies no longer protect the child by about 6 months of life. By 6 to 8 months, the newborn should be efficiently protected by antibodies produced by its own B cells. In some infants, the development of antibody production is delayed, and a transient low level of antibody may persist for several months (transient hypogammaglobulinemia of infancy), during which the child has increased susceptibility to infections. Premature infants are particularly immunologically immature and are at increased risk for neonatal infections. The blood of infants born before 32 weeks’ gestation is generally devoid of maternal antibody.

Aging is also associated with a progressive depression in immune responses. Older adults generally have more severe bacterial and fungal infections, greater difficulty resolving those infections, and lower responses to vaccination.
Several meaningful changes occur during aging, although variations in the degree of change and a corresponding increased susceptibility to infection can be considerable among individuals. The thymus involutes over time, resulting in decreased production of fresh T cells. A concurrent depletion of memory T cells results in depressed responses to both new and “recall” antigens. A shift toward Th2 cells also may occur with a resultant decrease in Th1 cytokines. Total numbers of B cells may decrease. Numbers of NK cells may remain normal, although their activity is decreased. Similarly, neutrophil numbers may remain normal, with decreased phagocytosis and killing.

Psychologic Stress
The relationship between emotional stress and depressed immune function has become an area of intense clinical and research interest. For many decades anecdotal reports have suggested that increased incidences of infection and malignancy are associated with periods of both intense stress (e.g., the loss of a loved one, divorce) and relatively minor stress (e.g., final examination periods at colleges and universities). In addition, early studies showed that immune function, as demonstrated by delayed hypersensitivity skin test results, could be depressed through posthypnotic suggestion.

We are now beginning to understand the mechanisms of the relationship between emotional stress and the immune system. Many lymphoid organs are innervated and can be affected by nerve stimulation. In addition, lymphocytes have receptors for many hormones (e.g., sex hormones, neurotransmitters, and neuropeptides) and can respond to changing levels of these chemicals with increased or decreased function. For instance, stress-induced catecholamines affect the expression of adhesion molecules and movement of lymphocytes among lymphoid organs. (Further discussion of the effects of stress on susceptibility to disease is the subject of Chapter 10.)

Dietary Insufficiencies
Nutritional status can have a profound effect on immune function, and malnutrition is the predominant cause of secondary immune deficiencies worldwide. Severe deficits in calorie or protein intake lead to deficiencies in T-cell function and numbers. The humoral immune response is less affected by starvation, although complement activity, neutrophil chemotaxis, and bacterial killing within neutrophils often are depressed, resulting in infections with microorganisms that are normally destroyed by opsonization and phagocytosis.

Deficient zinc intake can profoundly depress both T- and B-cell function. Zinc is required as a cofactor for at least 70 different enzymes, some of which are found in lymphocytes and are necessary for their function. Secondary zinc deficiencies may be associated with malabsorption syndrome (failure to absorb zinc), chronic renal disease (loss of zinc in the urine), chronic diarrhea (loss of zinc through the gut), or burns or severe psoriasis (loss of zinc through the skin). Deficiencies of other enzyme cofactors, such as vitamins (e.g., pyridoxine, pantothenic acid, folic acid, vitamins A, C, E, and B₁₂), also may result in severe depressions of B- and T-cell function, phagocytosis, and complement activity.

Malignancies
Many malignancies are complicated by a wasting syndrome (cachexia) in the later stages, which can suppress the immune system secondary to the resultant malnutrition. Additionally, a very close relationship exists between the immune system and the development of malignancies. It is generally accepted that successful malignancies have developed mechanisms to avoid rejection by the individual’s immune system. Persons with primary immune deficiencies are usually at greater risk for developing malignancies, particularly malignancies of lymphoid tissues, such as leukemias or lymphomas. Malignancies aggressively depress the individual’s immune system. The effect is commonly nonspecific, resulting in a generalized deficiency of the immune response and a greatly increased susceptibility to developing life-threatening infections. In fact, many people with malignancies die from infection rather than from direct effects of the tumor.

