The most basic challenge to an organism is to distinguish self from nonself so that it can continue to exist. The chief role of the immune system is to protect the host from invasion by foreign agents. Immune responses can be elicited by a wide range of agents including parasites, bacteria, viruses, chemicals, toxins, drugs, and transplanted tissues. As components of host defense, immune responses are characterized by their ability to distinguish self from nonself, their ability to discriminate among potential invaders (specificity), and immune memory, coupled to the capacity for amplification (i.e., the ability to recall previous exposures and to mount an intensified or anamnestic response).

Humans possess physical barriers such as regionally adapted epithelia (e.g., thick skin, ciliated respiratory epithelium, and a nearly impervious urothelium), chemical–mechanical barriers (e.g., antibacterial lipids and mucus), and indigenous microbial flora that compete with potential pathogens. Patterned hemodynamic responses, cell surface-associated and soluble mediator systems (e.g., complement and coagulation systems), and antigen-nonspecific phagocytes (e.g., resident macrophages, neutrophils) are integral to protective inflammatory responses (see Chapter 2). Host defenses that are not antigen-specific are called the “innate” immune system. Antigen-specific or “adaptive” immune system encompasses lymphocytes, plasma cells, antigen-presenting cells (APCs), specific effector molecules (e.g., immunoglobulins), and a vast array of regulatory mediators.

As noted above, the defining features of adaptive immunity include specificity, memory, and the capacity for amplification. Specificity and immunologic memory are direct results of activation by antigens of lymphocyte clones that bear specific receptors. There are many linkages among the various layers of host defense. For example, an antibody can specifically bind to an epitope on a bacterium, leading to complement fixation, and, in turn, generation of chemotactic peptides that attract phagocytic neutrophils.

It is important to consider the relationships of specific immune system components within the general rubric of acute and chronic inflammation, cell injury, and cell death. For example, immediate (type I) hypersensitivity reactions are immunoglobulin (IgE)-mediated, depend on generation of vasoactive compounds, and feature inflammatory infiltrates rich in eosinophils. A type III hypersensitivity reaction, which is immune complex-
mediated, is characterized by an acute inflammatory infiltrate (mainly neutrophils). Type IV hypersensitivity reactions are triggered by antigen exposure and involve chronic inflammatory infiltrates (mononuclear phagocytes and T lymphocytes). Recognition of these mechanistic and morphologic relationships can be helpful diagnostically and therapeutically.

Biology of the Immune System

The Cells that Comprise the Immune System Derive from Hematopoietic Stem Cells

The cellular components of the immune system are derived from pluripotent hematopoietic stem cells (HSCs). Near the end of the first month of embryogenesis, HSCs appear in the extraembryonic erythroidic islands adjacent to the yolk sac. At 6 weeks, the primary site of hematopoiesis shifts from extraembryonic blood islands to fetal liver to bone marrow. The process begins at 2 months but by 6 months has completely shifted to bone marrow. Although there are well-defined sequential changes in the primary site of hematopoiesis, there are periods of overlap. By 8 weeks of gestation, lymphoid stem cells derived from HSCs and destined to become T cells circulate to the thymus where they differentiate into mature T lymphocytes. Lymphoid stem cells destined to become B cells differentiate first within fetal liver (8 weeks) and later within bone marrow (12 weeks). In the development of both thymic lymphocytes and bone marrow B lymphocytes, the microenvironments (e.g., thymic epithelium, bone marrow stromal cells, growth factors) are critical. Mature lymphocytes exit the thymus and bone marrow and “home” to peripheral lymphoid tissues (e.g., lymph nodes, spleen, skin, and mucosa). The population of peripheral lymphoid tissues by mature T and B lymphocytes and the rapid deployment and recycling of mature lymphocytes to different, often remote, parts of the immune system are anatomically specific. “Lymphocyte homing and recirculation” are orchestrated by a series of leukocyte and endothelial surface molecules called selectins and addressins. The processes of lymphocyte development and homing/recirculation are important for understanding immune responses, genetic immunodeficiency states, regional host defense, and the underpinnings of modern therapeutics (e.g., HSC transplantation).

The cells of the immune system express a vast array of surface molecules that are important in cellular differentiation and cell-to-cell communication. These surface molecules serve as useful markers of cellular identity. The International Workshop on Human Leukocyte Differentiation Antigens is responsible for nomenclature of these markers and assigns them so-called cluster designation (CD) numbers. Currently, some 300 different molecules have been assigned CD numbers. Currently, some 300 different molecules have been assigned CD numbers.

Hematopoietic Stem Cells

Pluripotent HSCs account for 1% of bone marrow mononuclear cells. They exhibit characteristic light-scattering properties as assessed by flow cytometry, usually express CD34 cell surface protein and lack cell surface molecules that characterize more mature lymphocyte subpopulations (e.g., CD2, CD3, CD5, CD7, CD14, CD15, and CD16). Recently, a smaller population of CD34+ HSCs was described. CD34+ HSCs also circulate, and account for 0.01% to 0.1% of mononuclear peripheral blood cells. Bone marrow and blood HSCs are heterogeneous in terms of selected lymphocyte marker expression, myeloid markers, and activation antigens, and in terms of their capacity to engraft bone marrow. Infusion of peripheral blood HSCs in sufficient numbers into transplant recipients leads to faster marrow recovery than occurs in patients who have received marrow-derived HSCs. HSCs are quantified following harvest and before infusion into recipient patients. In clinical HSC transplantation, it is now common practice for donors to receive recombinant growth factors prior to HSC harvest. This practice has led to higher yields of harvested HSCs, decreased time to engraftment, and improved rates of successful engraftment. The proportion of bone marrow transplant recipients who receive harvested peripheral blood HSCs rather than marrow-derived HSCs has increased dramatically in recent years.

Lymphopoiesis and Hematopoiesis

All mature lymphoid and hematopoietic cells are derived from a common population of pluripotential HSCs (Fig. 4-1). Each step in lymphopoiesis and hematopoiesis depends on a microenvironment that encompasses specific structural features and a complex array of growth factors. The primary branch point in differentiation is between lymphoid progenitors and myeloid progenitors. The former ultimately give rise to T lymphocytes, B lymphocytes, and natural killer (NK) cells; whereas the latter develop into granulocytic, erythroidic, monocytic–dendritic, and megakaryocytic colony-forming units (GEMM-CFUs). Downstream, CFUs become more lineage-specific. Examples include CFU-GM (granulocyte-monocyte), CFU-Eo (eosinophil), CFU-E (erythroid), and so forth. CFU refers to a cell that ultimately gives rise to a specified population of “offspring,” such as granulocytes, erythrocytes, monocytes, dendritic cells, and megakaryocytes.

Lymphocytes

There are three major types of lymphocytes—T cells, B cells, and NK cells—which account for 25% of peripheral blood leukocytes. Some 80% of blood lymphocytes are T cells, 10% B cells, and 10% NK cells. The relative proportions of lymphocytes in the peripheral blood and central and peripheral lymphoid tissues vary. In contrast to the blood, only 30% to 40% of splenic and bone marrow lymphocytes are T cells.

T lymphocytes can be subdivided into subpopulations by virtue of their specialized functions, by surface CD molecules, and in some cases, morphologic features. Lymphoid progenitor cells destined to become T cells exit the bone marrow and migrate to the thymus in waves. There, both alpha/beta (α/β) and gamma/delta (γ/δ) T lymphocytes are formed (Fig. 4-2). “Alpha/ beta” and “gamma/delta” are the two major classes of heterodimeric T cell receptors (TCRs) that specifically recognize and bind various antigens. The thymic microenvironment is determined by the epithelial stroma. The early thymus is formed from ectoderm and endoderm derived from the third branchial cleft and the third and fourth pharyngeal pouches. This thymic anlage is then colonized by HSCs that give rise to T cells, macrophages, and dendritic cells. The thymic cortex is composed of a meshwork of epithelial cell processes that surround groups of immature thymocytes that bear both CD4+ and CD8+ surface molecules (Fig. 4-3). As T lymphocytes mature, they percolate into thymic medulla where, in close proximity to nested groups of epithelial cells, they form more mature cells that are either CD4+ or CD8+. The thymic cortical medullary junction contains many bone marrow HSC-derived macrophages and dendritic cells. Much of
FIGURE 4-1. Pluripotent hematopoietic stem cells differentiate into either lymphoid or myeloid stem cells and, in the case of myeloid stem cells, into lineage-specific colony-forming units (CFUs). Under the influence of an appropriate microenvironment, CFUs give rise to definitive cell types. Lymphoid stem cells are precursors of natural killer (NK) cells, T lymphocytes, and B lymphocytes. B lymphocytes give rise to plasma cells. CD = cluster designation; CFU-GEMM = granulocytic, erythroid, monocytic–dendritic, and megakaryocytic colony-forming units; HLA = human leukocyte antigen.

the “positive selection” of thymocytes occurs in the cortex; “negative selection” tends to occur through exposure of developing thymocytes to corticomedullary dendritic cells. In positive thymic selection transient binding of cell surface TCRs to a person’s own major histocompatibility complex (MHC) class I or II molecules prevents cell death. Negative thymic selection is the converse process in which high-affinity TCR-mediated binding to one’s own MHC class I or II molecules results in cell death by apoptosis. These complementary thymic selection processes are pivotal to T lymphocyte development, so that T cells can interact with the host’s own cells but not in a manner that results in excessive self-reactivity (see below under discussion of autoimmune.)
CD4 or CD8. A smaller population (5%) of T cells expresses CD16^+, CD56^+ T lymphocytes exit the thymus and populate peripheral lymphoid tissues. In the thymus, antigen-specific TCRs are formed and differentiate in the bone marrow and give rise to clonal populations of surface immunoglobulin-producing B cells, which in turn can form plasma cells. CD = cluster designation, IL = interleukin.

Thymic selection and lineage-specific differentiation of T lymphocytes are processes fundamental to understanding autoimmunity and the immune response, respectively. Thymic T lymphocyte maturation includes several processes. Developing T cells recombine dispersed gene segments that encode the heterodimeric α/β or γ/δ TCRs. α/β T lymphocytes progress through stages of development that are characterized as CD4^+, CD8^-, then CD4^+, CD8^-, and then either CD4^+, CD8^- or CD4^-, CD8^- (see Fig. 4-2 and Fig. 4-3). Most CD4^+, CD8^- T cells function as helper cells; most CD4^-, CD8^- T cells are cytotoxic cells.

T lymphocytes exit the thymus and populate peripheral lymphoid tissues. In the thymus, antigen-specific TCRs are formed and are expressed in conjunction with CD3, an essential accessory molecule. Nearly 95% of circulating T lymphocytes express α/β TCRs. In turn, circulating α/β T cells also express either CD4 or CD8. A smaller population (5%) of T cells expresses γ/δ TCRs and CD3 but neither CD4 nor CD8.

B lymphocytes differentiate into antibody-secreting plasma cells in the bone marrow. Similarly to T lymphocyte development, the microenvironment of either the fetal liver or bone marrow, is critical to B lymphocyte development. In both organs, only B lymphocytes that pass through the many stages necessary to produce surface immunoglobulin survive. Conversely, developing B cells in which surface immunoglobulin binds too avidly to self-antigens are negatively selected and eliminated.

Analogous to T cells, B lymphocytes express a surface antigen-binding receptor, namely membrane immunoglobulin (mIg), which bears the same antigen-binding specificity as the soluble immunoglobulin that will ultimately be secreted by the corresponding terminally differentiated plasma cells. Like T cells, B lymphocytes also exhibit a degree of heterogeneity (e.g., CD5^+ [B1] and CD5^- [B2]).

TCRs, along with immunoglobulins and MHC class I and class II molecules (see below), confer specificity to the immune system by virtue of their capacity to specifically bind foreign antigens or interact with self-cells, respectively. TCR, immunoglobulin, and a portion of the MHC class I molecule are encoded by members of the immunoglobulin supergene family. The structural variability and, in turn, high specificity of TCRs and immunoglobulins are achieved through genetic recombination of segmented TCR and Ig genes. As noted above, an individual TCR is a heterodimer that forms an antigen-binding site (Fig. 4-4). The proteins that constitute TCRs and immunoglobulins each possesses an amino-terminal antigen-binding variable (V) domain and a carboxy-terminal constant (C) domain. TCRs anchor the antigen to the cell surface, whereas immunoglobulins either anchor the receptor to the B cell
Mononuclear Phagocytes, Antigen-Presenting Cells (APCs) and Dendritic Cells

Mononuclear phagocytes, chiefly monocytes, account for 10% of circulating white blood cells. Circulating monocytes give rise to resident tissue macrophages including, among others, Kupffer cells, alveolar macrophages, and microglial cells. Monocytes and macrophages express an array of specific cell surface molecules that are important for their host defense functions. These include MHC class II molecules, CD14 (a receptor that binds bacterial lipopolysaccharide and can trigger cell activation), several types of Fc immunoglobulin receptors, toll-like receptors, adhesion molecules, and a variety of cytokine receptors that participate in regulating monocyte/macrophage function. Activated macrophages produce a variety of cytokines and soluble mediators of host defense (e.g., interferon-γ [IFN-γ], interleukin [IL]-1β, tumor necrosis factor-α [TNF-α], and complement components).

APCs, defined by their function and derived from HSCs, acquire the capacity to present antigen to T lymphocytes in the context of histocompatibility, after cytokine-driven upregulation of MHC class II molecules (Fig. 4-5). Monocytes, macrophages, dendritic cells and under certain conditions, B lymphocytes, endothelial cells and epithelial cells, can act as APCs. In some locations, APCs are highly specialized for this function. For instance, in B cell-rich follicles of lymph nodes and spleen, specialized APCs are termed follicular dendritic cells. In these sites, through engagement of antibody and complement via Fc and C3b receptors, APCs trap antigen–antibody complexes. In the case of lymph nodes, such complexes arrive via afferent lymphatics, and in spleen, through the blood. Antigen presentation by follicular dendritic cells leads to generation of memory B lymphocytes (Fig. 4-6).

Dendritic cells are specialized APCs that are termed “dendritic” by virtue of their spiderlike morphologic appearance. They are found in B lymphocyte-rich lymphoid follicles, in thymic medulla, and in many peripheral sites, including intestinal lamina propria, lung, genitourinary tract, and skin (Fig. 4-6). Peripherally located dendritic cells are less mature than the APCs found in lymphoid follicles and express lower levels of accessory cell activation molecules (CD80 [B7-1], CD86 [B7-2]) than do mature dendritic cells. An example of a peripheral APC is the epidermal Langerhans cell. Upon exposure, the Langerhans cell engulfs antigen, migrates to a regional lymph node through an afferent lymphatic, and differentiates into a more mature dendritic cell. Langerhans cell-derived dendritic cells express high densities of MHC class I and II molecules and costimulatory molecules (CD80, CD86), and present antigen efficiently to T lymphocytes. Again, antigen presentation to T cells occurs through TCRs in the context of histocompatibility determined by MHC class II molecules.
Lympocyte Homing and Recirculation

The segments of DNA that encode the antigen-binding domains of TCRs and immunoglobulin are rearranged in developing T cells and B cells, respectively, to form “new” genes. Through this combinatorial process and a variety of other diversity-generating mechanisms, a large number of different antigen receptors is generated. Adults possess about $10^{12}$ lymphocytes, of which only 10% are in the circulation at a given time. Despite the large number of lymphocytes, the number with any specific antigen receptor is relatively small. In addition, the body surfaces that frequently serve as portals of entry for foreign invaders are very large (e.g., skin, 2 m$^2$; respiratory tract, 100 m$^2$; gastrointestinal tract, 400 m$^2$). Lymphocyte trafficking is a necessary aspect of host defense because it allows small numbers of any set of antigen-specific lymphocytes to move to sites of “need.” Lymphocyte trafficking, which entails homing and recirculation, has evolved to provide rapid, flexible, and widespread distribution of lymphocytes and a means of focusing specific immunologic processes in anatomically discrete sites (e.g., lymph node cortex).

Following completion of early development, naïve B and T lymphocytes circulate via the vascular system to secondary lym-
phoid organs and tissues. Included among these tissues are lymph nodes, mucosa-associated lymphoid tissues (e.g., Peyer's patches), and the spleen. Lymphocyte trafficking through lymph nodes occurs through specialized postcapillary venules termed **high endothelial venules (HEVs)** because of the high cuboidal shape of their endothelial cells. HEVs express cellular adhesion molecules (e.g., CD31), which allow lymphocyte binding. The cuboidal shape of HEV cells reduces flow-mediated shear forces and specialized intercellular connections facilitate egress of lymphocytes out of the vascular space. Lymphocytes that do not find
FIGURE 4-7. The highly polymorphic loci that encode major histocompatibility antigens are located on the short arm of chromosome 6. Class I and class II molecules exhibit different structures, but each participates in fundamentally important cell-cell interactions.

The Major Histocompatibility Complex Coordinates Interactions among Immune Cells

The discovery that the sera of multiparous women and multiply-transfused patients contain antibodies against foreign blood leukocytes led to the definition of an intricate system of cell surface proteins known as major histocompatibility antigens. These antigens are also referred to as human leukocyte antigens (HLAs) because they were first identified on leukocytes and are expressed in high concentrations on lymphocytes. HLAs orchestrate many of the cell–cell interactions fundamental to the immune response. Important interactions between cells of the immune system require histoincompatibility. Conversely, these antigens are major immunogens and are targets in transplant rejection. The MHC includes class I, II, and III antigens. (Class III antigens represent certain complement components and are not histocompatibility antigens per se.) Molecules structurally similar to “traditional” MHC class I and II molecules are encoded outside of the more restricted MHC region on the short arm of chromosome 6. Examples include MHC-1b and CD1d which can activate so-called NK T cells. NK
Class I MHC Molecules

Class I molecules are encoded by highly polymorphic genes in the A, B, and C regions of the MHC (see Fig. 4-7). These loci encode similarly structured molecules that are expressed in virtually all tissues. Class I histocompatibility antigens are heterodimeric structures consisting of two chains, a 44-kd polymorphic transmembrane glycoprotein, and a 12-kd nonpolymorphic molecule called β2-microglobulin. The latter is a superficial surface protein lacking a membrane component and is noncovalently associated with the larger heavy chain, β1-microglobulin, which is encoded by a gene on chromosome 15. Structural polymorphism occurs primarily in the extracellular domains of the α-chain. Since the alleles are expressed codominantly, tissues bear class I antigens inherited from each parent. These antigens are recognized by cytotoxic T cells during graft rejection or T lymphocyte-mediated killing of virus-infected cells.

Class II Histocompatibility Molecules

Class II molecules are encoded by multiple loci in the D region: DP, DN, DM, DO, DQ, and DR. The D region locus encodes structurally similar molecules that are expressed primarily on accessory cells involved in antigen presentation. As noted above, the chief APCs include monocytes, macrophages, dendritic cells, and B lymphocytes. Class II antigens have also been referred to as “Ia” (immunity-associated) antigens. Class II molecules are heterodimers that consist of two noncovalently linked glycoprotein chains. The 34-kd α-chain possesses a single disulfide bond; its extracellular domain is the major site of class II antigenic variability. The 29-kd β-chain has two disulfide bonds. Both chains are transmembrane proteins. As with class I antigens, D alleles are expressed codominantly and tissues bear antigens from each parent.

Clinical Tissue Typing

“Histocompatibility, HLA, or tissue-typing” laboratories now use several approaches to identify the class I and class II antigens expressed by both potential donor tissues and recipient prior to organ transplantation. Class I antigens have been defined serologically: antisera against various antigens are tested against tissues that express the antigen to be typed. The system of nomenclature for class I antigens is based on the locus of origin (A1, A2, A3, B4, B6, C1, C2, etc.). Tissue typing reveals the two different antigens codominantly expressed at each locus; one antigen (double dose) when there is homozygosity. Accordingly, a tissue might express A1, A2, B4, B6, DR3, and DR4 antigens. The products of all loci are not universally typed in clinical laboratories. Increasingly, tissue-typing laboratories are using molecular methods including DNA sequence analysis to identify class I and II antigens.