Malignancies of lymphoid tissues, such as Hodgkin disease, acute or chronic leukemia, or myeloma, result in depletion of normal lymphocytes and their replacement by the malignant cells. Thus the number of B or T cells capable of responding to infections is depleted. Many malignancies, even those of nonlymphoid tissues, produce cytokines (e.g., transforming growth factor-beta [TGF-β] and vascular endothelial growth factor [VEGF]) that nonspecifically suppress the immune responses.

Metabolic Diseases or Genetic Syndromes
Diabetes suppresses many aspects of the immune and inflammatory responses, including phagocytosis and chemotaxis, lymphocyte proliferation, and glucose metabolism. The effects of trisomy 21 are less severe, but primarily include diminished neutrophil function. Patients with cystic fibrosis have decreased airway clearance of bacteria, thus increasing the probability of major respiratory tract infections.

Environmental
Individuals are constantly exposed to environmental agents that affect the immune system. UV light from sun exposure or tanning salons induces apoptosis of lymphoid stem cells, increases production of Treg cells that suppress defenses against cancer, and increases the production of anti-inflammatory cytokines. Ionizing radiation affects rapidly dividing cells, including those of the immune system. At very high doses, the entire immune system can be depleted.

Physical Trauma
Trauma that compromises the epithelial barrier also predisposes an individual to infection. Burn victims are susceptible to severe bacterial infections. Thermal burns appear to be associated with suppressed neutrophil function (especially chemotaxis), complement levels, cell-mediated immunity, and primary humoral responses, although secondary humoral
responses are normal. The mechanism of this immunosuppression may be twofold. Blood from burned individuals contains nonspecific immunosuppressive factors (all immune responses are suppressed, regardless of the antigen involved). In addition, burn victims also have increased regulatory T-cell function, which may increase antigen-specific suppression.

Medical Treatments

Medical treatments themselves may produce suppression of immune responses. Depression of B- and T-cell formation is manifested as a progressive increase in infections with opportunistic microorganisms (especially P. jirovecii, cytomegalovirus, C. albicans, and other fungi), the extent and location of which are unusual.

Many drugs that are used to fight cancer (e.g., cancer chemotherapeutic agents) are not specific for cancer cells, but are designed to attack cells in susceptible stages in their cell cycles or rapidly proliferating cells, which includes cells of the immune system as well as malignant cells. The immunosuppressive effects of chemotherapeutic drugs are exacerbated by concurrent treatment with ionizing radiation (x-rays), which also affect cells that are rapidly making new DNA. Therefore, a person’s immune response can be profoundly depressed as a result of the therapy. Other drugs, such as corticosteroids, are intentionally used to suppress the immune system and control hypersensitivity diseases (especially autoimmune disease) or prevent rejection of transplants. Because of their nonspecific activity, however, immune responses against infectious agents also can be suppressed, increasing an individual’s susceptibility to infection. The list of drugs that affect the immune response is ever increasing and includes analgesics, antithyroid medications, anticonvulsants, antihistamines, antimicrobial agents, antilymphocyte antibodies, and tranquilizers.

Surgery and anesthesia also can suppress T- and B-cell function. Transient, severe lymphopenia is a common postoperative condition that can last as long as 1 month. Surgery to remove the spleen (splenectomy) can result in a depressed humoral response against encapsulated bacteria (especially S. pneumoniae, H. influenzae, S. aureus, group A streptococci, and N. meningitidis), depressed serum IgM levels, and decreased levels of opsonins.

Infections

Many infectious microorganisms are successful at invading the human body because they have evolved mechanisms for fighting off specific immune/inflammatory responses against themselves (discussed in Chapter 9). However, some infectious agents (e.g., human immunodeficiency virus [HIV], Epstein-Barr virus [EBV], CMV, herpes simplex virus type 6, measles) can generally suppress the immune response. HIV is one of the few microorganisms that directly attacks the central processes involved in the development of an immune response (discussed in detail in Chapter 9). It infects and destroys the T-helper cell, which is necessary to provide help for the maturation of both plasma cells and cytotoxic T cells. Therefore, HIV suppresses the immune response against itself and secondarily creates a generalized immune deficiency by suppressing the development of immune responses against other pathogens and opportunistic microorganisms.