Class II antigens were traditionally defined by serological and functional assays, but these have largely been replaced by molecular techniques, which have demonstrated greater genetic (and structural) variability than was recognized when the standard for typing was serological. The nomenclature for histocompatibility genes and antigens has thus become more complex, a fact reflected in a more detailed system of nomenclature. An example is “HLA-B27” (based on serology) and its sequence based definition B*2701-2725 which encompasses 25 different molecules.

Integrated Cellular and Humoral Immune Responses

Protect against Invasion by Foreign Agents

T Lymphocyte Interactions

T lymphocytes recognize specific antigens, usually proteins or haptons bound to proteins. They undergo a series of maturational events when engaged via the TCR in the context of a histocompatible (i.e., MHC-matched) APC. Exogenous signals are delivered by cytokines. CD4+ and CD8+ T cell subsets possess a variety of effector and regulatory functions. Effector functions include secretion of proinflammatory cytokines and killing of cells that express foreign or altered membrane antigens. Regulatory functions include augmenting and suppressing immune responses, usually by secreting specific helper or suppressor cytokines.

CD4+ T cells, and possibly also CD8+ cells, can be further distinguished by the types of cytokines produced. Helper type 1 or Th1, cells produce IFN-γ and IL-2, whereas helper type 2, or Th2, cells secrete IL-4, IL-5, and IL-10. Th1 lymphocytes have been associated with cell-mediated phenomena and Th2 cells with allergic responses. In general, CD4+ T cells promote antibody and inflammatory responses. By contrast, CD8+ cells for the most part exert suppressor and cytotoxic functions. Suppressor cells inhibit the activation phase of immune responses; cytotoxic cells can kill target cells that express specific antigens. However, there is some overlap, as CD8+ cells secrete helper cytokines and CD4+ Th1 and Th2 cells display cross-regulatory suppressive effects.

An important aspect of T cell antigen recognition is the requirement for antigen to be presented on the surface of another cell in association with a histocompatible membrane protein (see Fig. 4-5 and Fig. 4-6). As noted above, T cells bear membrane receptor complexes (α/β TCRs plus CD3 accessory molecules) on their surface. For maximal immune responses, the TCR-CD3 complex must interact with a foreign antigen in the context of cell-to-cell histocompatibility. Thus, antigens are presented to T cells by accessory cells (APCs) that bear appropriate histocompatibility molecules. Antigens may also be presented to T cells by cells that do not “present” antigens but rather express on their surface a foreign or altered self-protein in association with an appropriate histocompatibility molecule.

CD8+ cells (cytotoxic T cells) recognize antigens in conjunction with class I molecules, whereas CD4+ cells (helper T cells) recognize antigens together with class II molecules. The membrane CD4 and CD8 molecules of α/β T cells help to stabilize binding interactions. γ/δ T cells may also acquire CD8 outside the thymus and thereby use class I antigens for binding target cells. Foreign class I and class II molecules, which are not histocompatible with the host (e.g., transplanted histocompatibility antigens), are themselves potent immunogens and can be recognized by host T cells. This is why tissue transplantation requires that donor and recipient be HLA-matched. In addition to the binding of foreign peptides presented by MHC molecules to the TCR complex, a number of other receptor–ligand interactions must occur to maximally activate lymphocytes. See Figure 4-5, which summarizes some of the key interactions that occur between CD4+ T helper cells and APCs. A CD4+ T cell becomes an activated effector cell when stimulated via the TCR complex and “accessory” receptors (CD28 and cytotoxic lymphoid line [CTLL]-4), which engage costimulatory
molecules (e.g., B7 and B7.2). In turn, an activated T helper cell recognizes an antigen-specific B cell via its receptor. The T helper cell then provides costimulatory and regulatory signals, such as CD40 ligand and “helper” cytokines (e.g., IL-4, IL-5).

**B Lymphocyte Interactions**

Mature B lymphocytes exist primarily in a resting state, awaiting activation by foreign antigens. Activation requires cross-linking of membrane immunoglobulin receptors by antigens presented by accessory cells and/or interactions with membrane molecules of helper T cells via a mechanism called cognate T cell-B cell help (see Fig. 4-5). The initial stimulus leads to B cell proliferation and clonal expansion, a process amplified by cytokines from both accessory cells and T cells. If no additional signal is provided, proliferating B cells return to a resting state and enter the memory cell pool. These events occur largely in lymphoid tissues and can be seen as germinal centers. Within germinal centers, B cells also undergo further somatic gene rearrangements, leading to generation of cells that produce the various immunoglobulin isotypes and subclasses.

An **isotype** is the class of the defining heavy chain of an immunoglobulin molecule. In turn, each immunoglobulin subtype exhibits a different array of biological activities. In the absence of antigenic stimulation, different B cell clones express a variety of heavy-chain isotypes and subclasses: IgG (γ1, γ2, γ3, γ4), IgA (α1, α2) or IgE (ε). T cells also influence B cell differentiation. In the presence of antigen, T cells produce helper cytokines that stimulate isotype switching or induce proliferation of previously committed isotype populations. For example, IL-4 induces switching to the IgE isotype.

The final stage of B cell differentiation into antibody-synthesizing plasma cells requires exposure to additional products of T lymphocytes (e.g., IL-3, IL-6), especially in the case of protein antigens. However, some polyvalent agents induce B cell proliferation and differentiation into plasma cells directly, bypassing the requirements for B-cell growth and differentiation factors. Such agents are called **polyclonal B-cell activators** because they do not interact with antigen-binding sites and hence are not specific antigens. Examples of polyclonal B-cell activators are bacterial products (lipopolysaccharide, staphylococcal protein A) and certain viruses (Epstein-Barr virus [EBV], cytomegalovirus [CMV]).

The predominant type of immunoglobulin produced during an immune response changes with age. Newborns tend to produce predominantly IgM. By contrast, older children and adults initially produce IgM following antigens challenge but rapidly shift toward IgG synthesis.

**Mononuclear Phagocyte Activities**

**Mononuclear phagocyte** is a general term applied to phagocytic cell populations in virtually all organs and connective tissues. Among these cells are macrophages, monocytes, Kupffer cells of the liver, and lung alveolar macrophages. The older term “histiocyte” is synonymous with **macrophage**, either a circulating or a fixed tissue macrophage. Subpopulations of macrophages exhibit different functions and phenotypes. Precursor cells (monoblasts and promonocytes) arise in bone marrow, enter the circulation as monocytes, and then migrate into tissues, where they take up residence as tissue macrophages. In the lung, liver, and spleen, numerous macrophages populate sinuses and peri-capillary zones to form an effective filtering system that removes effete cells and foreign particulate material from blood. This system, formerly known as the “reticuloendothelial system,” is now termed the **mononuclear phagocyte system**. In addition to their “housekeeping” functions, macrophages are critical in inducing immune responses and in maintenance and resolution of inflammatory reactions.

Macrophages are important accessory cells by virtue of their expression of class II histocompatibility antigens. They ingest and process antigens for presentation to T cells in conjunction with class II MHC molecules. The subsequent T cell responses are further amplified by macrophage-derived cytokines. One of the best characterized cytokines is IL-1, which, among a pleiotropic set of activities, promotes expression of IL-2 receptor on T cells, augmenting T cell proliferation, which is driven by IL-2. Among many effects of IL-1 on other tissues is preparation of the body to combat infection. For example, IL-1 induces fever and promotes catabolic metabolism.

Macrophages are dominant participants in subacute and chronic inflammatory reactions. During persistent inflammation, increased numbers of monocytes are recruited from the bone marrow. Under chemotactic influences, they migrate into sites of inflammation, where they mature into macrophages. Both recruited and local tissue macrophages proliferate in these foci, where they secrete proteins, lipids, nucleotides, and reactive oxygen metabolites. Functionally, these molecules are digestive, opsonic, cytotoxic, growth-promoting, and growth-inhibiting.

The functional activities of macrophages and the spectrum of molecules that they produce are regulated by external factors, such as T cell-derived cytokines. Macrophages exposed to such factors become “activated,” that is, they acquire a greater capacity to produce reactive oxygen metabolites, kill tumor cells, and eliminate intracellular microorganisms.

If an agent that incites an inflammatory process is difficult to digest, a granulomatous reaction may ensue (see Chapter 2). Under such conditions, macrophages mature further, to become “epithelioid” cells and multinucleated giant cells. Giant cells result from macrophage fusion and are syncytial with multiple nuclei. Different inciting agents elicit different types of giant cells. For example, granulomas caused by mycobacteria often contain Langhans-type giant cells, which have a semicircular arrangement of nuclei. Giant cells of foreign body granulomas exhibit a random distribution of nuclei. Both epithelioid cells and giant cells are poor phagocytes: they mainly sequester and digest foreign material.

**Clinical Evaluation of Immune Status**

Suspicion of an immune disorder should trigger testing of immune function. For example, patients with chronic, recurrent, or unusual infections, may have an **immune deficiency**. Alternatively, persons who consistently present with localized edema and itching following contact with an object in their environment may be suspected of having a hypersensitivity response to an antigen associated with that object.

Defects in the humoral arm usually result in a patient having difficulty clearing encapsulated bacteria from the bloodstream, which may result in life-threatening infections. The bacteria seen in these immunocompromised states are mostly Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis. Defects in humoral immunity may be primary and often present since birth, or they may be acquired. They are quite diverse and include such diseases as selective IgA deficiency, common variable immune deficiency in which immunoglobulin levels are depressed,
and the acquired immune deficiency state caused by human immunodeficiency virus (HIV)-1 in which immunoglobulin levels are elevated but disordered secondary to immune dysregulation and are therefore ineffective. It is important to realize that patients with asplenia, whether secondary to a functional defect or frank absence, are also at greatly increased risk of overwhelming bacteremia, especially with encapsulated bacteria and subsequent life-threatening sepsis syndrome.