Several viruses (e.g., hepatitis B, rubella, CMV) can establish congenital infections through transmission from an infected mother to her child at birth when the child’s immune system is immature. These children may have suppressed immune responses, although the degree of the deficiency is not usually severe, but as the child’s immune system develops, the viral antigens may be partially seen as “self” so that a chronic infection is established.

Clinical Evaluation of Immunity

Evaluation and Care of Those with Immune Deficiency

Routine care of individuals with immune deficiencies must be tempered with the knowledge that the immune system may be totally ineffective. Administration of conventional immunizing agents or blood products to these individuals may be unsafe because of the risk that the immunizing agent will cause an uncontrolled infection. Attenuated vaccines contain live but weakened microorganisms (e.g., live polio vaccine, vaccines against measles, mumps, and rubella) that can cause disseminated infection. Although the vaccine virus is attenuated enough to be destroyed by a normal immune system, it can survive, multiply, and cause severe disease in an immune-deficient recipient. Additionally, even healthy recipients of vaccines containing live microorganisms can shed those microorganisms for a short time, increasing the risk of infection to family members or other close associates who are immune deficient. Even simple procedures, such as penetrating the skin for routine blood tests, may lead to fatal septicemia (bacterial infection of the blood) in the immune-deficient person.

Individuals with immune deficiencies are also at risk for graft-versus-host disease (GVHD). Mature T cells in a transplanted graft (e.g., transfused blood) are capable of a destructive cell-mediated reaction against unmatched histocompatibility antigens on the tissues in the graft recipient. Symptoms of an acute graft-versus-host reaction usually appear within 10 to 30 days after the transplant. The primary targets for GVHD are the skin (e.g., rash, loss or increase of pigment, thickening of skin), liver (e.g., damage to bile duct, hepatomegaly), mouth (e.g., dry mouth, ulcers, infections), eyes (e.g., burning, irritation, dryness), and gastrointestinal tract (e.g., severe diarrhea) and may lead to death from infections.

GVHD is not a problem when the recipient is immunocompetent, that is, has an immune system that can control the donor’s lymphocytes. If, however, the recipient’s immune system is deficient, the grafted T cells remain unchecked and attack the recipient’s tissues. Most GVHD is prevented by treating whole blood with irradiation to kill white blood cells before transfusion.

The most common presenting symptom of immune deficiencies is recurrent severe infections. Significant information concerning the nature of the specific immune deficiency can be obtained by noting the types of infection, as well as certain
characteristics of the affected individual, including gender, age of disease onset, the presence of any associated anomalies, family history, and risk factors associated with secondary immune deficiencies. Humoral deficiencies are generally characterized by recurrent sinopulmonary infections with encapsulated bacteria, gastrointestinal malabsorption, and poor growth. T-cell defects generally present with failure to thrive, chronic diarrhea, persistent thrush, and opportunistic infections (e.g., Mycobacterium, Pneumocystis, Candida, and certain viruses). Phagocytic defects are usually associated with recurrent abscesses, oral ulcers, and infections with specific bacteria (e.g., catalase-positive bacteria). Complement defects may be linked to SLE-like disease and recurrent and disseminated infections with Neisseria spp.

A variety of laboratory tests are available to evaluate specific immune deficiencies (Table 8-7). The choice of which particular tests to perform is determined on the characteristics described previously. A basic screening test is a complete blood count (CBC) with a differential. The CBC provides information on the numbers of red cells, white cells, and platelets, and the differential indicates the quantities of lymphocytes, granulocytes, and monocytes in the blood. Quantitative determination of immunoglobulins (IgG, IgM, IgA) is a screening test for antibody production, and an assay for total complement (total hemolytic complement, CH₅₀) is useful if a complement defect is suspected.