The cellular component fights viral infections and performs immune surveillance and may prevent or delay malignancy. The best example for the role of T lymphocytes is in advanced HIV-1 disease, acquired immune deficiency syndrome (AIDS), when CD4+ T cells are severely depleted. Such patients develop opportunistic infections with fungi such as cryptoccocus, viruses such as CMV and adenovirus, and mycobacteria such as Mycobacterium tuberculosis and Mycobacterium avium-intracellulare complex.

**Immunoglobulin Concentrations are Measured by Electrophoresis**

Total aggregate concentrations of IgG, IgA, and IgM can be estimated by serum protein electrophoresis (SPEP). Serum proteins are separated by electrophoresis, stained with dyes that bind to proteins, and quantitated by densitometry. Characteristic electrophoretic patterns of a normal person and a person with hypogammaglobulinemia are compared in Figure 4-8. Immunoglobulins comprise the gammaglobulin fraction, which migrates toward the cathode and is reduced in the patient with hypogammaglobulinemia.

Individual immunoglobulin (i.e., IgG, IgA, IgM) concentrations can be better measured by quantitating individual isotypes using specific antibodies. Quantitation allows identification of selective immunoglobulin subclass deficiencies and, like SPEP, provides a measure of total serum immunoglobulin concentration. There are numerous conditions that involve selective deficiencies of serum IgM, IgG, IgA, or secretory IgA.

**Antibody-Dependent Immunity Can be Assessed by Testing for Antibodies Against Specific Antigens**

Subtle humoral immune deficiencies are detected by quantitating circulating antibodies to specific antigens to which most people have been exposed via vaccination or common environmental contact (e.g., multivalent pneumococcal vaccine, tetanus toxoid, diphtheria toxoid, rubella virus). These serologic methods may be useful in highlighting deficiencies in specific facets of the humoral immune system, even if total serum immunoglobulin levels may be normal. It may be useful to vaccinate a patient with a “killed” vaccine such as the pneumococcal vaccine, and then recheck levels of antibody to these specific antigens, usually 4 weeks postvaccination. This will allow the clinician to assess the immune system response.

**Cell-Mediated Immunity Can Be Measured Using Peripheral Blood T Cells or Skin Sensitivity Testing**

Since the large majority (approximately 80%) of blood lymphocytes are T cells, the total lymphocyte count is a crude index of the ability of the body to generate adequate numbers of T cells. Functional screening of T cell function can be done by skin testing for delayed-type hypersensitivity to antigens with which most people are assumed to have come into contact. Subjects receive intradermal injections of small amounts of such antigens (e.g., *Candida albicans*). A normal response is defined by the specific antigen preparation but typically involves development of a specified area of redness and/or induration in a characteristic time frame.
More sophisticated analyses of T cell function may involve in vitro studies using purified blood lymphocyte preparations. For example, T cell proliferation in response to specific or nonspecific stimuli can provide an indication of T lymphocyte function. Normal T cells (and B cells) proliferate in response to particular mitogenic stimuli. T cell proliferation requires new DNA synthesis, which can be measured by adding labeled nucleotides to the tissue culture medium. Thus, a strong proliferative response to plant lectin phytohemagglutinin (PHA), indicates that the T cell recognition arm of the immune system is likely to be intact. Weak proliferation in response to PHA suggests a qualitative or quantitative defect in T cells or a problem in regulation of T cell proliferation.

Lymphocyte Populations are Commonly Quantitated by Flow Cytometry

Another approach to assessing T and B cell arms of the immune system is quantitating B and T lymphocytes in the blood, usually by flow cytometry (FACS). Peripheral blood lymphocytes are treated with antibodies against specific B or T cell membrane antigens, many of which belong to the system of “cluster designation,” or CD, antigens. For example, CD20 is a B cell antigen, whereas a commonly used marker of T cells is CD3. T cells are often further subcategorized by expression of CD4 (helper T cells) or CD8 (effector T cells). CD4 is not unique to T cells; it is also expressed by many mononuclear phagocytes. An example of the clinical utility of lymphocyte subpopulation quantitation is the serial measurement of CD4+ T cells in patients infected with HIV-1.

Monoclonal antibodies against individual antigens, conjugated to fluorescent dyes such as fluorescein or rhodamine (fluorophores), react with the cells in question. A flow cytometer disperses cells from the whole population in microdroplets that each contain a single cell. As the cell falls, it passes several laser light beams that specifically excite a fluorophore. If the cell bears the antigen recognized by the fluorophore-labeled antibody, the fluorophore is excited and emits light of a particular wavelength, which is measured by a detector. The flow cytometer then counts the cells that emitted light of that wavelength(s) and measures the intensity of those emissions. Depending on the number of lasers in the machine, one or more cell membrane markers can be tested at once.

Such quantitation of T lymphocyte populations is routinely used, e.g., to follow the clinical status of patients infected with HIV-1, and to assess the effectiveness of highly active antiretroviral therapy (HAART).

Molecular Evaluation of Immune Status Facilitates Diagnosis of Rare Immune System Defects

A large number of specific, often rare, immunodeficiency disorders have been defined on the basis of mutations within genes that encode various cell membrane-associated, cell-cell communication molecules (e.g., β2-integrins), cytosolic signal-transduction molecules (e.g. Janus kinase 3), cytosolic enzymes (e.g. adenosine deaminase), and transcription factors that are involved in the regulation of host defense gene expression. More than 100 specific genetic defects that can result in impaired immune status have been defined.

Immunologically Mediated Tissue Injury

Immune responses not only protect against invasion by foreign organisms, but may also cause tissue damage. Thus, many inflammatory diseases are examples of “friendly fire” in which the immune system attacks the body’s own tissues. A variety of foreign substances (e.g. dust, pollen, bacteria, viruses) may act as antigens and provoke protective immune responses. In certain situations, the protective effects of an immune response give way to deleterious events that elicit a spectrum of lesions. Such lesions can produce manifestations that range from temporary discomfort to substantial injury. For example, in the process of phagocytizing and destroying bacteria, phagocytic cells (neutrophils and macrophages) often cause injury to surrounding tissue. An immune response that leads to tissue injury or disease is broadly called a hypersensitivity reaction. Many diseases are categorized as immune disorders or immunologically mediated conditions, in which an immune response to a foreign or self-antigen causes injury. Immune, or hypersensitivity-mediated, diseases are common and include such entities as hives (urticaria), asthma, hay fever, hepatitis, glomerulonephritis, and arthritis.

Hypersensitivity reactions are classified according to the type of immune mechanism (Table 4-1). Type I, II, and III hypersensi-

<table>
<thead>
<tr>
<th>TABLE 4-1</th>
<th>Modified Gell and Coombs Classification of Hypersensitivity Reactions</th>
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<tbody>
<tr>
<td>Type</td>
<td>Mechanism</td>
</tr>
<tr>
<td>Type I (anaphylactic type): Immediate hypersensitivity</td>
<td>IgE antibody-mediated mast cell activation and degranulation</td>
</tr>
<tr>
<td></td>
<td>Non-IgE-mediated</td>
</tr>
<tr>
<td>Type II (cytotoxic type): Cytotoxic antibodies</td>
<td>Cytotoxic (IgG, IgM) antibodies formed against cell surface antigens; complement usually involved</td>
</tr>
<tr>
<td></td>
<td>Noncytotoxic antibodies against cell surface receptors</td>
</tr>
<tr>
<td>Type III (immune complex type): Immune complex disease</td>
<td>Antibodies (IgG, IgM, IgA) formed against exogenous or endogenous antigens; complement and leukocytes (neutrophils, macrophages) often involved.</td>
</tr>
<tr>
<td>Type IV (cell-mediated type): Delayed-type hypersensitivity</td>
<td>Mononuclear cells (T lymphocytes, macrophages) with interleukin and lymphokine production</td>
</tr>
</tbody>
</table>

Ig = immunoglobulin; SLE = systemic lupus erythematosus.
tivity reactions all require formation of a specific antibody against an exogenous (foreign) or an endogenous (self) antigen. An exception is a subset of type I reactions. The antibody class is a critical determinant of the mechanism by which tissue injury occurs.

In most type I, or immediate-type hypersensitivity reactions, IgE antibody is formed and binds to high-affinity receptors on mast cells and/or basophils via its Fc domain. Subsequent binding of antigen and crosslinking of IgE triggers rapid (immediate) release of products from these cells, leading to the characteristic symptoms of such diseases as urticaria, asthma, and anaphylaxis.

In type II hypersensitivity reactions, IgG or IgM antibody is formed against an antigen, usually a protein on a cell surface. Less commonly, the antigen is an intrinsic structural component of the extracellular matrix (e.g., part of the basement membrane). Such antigen–antibody coupling activates complement, which in turn lyses the cell (cytotoxicity) or damages the extracellular matrix. In some type II reactions, other antibody-mediated effects are operative.

In type III hypersensitivity reactions, the antibody responsible for tissue injury is also usually IgM or IgG, but the mechanism of tissue injury differs. The antigen circulates in the vascular compartment until it is bound by antibody. The resulting immune complex is deposited in tissues. Complement activation at sites of antigen–antibody deposition leads to leukocyte recruitment, which is responsible for the subsequent tissue injury. In some type III reactions, antigen is bound by antibody in situ.

Type IV reactions, also known as cell-mediated, or delayed-type, hypersensitivity reactions, do not involve antibodies. Rather, antigen activation of T lymphocytes, usually with the help of macrophages, causes release of products by these cells, thereby leading to tissue injury.

Many immunologic diseases are mediated by more than one type of hypersensitivity reaction. Thus, in hypersensitivity pneumonitis, lung injury results from hypersensitivity to inhaled fungal antigens. Types I, III, and IV hypersensitivity reactions all appear to be operative in hypersensitivity pneumonitis.

**Type I or Immediate Hypersensitivity Reactions Are Triggered by IgE Bound to Mast Cells**

Immediate-type hypersensitivity is manifested by a localized or generalized reaction that occurs immediately (within minutes) after exposure to an antigen or “allergen” to which the person has previously been sensitized. The clinical manifestations of a reaction depend on the site of antigen exposure and extent of sensitization. For example, when a reaction involves the skin, the characteristic local reaction is a “wheal and flare,” or urticaria. When the localized manifestations of immediate hypersensitivity involve the upper respiratory tract and conjunctiva, causing sneezing and conjunctivitis, we speak of hay fever (allergic rhinitis). In its generalized and most severe form, immediate hypersensitivity reactions are associated with bronchoconstriction, airway obstruction, and circulatory collapse, as seen in anaphylactic shock. There is a high degree of variability in susceptibility to type I hypersensitivity reactions, which is genetically determined. A variety of linkages and candidate genes have been identified. Particularly susceptible individuals are said to be “atopic.”

Type I hypersensitivity reactions usually feature IgE antibodies, which are formed by a CD4+ T cell–dependent mechanism and which bind avidly to Fc-epsilon (Fcε) receptors on mast cells and basophils. The high avidity of binding of IgE accounts for the term cytophilic antibody. Once exposed to an specific allergen that elicits IgE, a person is sensitized; subsequent exposures to that allergen or a cross-reacting epitope induce immediate hypersensitivity reactions. After IgE is elicited, repeat exposure to antigen typically induces additional IgE antibody, rather than antibodies of other classes, such as IgM or IgG.

IgE can persist for years bound to Fcε receptors on mast cells and basophils, a feature unique to these cells. Upon subsequent reexposure, the soluble antigen or allergen binds the IgE coupled to its surface Fcε receptor and activates the mast cell or basophil. This event releases potent inflammatory mediators that are responsible for the manifestations of this type I hypersensitivity reaction. As shown in Figure 4-9, the antigen (allergen) binds to IgE antibody through its Fab sites. Cross-linking of the antigen to more than one IgE antibody molecule is required to activate the cell. Most cells and basophils can also be activated by agents other than antibodies. For example, some individuals may develop urticaria following exposure to an ice cube (physical urticaria). As also shown in Figure 4-9, the complement-derived anaphylatoxic peptides, C3a and C5a, can directly stimulate mast cells by a different receptor-mediated process. These cell-activating events trigger release of stored granule constituents and rapid synthesis and release of other mediators. Some compounds, such as melittin (from bee venom) and some drugs (e.g., morphine) directly activate mast cells and induce release of granular constituents.

Regardless of how mast cell activation is initiated, cytosolic calcium influx is required. A rise in cytosolic free calcium is associated with increases in cyclic adenosine 3’,5’-monophosphate (cAMP), activation of several metabolic pathways within the mast cell and the subsequent secretion of both preformed and newly synthesized products. A number of potent mediators are released from granules within minutes. Because they are preformed and stored in granules, they exert immediate biological effects following their release. Of the granule constituents listed in Figure 4-9, the biogenic amine histamine is particularly important. Histamine induces constriction of vascular and nonvascular smooth muscle, causes microvascular dilation, and increases venule permeability. These biological effects are largely mediated through H1 histamine receptors. Histamine also increases gastric acid secretion through H2 histamine receptors. In the skin, histamine provokes the wheal-and-flare reaction. In the lung, it is responsible for the early manifestations of immediate hypersensitivity, including bronchospasm, vascular congestion, and edema. Other preformed products released from mast cell granules include heparin, a series of neutral proteases (trypsin, chymotrypsin, carboxypeptidase, and acid hydrolases) and at least two chemotactic factors: a neutrophil chemoattractant factor and an eosinophil chemoattractant factor. The latter is responsible for the accumulation of eosinophils, a characteristic finding in immediate hypersensitivity. The synthesis and secretion of cytokines by mast cells, by other recruited inflammatory cells and even by indigenous cells (e.g., epithelium) are important in the so-called “late-phase” reaction of immediate hypersensitivity. Late-phase responses typically last for 2 to 24 hours, are marked by a mixed inflammatory infiltrate, and are mediated by many cytokines including IL-1, IL-3, IL-4, IL-5, IL-6, TNF, granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage-inflammatory proteins (MIP)-1α and MIP-1β.

Activation of mast cells also results in the synthesis of potent inflammatory mediators. Foremost among these molecules are various products of the arachidonic acid pathway that are...
formed following activation of phospholipase A₂. Products derived from the activities of cyclooxygenase (prostaglandins D₂, E₂, F₂, and thromboxane) and lipoxygenase (leukotrienes B₄, C₄, D₄, E₄) are formed. Arachidonic acid products, which are also generated by a variety of other cell types, induce smooth muscle contraction, vasodilation, and edema. Leukotrienes C₄, D₄, and E₄, previously known as the “slow-reacting substances of anaphylaxis” (SRS-As), are important molecules in the delayed bronchoconstriction phase of anaphylaxis. Leukotriene B₄, a potent chemotactic factor for neutrophils, macrophages, and eosinophils, is formed during anaphylaxis and is involved in attracting inflammatory cells into tissues.

Another inflammatory mediator synthesized by mast cells is platelet activating factor (PAF), a lipid derived from membrane phospholipids. As its name implies, PAF is a potent inducer of platelet aggregation and release of vasoactive amines from platelets. It is also a potent neutrophil chemotaxin. It has a broad range of biological activities and can activate all types of phagocytic cells.

As mentioned above, activated T cells, specifically Th₂ type, produce cytokines that have important roles in allergic responses. Activated Th2 T cell subsets produce IL-4, IL-5, and IL-13, leading to IgE production and increased numbers of mast cells and eosinophils. In allergy-prone persons, a similar response occurs via T cell clones that produce IL-4, IL-6, and IL-2, concentrations of which are also increased in allergic individuals. These persons also have reduced levels of IFN-γ, which suppresses development of Th2 clones and subsequent production of IgE.

To summarize, type I (immediate) hypersensitivity reactions are characterized by a specific cytophilic antibody (IgE), which binds to high-affinity receptors on basophils and mast cells and reacts with a specific antigen. Activated mast cells and basophils release preformed (granule) products and synthesize mediators that cause the classic manifestations of immediate hypersensitivity and the late-phase reaction.

**Type II Hypersensitivity Reactions Are Mediated by Antibodies against Fixed Cellular or Extracellular Antigens**

IgG and IgM typically mediate type II reactions. An important characteristic of these antibodies is their ability to activate
complement through the immunoglobulin Fc domain. There are several antibody-dependent mechanisms of tissue injury.

The prototypic model of antibody-mediated erythrocyte cytotoxicity is illustrated in Figure 4-10. IgM or IgG antibody binds an antigen on the surface of the erythrocyte membrane. At sufficient density, bound immunoglobulin leads to complement fixation via C1q and the classic pathway (see Chapter 2). Once activated, complement can destroy target cells by several distinct mechanisms. Complement products can directly lyse target cells via C5b-9 complement complexes (see Fig. 4-10). This complex is referred to as the membrane attack complex because it inserts like the staves of a barrel into the plasma membrane and forms holes or ionic channels, destroying the permeability barrier and inducing cell lysis. This type of complement-mediated cell lysis is exemplified by certain types of autoimmune hemolytic anemias that involve formation of antibodies against blood group antigens on erythrocytes. In transfusion reactions that result from major blood group incompatibilities, hemolysis occurs through activation of complement.

Complement and antibody molecules can also lead to destruction of a target cell by opsonization. Target cells coated (opsonized) with immunoglobulin and/or C3b molecules are bound by phagocytes that express Fc or C3b receptors. Complement activation in proximity to a target cell surface leads to formation and covalent bonding of C3b (Fig. 4-11). Many phagocytic cells, including neutrophils and macrophages, have cell membrane Fc and C3b receptors. By binding to its receptor, immunoglobulin or C3b bridges the target cell and the effector (phagocytic) cell, thereby enhancing phagocytosis and the subsequent intracellular destruction of the antibody- or complement-coated cell. Certain types of autoimmune hemolytic anemias and some drug reactions are mediated by antibody- and complement-mediated opsonization.

There is another type of antibody-mediated cytotoxicity that does not require complement. Antibody-dependent cell-mediated cytotoxicity (ADCC) involves cytolytic leukocytes that attack antibody-coated target cells after binding via Fc receptors. Phagocytic cells and NK cells can function as effector cells in ADCC. The mechanisms by which target cells are destroyed in these reactions are not entirely understood. Among
an array of mediators, effector cells synthesize homologues of terminal complement proteins (e.g., perforins), which participate in cytotoxic events (see preceding discussion of NK cells). Only rarely is antibody alone directly cytotoxic. In cases involving primarily lymphoid cells, apoptosis is activated. ADCC may also be involved in the pathogenesis of some autoimmune diseases (e.g., autoimmune thyroiditis).

In some type II reactions, antibody binding to a specific target cell receptor does not lead to cell death but rather to a change in function. Autoimmune diseases such as Graves disease and myasthenia gravis feature autoantibodies against cell surface hormone receptors (Fig. 4-12). In Graves disease, autoantibody directed against thyroid-stimulating hormone (TSH) receptor on thyrocytes mimics the effect of TSH, stimulating thyroxine production and leading to hyperthyroidism (see Chapter 21). In contrast, in myasthenia gravis, autoantibodies to acetylcholine receptors in neuromuscular endplates either block acetylcholine binding or mediate internalization or destruction of receptors, thereby inhibiting efficient synaptic transmission (see Chapter 27). Patients with myasthenia gravis thus suffer from muscle weakness. Modulatory autoantibodies against receptors for insulin, prolactin, growth hormone, and other messengers are reported.

Some type II hypersensitivity reactions result from antibody against a structural connective tissue component. Classic examples are Goodpasture syndrome and bullous skin diseases, pemphigus and pemphigoid. In these diseases, circulating antibody binds to intrinsic connective tissue antigens and evokes a destructive local inflammatory response. In Goodpasture syndrome, antibody binds the noncollagenous domain of type IV collagen, which is a major structural component of pulmonary and glomerular basement membranes (Fig. 4-13). Local complement activation results in recruitment of neutrophils into the site, tissue injury, and pulmonary hemorrhage and glomerulonephritis. Direct complement-mediated damage to the basement membranes of the glomeruli and the lung alveoli through formation of membrane attack complexes may also be involved.