If the nature of the immune deficiency remains uncertain after the screening tests, additional relatively common tests can be performed. For instance, subpopulations of lymphocytes (T or B) or antibodies (IgG, IgM, IgA) can be quantified. The proportion of B and T lymphocytes can be determined using characteristic surface markers, such as surface immunoglobulin for B cells and CD3 for T cells. T-cell populations can be further subdivided using additional surface markers, such as CD4 (helper T cells) or CD8 (cytotoxic T cells). For antibodies, routine assays are available to quantify subclasses of IgG, such as IgG2.

An additional level of testing would include determination of immune responses against specific antigens. Determination of isohemagglutinins is informative about antigen-specific IgM production. Antibody responses to vaccines (e.g., tetanus, pertussis, measles, diphtheria, hepatitis B) are usually indicative of IgG responses. T-cell immunity against specific antigens can be measured by skin tests against antigens to which the individual had been exposed: “recall antigens.” These include antigens from vaccines (e.g., mumps, tetanus) or from microorganisms with which the person had a previous active infection (e.g., Candida). An adequate T-cell immunity results in a positive delayed hypersensitivity skin test reaction.

If the tests do not identify the immune deficiency, more esoteric tests are offered by reference laboratories or research laboratories. These include quantification of individual complement components, in vitro proliferation (mitogenic response) of T or B cells to antigens or nonspecific mitogens, and a variety of tests of phagocyte function (e.g., nitroblue tetrazolium test [NBT] for hexose-monophosphate shunt activity, specific tests for phagocytosis, chemotaxis, or bacterial killing).

### Replacement Therapies for Immune Deficiencies

#### Gamma-Globulin Therapy

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

Commercial gamma-globulin preparations are usually administered intramuscularly or by intravenous (IV) infusion. The dosage varies among individuals and is primarily determined by body weight. The schedule and dosage are also determined according to titers of circulating immunoglobulins and the incidence of infections in the individual. Commercial gamma-globulin preparations usually contain small amounts of IgM and IgA. Individuals with selective IgA deficiency occasionally develop allergic reactions to IgA in gamma-globulin preparations.

Individuals who need larger amounts of IgM or IgA can be given fresh frozen plasma in monthly IV infusions. Complications associated with plasma therapy include the potential transmission of hepatitis or AIDS. The plasma is irradiated to destroy immunocompetent T cells and to avoid GVHD in individuals with accompanying T-cell deficiencies. Administration of fresh frozen plasma is successful in individuals with WAS (IgM deficient), AT (IgA deficient), or complement component deficiencies.

Transplantation and Transfusion
Several primary immune deficiencies originate from defects in lymphoid stem cells that interfere with their development in the primary lymphoid organs. Some of these (e.g., SCID, WAS, leukocyte adhesion defect) have benefited from replacement of stem cells through transplantation of bone marrow, umbilical cord cells, or other cell populations that are rich in stem cells. 279 280

The source of donor cells, particularly bone marrow, may contain a mixed population of stem cells and more mature T lymphocytes. In order to avoid GVHD, the preferred donor would be matched with the recipient for HLA antigens. Several other diseases involving depletion of the bone marrow (i.e., aplastic anemia, leukemia requiring eradication of tumor cells in the marrow) also are treated by bone marrow transplantation. At least 75% of bone marrow transplants between individuals who are matched for HLA-A, HLA-B, HLA-C, and HLA-DR are accepted. In immunocompetent recipients, most rejections of HLA-matched transplants occur because of recognition of minor histocompatibility antigens by individuals who have received multiple blood transfusions and are, as a result, sensitized against those antigens, which are not evaluated in tissue typing. For stem cell transplants, differences in minor histocompatibility antigens may lead to GVHD. Because HLA antigens are inherited in a codominant fashion, the preferred donor would be a relative, especially a sibling. Although the donor is not tested for minor histocompatibility antigens, the use of a close relative also would minimize differences at those loci.