In summary, type II hypersensitivity reactions are directly or indirectly cytotoxic through action of antibodies against antigens on cell surfaces or in connective tissues. Complement participates in many of these cytotoxic events. Lysis is mediated directly by complement, indirectly by opsonization and phagocytosis, or via chemotactic attraction of phagocytic cells, which produce a large variety of tissue-damaging products. Complement-independent reactions, such as ADCC, also fall into this category.

FIGURE 4-12. In a type II hypersensitivity reaction, antibodies bind to a cell surface receptor and induce activation (e.g., thyroid-stimulating hormone [TSH] receptors in Graves disease) or inhibition/destruction (e.g., acetylcholine receptors in myasthenia gravis).

FIGURE 4-13. Goodpasture syndrome. In a type II hypersensitivity reaction, antibody binds to a surface antigen, activates the complement system, and leads to the recruitment of tissue-damaging inflammatory cells. Several complement-derived peptides (e.g., C5a) are potent chemotactic factors. GBM = glomerular basement membrane; PMN = polymorphonuclear neutrophil.
In Type III Hypersensitivity Reactions Immune Complex Deposition or Formation in Situ Leads to Complement Fixation and Inflammation

IgG, IgM, and occasionally IgA antibody against either a circulating antigen or an antigen that is deposited or “planted” in a tissue can cause a type III response. Physicochemical characteristics of the immune complexes, such as size, charge, and solubility, in addition to immunoglobulin isotype, determine whether an immune complex can deposit in tissue or fix complement. “Phlogistic” immune complexes elicit inflammatory responses by activating complement, leading to chemotactic recruitment of neutrophils and monocytes to the site. Activated phagocytes release tissue-damaging mediators, such as proteases and reactive oxygen intermediates.

Immune complexes have been implicated in many human diseases (Fig. 4-14). The most compelling cases are those in which demonstration of immune complexes in injured tissue correlates with development of injury. Convincing examples include cryoglobulinemic vasculitis associated with hepatitis C infection, Henoch-Schönlein purpura (in which IgA deposits are found at sites of vasculitis), and systemic lupus erythematosus (SLE) (anti–double-stranded DNA in vasculitic lesions). In many diseases, immune complexes can be detected in plasma without concomitant evidence of tissue injury. The physicochemical properties of circulating immune complexes frequently differ from those of complexes deposited in tissues. In some cases, vasopermeability factors may play a role in the localization of circulating immune complexes. Diseases that seem to be most clearly attributable to immune complex deposition are autoimmune diseases of connective tissue, such as SLE and rheumatoid arthritis, some types of vasculitis, and many varieties of glomerulonephritis.

Serum sickness is an acute, self-limited disease that typically occurs 6 to 8 days after injection of a foreign protein. Human serum sickness is uncommon, but it does occur in patients who have received foreign proteins therapeutically (e.g., antilymphocyte globulin). It is characterized by fever, arthralgias, vasculitis, and acute glomerulonephritis. In experimental acute serum sickness, levels of exogenously injected antigen in the circulation remain constant until about day 6, after which they
fall rapidly (see Fig. 4-14). At the same time, immune complexes (containing IgM or IgG bound to antigen) appear in the circulation. Some of these circulating complexes deposit in tissues such as renal glomeruli and blood vessel walls. They are rendered more soluble by their interaction with the complement system, which enhances tissue deposition. Interaction of immune complexes with complement also generates C3a and C5a, which increase vascular permeability.

Once phlogistic immune complexes are deposited in tissues, they trigger an inflammatory response. Local activation of complement by immune complexes results in formation of C5a, which is a potent neutrophil chemoattractant. Recruitment of inflammatory cells is mediated by chemotactic agents such as C5a, leukotriene B4, and IL-8. Neutrophil adherence and migration into the sites of immune complex deposition are then mediated by a series of cytokine-mediated adhesive interactions (see Chapter 2). A number of cytokines have been implicated in modulating this response. Early production of IL-1 and TNF-α mediates upregulation of adhesion molecules on endothelial cells and production of other proinflammatory cytokines. These include platelet-derived growth factor (PDGF); transforming growth factor-beta (TGF-β); and IL-4, IL-6, and IL-10; which modulate activation of leukocytes and fibroblasts. Not all cytokines are proinflammatory; IL-10, in particular, downregulates the inflammatory response. Once neutrophils arrive, they are activated through contact with, and ingestion of, immune complexes. Activated leukocytes release many inflammatory mediators, including proteases, reactive oxygen intermediates, and arachidonic acid products, which collectively produce tissue injury. The tissue injury associated with experimental serum sickness mimics that seen in many types of human vasculitis and glomerulonephritis.

The Arthus reaction has been characterized in an experimental model of vasculitis in which a localized injury is induced by immune complexes (Fig. 4-15). This reaction is classically seen in dermal blood vessels after local injection of an antigen to which an individual was previously sensitized. The circulating antibody and locally injected antigen diffuse toward each other and form immune complex deposits in the walls of small blood vessels. Resulting vascular injury is mediated by complement fixation, followed by recruitment and activation of neutrophils, which release their tissue-damaging mediators. Because injury in the Arthus reaction is caused by recruited neutrophils and their products, 2 to 10 hours are required for evidence of tissue injury. This is in marked contrast to more rapidly evolving type I (immediate) hypersensitivity reactions. The walls of affected vessels contain numerous neutrophils and show evidence of damage, with edema and hemorrhage into surrounding tissue. In addition, the presence of fibrin creates the classic appearance of an immune complex-induced vasculitis, namely, fibrinoid necrosis. This experimental model of localized vasculitis is the prototype for many forms of vasculitis seen in humans, for example, the cutaneous vasculitides that characterize certain drug reactions.

To summarize, type III hypersensitivity reactions are immune complex-mediated injuries. Antigen–antibody complexes are either formed in the circulation and deposited in the tissues, or are formed in situ. These immune complexes then induce a localized inflammatory response by fixing complement, which leads to recruitment of neutrophils and monocytes. Activation of these inflammatory cells by immune complexes and complement, accompanied by release of potent inflammatory mediators, is directly responsible for injury (see Fig. 4-15). Many human diseases, including autoimmune diseases such as SLE and many types of glomerulonephritis, are mediated by type III hypersensitivity reactions.

**Type IV, or Cell-Mediated, Hypersensitivity Reactions are Cellular Immune Responses That Do Not Involve Antibodies**

Included among these reactions are delayed-type cellular inflammatory responses and cell-mediated cytotoxic effects. Type IV reactions often occur together with antibody reactions, which can make it difficult to distinguish these processes. Both clinical observations and experimental studies suggest that the type of tissue response is largely determined by the nature of the inciting agent.

Classically, delayed-type hypersensitivity is a tissue reaction, primarily involving lymphocytes and mononuclear phagocytes, which occurs in response to a soluble protein antigen and reaches greatest intensity 24 to 48 hours after initiation. A classic example of a type IV reaction is the contact sensitivity response to poison ivy. Although chemical ligands in poison ivy are not proteins, they bind covalently to cell proteins, after which the compound molecules are recognized by antigen-specific lymphocytes.

Figure 4-16 summarizes the stages of a delayed-type hypersensitivity reaction. In the initial phase, foreign protein antigens or chemical ligands interact with accessory cells that express class II HLA molecules (Fig. 4-16A). Such accessory cells (macrophages, dendritic cells) secrete IL-12, which along with processed and presented antigen, activates CD4+ T cells (Fig. 4-16B). In turn, activated CD4+ T cells secrete IFN-γ and IL-2, which activate more macrophages and trigger T lymphocyte proliferation, respectively (Fig. 4-16C). The protein antigens are actively processed into short peptides within phagolysosomes of macrophages and then presented on the cell surface in conjunction with class II HLA molecules. Processed and presented antigens are recognized by MHC-restricted, antigen-specific CD4+ T cells, which become activated and synthesize an array of cytokines. Such activated CD4+ cells are referred to as T1/h1 cells. In turn, the cytokines recruit and activate lymphocytes, monocytes, fibroblasts, and other inflammatory cells. If the antigenic stimulus is eliminated, the reaction spontaneously resolves after about 48 hours. If the stimulus persists (e.g., poorly biodegradable mycobacterial cell wall components), an attempt to sequester the inciting agent may result in a granulomatous reaction.

Other mechanisms by which T cells (especially CD8+) mediate tissue damage is direct cytolysis of target cells (Fig. 4-17). These immune mechanisms are important in destroying and eliminating cells infected by viruses, and possibly tumor cells that express neoantigens. Cytotoxic T cells also play an important role in transplant graft rejection.

Figure 4-17 summarizes the events in T cell-mediated cytotoxicity. In contrast to delayed-type hypersensitivity reactions, cytotoxic CD8+ T cells specifically recognize target antigens in the context of class I MHC molecules (Fig. 4-17). In the case of virus-infected cells and tumor cells, foreign antigens are actively presented together with self-MHC antigens. In graft rejection, foreign MHC antigens are themselves potent activators of CD8+ T cells. Once activated by antigen, proliferation of cytotoxic cells is promoted by helper cells and mediated by soluble growth factors such as IL-2 (see Fig. 4-17C). An expanded population of antigen-specific cytotoxic cells is thus generated. Actual cell killing involves several mechanisms (see Fig. 4-17D).
FIGURE 4-15. The Arthus reaction is a type III hypersensitivity reaction characterized by the deposition of immune complexes and the induction of an acute inflammatory response within blood vessel walls. Some vasculitic lesions exhibit fibrinoid necrosis. 

Cytolytic T cells (CTLs) secrete perforins that form pores in target cell membranes and introduce granzymes that activate intracellular caspases, leading to apoptosis. CTLs can also kill targets via engagement of Fas ligand (by the CTL) and Fas (on the target). Fas ligand-Fas interaction triggers apoptosis of the Fas-bearing cell.

The defining characteristics of NK cells have been described, but the extent to which such cells participate in tissue-damaging reactions is unclear. Mounting evidence indicates that NK cells exert both effector and immunoregulatory functions.

Figure 4-18 summarizes target cell killing by NK cells. NK cells can recognize a variety of target cells. Target molecules include membrane glycoproteins expressed by certain virus-infected cells and tumor cells. In a series of events similar to those described for cytotoxic T cells, NK cells bind to target cell through their membrane receptors and then deliver molecular
In sum, in Type IV hypersensitivity reactions, antigens are processed by macrophages and presented to antigen-specific T lymphocytes. These lymphocytes become activated and release a variety of mediators that recruit and activate lymphocytes, macrophages, and fibroblasts. The resulting injury is caused by T lymphocytes themselves, macrophages or both. No antibodies are involved. The chronic inflammation in many autoimmune diseases—including type 1 diabetes, chronic thyroiditis, Sjögren syndrome, and primary biliary cirrhosis—is the result of type IV hypersensitivity.

Immunodeficiency Diseases

Immunodeficiency diseases are classified according to two characteristics: whether the defect is congenital (primary) or acquired (secondary), and the host defense system that is defective. The great majority of primary immunodeficiency disorders are genetically determined. Disorders of the complement system and primary defects of phagocytes are discussed elsewhere (see Chapters 2 and 20). In contrast to the low prevalence of congenital immunodeficiency disorders, acquired immune deficiencies like that caused by HIV-1 infection (AIDS) are common. AIDS affects tens of millions of people worldwide.

Functional defects in lymphocytes can be localized to particular maturational stages in the ontogeny of the immune system or to interruption of discrete immune activation events (Fig. 4-19). The explosive growth of knowledge regarding molecular mechanisms of immunodeficiency disorders has led to improved diagnosis, clinical management, and therapeutic strategies. Identification of specific molecular defects and mechanistic understanding of the pathophysiology of various disorders have also provided great insight into the function of the immune system. A detailed classification scheme for primary immunodeficiency disorders is available via the World Health Organization (WHO).

Primary Antibody Deficiency Diseases Feature Impaired Production of Specific Antibodies

These diseases are characterized by recurrent bacterial infections, a limited number of specific types of viral infections (e.g., echovirus infections of the central nervous system [CNS] in patients with Bruton agammaglobulinemia) and subnormal serum concentrations of either all or specific isotypes of immunoglobulin. There are a variety of immunoglobulin isotype and subclass deficiency states (Table 4-2). These include selective deletions of immunoglobulin heavy chains and selective loss of light-chain expression. In addition, some patients have normal levels of immunoglobulins but fail to produce antibodies against specific antigens, usually polysaccharides. The clinical manifestations of these entities are highly variable; some patients suffer from recurrent mucosal tract infections, whereas others are asymptomatic.

Bruton X-Linked Agammaglobulinemia

The congenital disorder Bruton X-linked agammaglobulinemia typically presents in male infants at 5 to 8 months old, the period during which maternal antibody levels have declined. The infant suffers from recurrent pyogenic infections and severe hypogammaglobulinemia involving all immunoglobulin isotypes. Occasional patients develop chronic enterovirus infections of the CNS. Immunization with live attenuated poliovirus can lead to paralytic poliomyelitis. Approximately a third of Bruton’s pa-
**TARGET CELLS**

- Viral
- HLA
- Tumor

**TARGET ANTIGENS**

- Virally-coded membrane antigen
- Foreign or modified histocompatibility antigen
- Tumor-specific membrane antigens

**RECOGNITION OF ANTIGEN BY T CELLS**

- T-helper cells recognize antigen plus class II molecules
- T-cytotoxic/killer cells recognize antigen plus class I molecules

**ACTIVATION AND AMPLIFICATION**

- T-helper cells activate and proliferate, releasing helper molecules (e.g., IL-2)
- T-cytotoxic/killer cells proliferate in response to helper molecules

**TARGET CELL KILLING**

- T-cytotoxic/killer cells bind to target cell
- Killing signals perforin release and target cell loses membrane integrity
- Target cell undergoes lysis

**FIGURE 4-17.** In T cell-mediated cytotoxicity, potential target cells include (A) virus-infected host cells, malignant host cells, and foreign (histoincompatible transplanted) cells. B. Cytotoxic T lymphocytes recognize foreign antigens in the context of human leukocyte antigen (HLA) class I molecules. C. Activated T cells secrete lytic compounds (e.g., perforin and other mediators) and cytokines that amplify the response, that is apoptosis (target cell killing). D. Ca$^{2+}$ = calcium ion; IL = interleukin; K$^+$ = potassium ion; Na$^+$ = sodium ion.

Patients have a poorly understood form of arthritis, believed in some cases to be caused by *Mycoplasma*. There are no mature B cells in peripheral blood or plasma cells in lymphoid tissues. Pre-B cells, however, can be detected. The genetic defect, on the long arm of the X chromosome (Xq21.22), inactivates the gene that encodes B-cell tyrosine kinase (Bruton tyrosine kinase [BTK]), an enzyme critical to B-lymphocyte maturation (see Table 4-2).

**Selective IgA Deficiency**

Characterized by low serum and secretory concentrations of IgA, selective IgA deficiency is the most common primary immunodeficiency syndrome. Its incidence ranges from 1:700 among Europeans to 1:18,000 in Japanese. Although patients are often asymptomatic, they occasionally present with respiratory or gastrointestinal infections of varying severity. They also display a strong predilection for allergies and collagen vascular diseases. Patients with IgA deficiency have normal numbers of IgA-bearing B cells; their varied defects result in an inability to synthesize and secrete IgA subclasses (see Table 4-2). Some patients have concomitant IgG subclass deficiencies. Patients with selective IgA deficiency are at risk of allergic, occasionally anaphylactic, reactions to IgA-containing transfused blood products.

**Common Variable Immunodeficiency (CVID)**

CVID is a heterogenous group of disorders characterized by pronounced hypogammaglobulinemia (see Table 4-2). A variety of defects in either B lymphocyte maturation or T lymphocyte-mediated B lymphocyte maturation appear to be opera-
A virally infected Target cell

NK cell

Tumor

FIGURE 4-18. In natural killer (NK) cell-mediated cytotoxicity, potential target cells include virus-infected and neoplastic cells (A). NK cells bind target cells (B), are activated, and secrete lytic compounds (C). Ca²⁺ = calcium ion; K⁺ = potassium ion; Na⁺ = sodium ion.

pathic. Many relatives of patients with CVID have selective IgA deficiency. Affected patients present with recurrent severe pyogenic infections, especially pneumonia and diarrhea, the latter often due to infestation with *Giardia lamblia*. Recurrent attacks of herpes simplex are common; herpes zoster develops in one fifth of patients. The disease appears years to decades after birth, with a mean age at onset of 30 years. Incidence is estimated to be between 1:50,000 and 1:200,000. The inheritance pattern is variable and the malady features a variety of maturational and regulatory defects of the immune system. A high incidence of malignant disease is seen in CVID, including a 50-fold increase in stomach cancer. Interestingly, lymphoma is 300 times more frequent in women with this immunodeficiency than in affected men. Malabsorption secondary to lymphoid hyperplasia and inflammatory bowel diseases is more frequent than in the general population. CVID patients are also susceptible to other autoimmune disorders, including hemolytic anemia, neutropenia, thrombocytopenia, and pernicious anemia.

**Transient Hypogammaglobulinemia of Infancy**

Prolonged hypogammaglobulinemia occurs in transient hypogammaglobulinemia of infancy after maternal antibodies in the infant have reached their nadir. Some affected infants develop recurrent infections and require therapy, but all eventually produce immunoglobulins. Infants with transient hypogammaglobulinemia possess mature B cells that are temporarily unable to produce antibodies. The defect is not well understood but is thought to represent a delay in helper T cell signal-generating capacity.

**Hyper-IgM Syndrome**

The hyper-IgM syndrome is often classified as a humoral immunodeficiency because immunoglobulin production is disordered. It could also be classed as a combined humoral and T lymphocyte defect because the genetic lesion that accounts for the most common X-linked form, located on (Xq26), results in failure to express the T cell molecule, CD40 ligand (Table 4-3). In the remaining 30% of patients with hyper-IgM syndrome, mutations affect the genes that encode CD40, DNA-editing enzyme, activation-induced deaminase. Infants with the X-linked form of the disease exhibit pyrogenic and opportunistic infections, especially with *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*). They also tend to develop autoimmune diseases involving the formed elements of the blood, especially autoimmune hemolytic anemia, thrombocytopenic purpura, and recurrent, severe neutropenia. Serum levels of IgG and IgA are low, but those of IgM are high normal or conspicuously elevated. Circulating B cells bear only IgM and IgD. The defect appears to be at the level of the “switch” from IgD/IgM to other heavy-chain isotypes. In this context, interaction of the CD40 receptor on the B cell surface with CD40 ligand is required for isotype switching (see Fig. 4-19).

**Primary T Cell Immunodeficiency Diseases Typically Result in Recurrent or Protracted Viral and Fungal Infections**

**DiGeorge Syndrome**

In its complete form, the DiGeorge syndrome is one of the most severe T lymphocyte immunodeficiency disorders. It usually appears in an infant with conotruncal congenital heart defects and severe hypocalcemia (due to hypoparathyroidism) and is recognized shortly after birth. Some patients exhibit characteristically abnormal facial features. Infants who survive the neonatal period are subject to recurrent or chronic viral, bacterial, fungal, and protozoal infections. The syndrome is caused by defective embryologic development of the third and fourth pharyngeal pouches, which give rise to the thymus, parathyroid glands, and influence conotruncal cardiac development. Most patients have a point deletion in the long arm of chromosome 22. DiGeorge syndrome is consid-
**IgM**

**Mature B cells**

**Plasma cells**

**IgM**

**Hyper IgM syndrome**

**CD4+ & CD8+**

**MHC class II deficiency**

**Immature T cell**

**CD3**

**MHC class I deficiency**

**CD4+ & CD8+**

**Pre-B cell**

**Immunoglobulins**

**α & β**

**Peripheral sites**

**Hemopoietic**

**stem cell**

**Lymphoid progenitor**

**B LYMPHOCYTE MATURATION**

**T LYMPHOCYTE MATURATION**

**Autosomal recessive severe combined immunodeficiency**

**X-linked severe combined immunodeficiency**

**CD3**

**MHC class I deficiency**

**CD3**

**Peripheral sites**

**Thymus**

**Bone marrow**

**FiguRE 4-19.** Hematopoietic stem cells give rise to lymphoid progenitor cells that, in a predetermined manner, populate either the bone marrow or thymus. A number of primary immunodeficiency disorders have been characterized at genetic and molecular mechanistic levels. In a number of immunodeficiency disorders, a discrete molecular defect results in a form of “maturational arrest” in the development of fully differentiated and functional lymphocytes. Ig = immunoglobulin.