Chronic GVHD appears in 30% to 50% of transplants between HLA-matched siblings and 60% to 70% of transplants between unrelated donors. Symptoms may appear about 4 to 7 months after the transplant, but may begin much earlier or later. Depletion of T cells from bone marrow before transplantation significantly lowers the incidence of both acute and chronic GVHD. One method of doing this is to infuse the graft with monoclonal antibody against plasma membrane antigens found only on mature T cells. Another is to use fetal tissue as the graft. For example, fetal liver, which contains stem cells but not immunocompetent lymphocytes, is sometimes grafted in place of bone marrow if an HLA-matched donor cannot be found.

One therapy for deficiency diseases in which the individual lacks a thymus or thymic function (e.g., DiGeorge syndrome, ataxia-telangiectasia, or chronic mucocutaneous candidiasis) is reconstitution of thymic function. The procedure is to transplant fetal thymus tissue, which lacks immunocompetent T cells, or thymic epithelial cells (the cells that produce the thymic hormones) from which mature T cells have been removed. In some individuals transplantation increases the number of circulating mature T cells, but in most cases improvement is only temporary.

Enzymatic defects that cause SCID (e.g., adenosine deaminase deficiency) have been treated successfully with transfusions of glycerol frozen-packed erythrocytes. The donor erythrocytes contain the needed enzyme and can, at least temporarily, provide sufficient enzyme for normal lymphocyte function. An alternative method is administration of purified adenosine deaminase that has been stabilized with polyethylene glycol (PEG).

Treatment with Soluble Immune Modulators
The administration of soluble materials that affect lymphocyte function can restore T-cell function, especially in individuals with WAS or chronic mucocutaneous candidiasis. Successful for some individuals is the use of transfer factor, a low-molecular-weight nucleoprotein prepared from lymphocyte lysates, which can confer specific reactivity against certain antigens. Thymosin, a thymic hormone, also has been used, although with limited success. Cytokine therapy also has been effective in some cases of chronic granulomatous disease.

Gene Therapy
The first successful therapeutic replacement of defective genes was performed in two girls with SCID caused by an ADA deficiency. 80 81 The normal gene for ADA was cloned and inserted into a retroviral vector. The gene for ADA replaced some retroviral genes, resulting in a virus that carried the normal human gene but did not cause disease. The virus was used to infect bone marrow stem cells from these children. The retrovirus inserted the normal ADA gene into the individuals’ genetic material. The genetically altered stem cells were infused into the children, resulting in reconstitution of their immune systems.
SUMMARY REVIEW

Hypersensitivity: Allergy, Autoimmunity, and Alloimmunity

1. Inappropriate immune responses are misdirected against the host's own tissues (autoimmunity); directed against beneficial foreign tissues, such as transplants or transfusions (alloimmunity); exaggerated responses against environmental antigens (allergy); or insufficient to protect the host (immune deficiency).

2. Allergy, autoimmunity, and alloimmunity are collectively known as hypersensitivity reactions.

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

4. Hypersensitivity reactions can be immediate (developing within minutes to a few hours) or delayed (developing within several hours or days).

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

6. Allergens are antigens that cause allergic responses.

7. Type I (IgE-mediated) reactions are mediated through the binding of IgE to Fc receptors on mast cells and cross-linking of IgE by antigens that bind to the Fab portions of IgE. Cross-linking causes mast cell degranulation and the release of histamine (the most potent mediator) and other inflammatory substances.

8. Histamine enhances the chemotaxis of eosinophils into sites of type I allergic reactions.

9. Atopic individuals tend to produce higher quantities of IgE and to have more Fc receptors for IgE on their mast cells.

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

11. Type III (immune complex-mediated) reactions are caused by the formation of immune complexes that are deposited in target tissues, where they activate the complement cascade, generating chemotactic factors that attract neutrophils into the inflammatory site. Neutrophils release lysosomal enzymes that result in tissue damage.

12. Intermediate-sized immune complexes are the most likely to have severe pathologic consequences.

13. Immune complex disease can be a systemic reaction, such as serum sickness, or localized, such as the Arthus reaction.

14. Type IV (cell-mediated) reactions are caused by either cytotoxic T lymphocytes (Tc cells) or lymphokine-producing Th1 cells.

15. Typical allergens include pollen, molds and fungi, certain foods (milk, eggs, fish), animals, certain drugs, cigarette smoke, and house dust.

16. Clinical manifestations of allergic reactions usually are confined to the areas of initial intake or contact with the allergen. Ingested allergens induce gastrointestinal symptoms, airborne allergens induce respiratory or skin manifestations, and contact allergens induce allergic responses at the site of contact.

17. Autoimmunity is a breakdown of immunologic homeostasis, the immune system's tolerance of self-antigens. Central tolerance develops during the embryonic period. Peripheral tolerance is maintained in secondary lymphoid organs by regulatory T lymphocytes or antigen-presenting dendritic cells.

18. Autoimmune disease can be caused by the exposure of a previously sequestered antigen, the development of a neoantigen, the complications of infectious disease, the emergence of a forbidden clone of lymphocytes, or ineffective peripheral tolerance.

19. Alloimmunity is the immune system's reaction against antigens on the tissues of other members of the same species.

20. Alloimmune disorders include transient neonatal disease, in which the maternal immune system becomes sensitized against antigens expressed by the fetus, transplant rejection, and transfusion reactions, in which the immune system of the recipient of an organ transplant or blood transfusion reacts against foreign antigens on the donor's cells.

21. SLE is a chronic, multisystem, inflammatory disease and is one of the most serious of the autoimmune disorders. SLE is characterized by the production of a large variety of autoantibodies.

22. Hyperacute graft rejection (preexisting antibody) is immediate and rare, acute rejection is cell mediated and occurs days to months after transplantation, and chronic rejection is caused by inflammatory damage to endothelial cells as a result of a weak cell-mediated reaction.

23. Red blood cell antigens may be the targets of autoimmune or alloimmune reactions. The most important of these, because they provoke the strongest humoral immune response, are the ABO and Rh systems.

Deficiencies in Immunity

1. Disorders resulting from immune deficiency are the clinical sequelae of impaired function of components of the immune or inflammatory response, phagocytes, or complement.

2. Immune deficiency is the failure of mechanisms of self-defense to function in their normal capacity.

3. Immune deficiencies are either congenital (primary) or acquired (secondary). Primary immune deficiencies are caused by genetic defects that disrupt lymphocyte development, whereas secondary immune deficiencies are secondary to disease or other physiologic alterations.

4. The clinical hallmark of immune deficiency is a propensity to unusual or recurrent severe infections. The type of infection usually reflects the immune system defect.

5. The most common infections in individuals with defects of cell-mediated immune response are fungal and viral, whereas infections in individuals with defects of the humoral immune response or complement function are primarily bacterial.

6. Defects in B-cell function are diverse, ranging from a complete lack of the human bursal equivalent function, the lymphoid organs required for B-cell maturation (as in Bruton's agammaglobulinemia), to deficiencies in a single class of immunoglobulins (e.g., selective IgA deficiency).

7. DiGeorge syndrome (congenital thymic aplasia or hypoplasia) is characterized by complete or partial lack of the thymus (resulting in depressed T-cell immunity) and the parathyroid glands (resulting in hypocalcemia) and the presence of cardiac anomalies.

8. SCID is a total lack of T-cell function and a severe (either partial or total) lack of B-cell function. SCID can result from mutations in critical enzymes (ADA deficiency, PNP deficiency), in cytokine receptors (X-linked SCID, JAK3 deficiency, IL-7 receptor deficiency), or in antigen receptors (RAG-1/RAG-2 deficiencies, CD45 deficiency, CD3 deficiency, ZAP-70 deficiency). Other combined defects may result from deficiencies in antigen-presenting molecules (bare lymphocyte syndrome), cytokkeletal proteins (WAS), or DNA repair (ataxia-telangiectasia).
9. Almost any portion of the complement cascade may be defective. The most severe defect is C3 deficiency, which results in recurrent life-threatening bacterial infections. Defects in proteins of the membrane-attack complex usually result in unusual disseminated infections with bacteria of the Neisseria spp.

10. Defects in phagocyte function, which include insufficient numbers of phagocytes or defects of chemotaxis, phagocytosis, or killing, can result in recurrent life-threatening infections such as septicemia and disseminated pyogenic lesions.

11. Acquired immunodeficiencies are caused by superimposed conditions, such as aging, malnutrition, infections, malignancies, physical or psychologic trauma, environmental factors, some medical treatments, or other diseases.

12. Deficiencies in immunity usually are treated by replacement therapy. Deficient antibody production is treated by replacement of missing immunoglobulins with commercial gamma-globulin preparations. Lymphocyte deficiencies are treated with the replacement of host lymphocytes with transplants of bone marrow, fetal liver, or fetal thymus from a donor.

### Key Terms

- ABO blood group
- Acute rejection
- Adenosine deaminase (ADA) deficiency
- Agammaglobulinemia
- Allergen
- Allergy
- Alloimmune disease
- Alloimmunity
- Anaphylaxis
- Antibody-dependent cell-mediated cytotoxicity (ADCC)
- Arthus reaction
- Ataxia-telangiectasia (AT)
- Atopic dermatitis
- Atopic
- Autoimmune disease
- Autoimmunity
- Autosomal agammaglobulinemia
- Autosomal hyper-IgM syndrome
- Bare lymphocyte syndrome
- Blood group antigen
- Blocking antibody
- B-lymphocyte deficiency
- Bruton’s agammaglobulinemia
- C1 deficiency
- C2 deficiency
- C3 deficiency
- C4 deficiency
- C9 deficiency
- C3 receptor deficiency
- Chédiak-Higashi syndrome
- Chronic granulomatous disease (CGD)
- Chronic mucocutaneous candidiasis
- Chronic reaction
- Combined T- and B-lymphocyte deficiency
- Common variable immune deficiency
- Complement deficiency
- Complete blood count (CBC)
- Contact dermatitis
- Cross-reactive antibody (T cell)
- Cytoglobulin
- Cyclic neutropenia
- Cytotoxic antibody
- Defective class-switch
- Delayed hypersensitivity reaction
- Desensitization
- DiGeorge syndrome
- Factor H deficiency
- Factor I deficiency
- Forbidden
- Graft-versus-host disease (GVHD)
- Hyperacute rejection
- Hypersensitivity
- Hypocomplementemia
- Hypogammaglobulinemia
- IgG subclass deficiency
- IL-7 receptor deficiency
- Immediate hypersensitivity reaction
- Immune deficiency
- Immunologically privileged site
- Immune complex
- Immunologic homeostasis
- Isohemaggulutinin
- JAK3 deficiency
- Leukocyte adhesion deficiency (LAD)
- Mannose-binding lectin (MBL)
- MHC class I deficiency
- MHC class II deficiency
- Molecular mimicry
- Myeloperoxidase deficiency
- Neopterin
- Phagocytic deficiency
- Primary (congenital) immune deficiency
- Properdin deficiency
- Purine nucleoside phosphorylase (PNP)
- RAG-1 deficiency
- RAG-2 deficiency
- Raynaud phenomenon
- Reagin
- Reticular dysgenesis
- Rh blood group
- Secondary (acquired) immune deficiency
- Selective IgA deficiency
- Serum sickness
- Severe combined immune deficiency (SCID)
- Severe congenital neutropenia
- Systemic lupus erythematosus (SLE)
- Tissue-specific antigen
- T-lymphocyte deficiency
- Transient hypogammaglobulinemia of infancy
- Type I (IgE-mediated) hypersensitivity reaction
- Type II (tissue-specific) hypersensitivity reaction
- Type III (immune complex-mediated) hypersensitivity reaction
- Type IV (cell-mediated) hypersensitivity reaction
- Universal donor
- Universal recipient
- Urticaria (hives)
- Wheal and flare reaction
- X-linked hyper-IgM syndrome
- X-linked SCID

### References


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