...continued to be a form of so-called 22q11 deletion syndrome. In the absence of a thymus, T cell maturation is interrupted at the pre-T cell stage. The disease has been corrected by transplanting thymic tissue. Most patients have a partial DiGeorge syndrome, in which a small remnant of thymus is present. With time, these persons recover T cell function without treatment. Some patients with the 22q11 mutation are not immunodeficient but suffer only from conotruncal cardiac defects.

**Chronic Mucocutaneous Candidiasis**

The yeast infection chronic mucocutaneous candidiasis is the result of a congenital defect in T cell function. It is characterized by susceptibility to candidal infections and is associated with an endocrinopathy (hyoparathyroidism, Addison disease, diabetes mellitus). Although most T cell functions are intact, there is an impaired response to *Candida* antigens. The precise cause of the defect in chronic mucocutaneous candidiasis is unknown, but it could occur at any of several points during T cell development. Recent studies suggest that persons with this disorder react to *Candida* antigens differently from normal individuals. In particular, they mount a type 2 (IL-4/IL-6) helper T cell response, which is ineffective in resisting the organism. By contrast, the normal response features type 1 (IL-2/IFN-γ) T cells, which effectively control candidal infections.
Adenosine Deaminase (ADA) deficiency
ADA deficiency is an autosomal recessive form of combined immunodeficiency with mutations in the adenosine deaminase gene (see Table 4-3). ADA participates in purine nucleotide catabolism, converting adenosine to inosine or deoxyadenosine to deoxyinosine. If the enzyme is defective or absent, deoxyadenosine and deoxyadenosine triphosphate accumulate. Deoxyadenosine triphosphate inhibits ribonucleotide reductase, thereby causing depletion of deoxyribonucleoside triphosphates and defective lymphocyte function. The clinical manifestations range from mild to severe dysfunction of T cells and B cells, and include characteristic developmental abnormalities of cartilage.

### TABLE 4–2

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mode of Inheritance</th>
<th>Locus/Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agammaglobulinemia</td>
<td>XL</td>
<td>Xq21.3/BTK</td>
</tr>
<tr>
<td>Selective antibody class/subclass deficiencies</td>
<td>AR</td>
<td>14q32.33</td>
</tr>
<tr>
<td>γ1 isotype</td>
<td>AR</td>
<td>14q32.33</td>
</tr>
<tr>
<td>γ2 isotype</td>
<td>AR</td>
<td>14q32.33</td>
</tr>
<tr>
<td>Partial γ3 isotype</td>
<td>AR</td>
<td>14q32.33</td>
</tr>
<tr>
<td>γ4 isotype</td>
<td>AR</td>
<td>14q32.33</td>
</tr>
<tr>
<td>IgG subclass ± IgA deficiency</td>
<td>?</td>
<td>–</td>
</tr>
<tr>
<td>α1 isotype</td>
<td>AR</td>
<td>14q32.33</td>
</tr>
<tr>
<td>α2 isotype</td>
<td>AR</td>
<td>14q32.33</td>
</tr>
<tr>
<td>e isotype</td>
<td>AR</td>
<td>14q32.33</td>
</tr>
<tr>
<td>IgA deficiency</td>
<td>Varied</td>
<td>–</td>
</tr>
<tr>
<td>Common variable immunodeficiency</td>
<td>Varied</td>
<td>–</td>
</tr>
</tbody>
</table>

* XL = X-linked; AR = autosomal recessive.

### TABLE 4–3

<table>
<thead>
<tr>
<th>Disease</th>
<th>Locus/Gene</th>
<th>Inheritance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe combined immunodeficiency (SCID)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB + SCID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jak3 deficiency</td>
<td>19p13.1/JAK3</td>
<td>AR</td>
</tr>
<tr>
<td>X-linked yc-chain</td>
<td>Xq13.1–q13.3</td>
<td>XL</td>
</tr>
<tr>
<td>TB-SCID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omenn syndrome</td>
<td>11p13/RAG1, RAG2</td>
<td>AR</td>
</tr>
<tr>
<td>RAG1 deficiency</td>
<td>11p13/RAG1</td>
<td>AR</td>
</tr>
<tr>
<td>RAG2 deficiency</td>
<td>11p13/RAG2</td>
<td>AR</td>
</tr>
<tr>
<td>Reticular dysgenesis</td>
<td>–</td>
<td>AR</td>
</tr>
<tr>
<td>Abnormal purine metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenosine deaminase (ADA) deficiency</td>
<td>20q13.2–q13.11</td>
<td>AR</td>
</tr>
<tr>
<td>Purine nucleoside phosphorlase (PNP) deficiency</td>
<td>14q13.1</td>
<td>AR</td>
</tr>
<tr>
<td>Hyper-IgM syndrome</td>
<td>Xq26.3–q27.1</td>
<td>XL</td>
</tr>
<tr>
<td>X-linked (CD40L deficiency)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Non-X-linked</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Major histocompatibility complex (MHC) deficiencies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MHC class I deficiency</td>
<td>6q21.3/TAP2</td>
<td>AR</td>
</tr>
<tr>
<td>MHC class II deficiencies</td>
<td>Multiple</td>
<td>AR</td>
</tr>
<tr>
<td>Other combined immunodeficiencies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD3 deficiencies</td>
<td>11q23/CD3E, CD3G</td>
<td>AR</td>
</tr>
<tr>
<td>IL-2 receptor α-chain deficiency</td>
<td>10p14–p15/IL2RA</td>
<td>AR</td>
</tr>
<tr>
<td>ZAP-70 deficiency</td>
<td>2q12/ZAP70</td>
<td>AR</td>
</tr>
</tbody>
</table>

* XL = X-linked; AR = autosomal recessive.
As noted above, a large number of specific genetic defects that lead to immunodeficiency have been described. Identification of these defects has provided an avenue for specific diagnosis, a basis for fundamental understanding of normal immune function, and rationale for some forms of targeted therapy.

Wiskott-Aldrich Syndrome (WAS) is an X-Linked Defect in Both B- and T-Cell Function

This rare syndrome is characterized by (1) recurrent infections, (2) hemorrhages secondary to thrombocytopenia, and (3) eczema. It typically manifests in boys within the first few months of life as petechiae and recurrent infections (e.g., diarrhea).

WAS is caused by numerous distinct mutations in a gene on the X chromosome (Xp11.22-11.23) that encodes a protein called WASP (Wiskott-Aldrich syndrome protein), which is expressed at high levels in lymphocytes and megakaryocytes. It binds members of the Rho family of guanosine triphosphatases (GTPases), which control many cellular processes, including cell morphology and mitogenesis. WASP itself controls assembly of actin filaments that are required to form microvesicles.

Cellular and humoral immunity are both impaired in WAS. Although levels of most immunoglobulins are normal or elevated, IgM is only about half of normal. Antibody responses to some antigens are normal, but responses to others may be absent. As many polysaccharide antigens, particularly some bacterial polysaccharides, elicit mainly IgM antibody responses, WAS patients are susceptible to infection with encapsulated organisms such as pneumococci.

Boys with WAS also have selective deficiencies in cell-mediated immunity. Numbers of CD4⁺ and CD8⁺ T cells are normal, but these children are largely anergic for cutaneous delayed hypersensitivity. Their lymphocytes respond normally to high levels in lymphocytes and megakaryocytes. It binds members of the Rho family of guanosine triphosphatases (GTPases), which control many cellular processes, including cell morphology and mitogenesis. WASP itself controls assembly of actin filaments that are required to form microvesicles.

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Boys with WAS also have selective deficiencies in cell-mediated immunity. Numbers of CD4⁺ and CD8⁺ T cells are normal, but these children are largely anergic for cutaneous delayed hypersensitivity. Their lymphocytes respond normally to plant lectins that are powerful T-cell mitogens (e.g., PHA), but poorly to specific antigens (e.g., Candida albicans). In addition, virus-specific cytotoxic T-cell immunity is usually absent, even though virus-specific antibody responses appear to be normal.

WAS patients typically have recurrent infections with Streptococcus pneumoniae, Haemophilus influenzae, and such opportunistic pathogens as P. jiroveci. They are also prone to viral infections such as CMV, and not infrequently die of disseminated herpes simplex or varicella. Thrombocytopenia may be severe (<30,000/μL), and the platelets are generally small. One third of these patients typically die of hemorrhage. Rarely, thrombocytopenia alone may be the sole manifestation of mutation in WAS.

A variety of autoimmune diseases may also complicate WAS, including autoimmune hemolytic anemia and thrombocytopenia, polyarthritis and vasculitis of coronary and cerebral arteries. These patients also have a high incidence of lymphoproliferative malignancies. The principal form of thrombocytopenia (nonimmune) is almost always cured by splenectomy. Bone marrow transplantation cures WAS in over 90% of cases.

Autoimmunity and Autoimmune Diseases

Autoimmune Disease Involves an Immune Response Against Self Antigens

Autoimmunity implies that the immune system can no longer differentiate between self- and non-self-antigens effectively. It was classically interpreted as an abnormal immune response that invariably caused disease, but it is now clear that autoimmune responses are common and are necessary in order to regulate the immune system. Anti-idiotype antibodies (antibodies against antigen-binding sites of immunoglobulins), are important in regulating the immune response; their presence is by definition an autoimmune response. When these regulatory mechanisms are in some way disrupted, uncontrolled production of autoantibodies or abnormal cell–cell recognition leads to tissue injury, and autoimmune disease results. While detecting specific autoantibodies is useful to diagnose autoimmune diseases, it is not sufficient for a designation of autoimmune disease. One must demonstrate that the autoimmune reaction (whether cellular or humoral) is directly related to the disease process. Autoimmune diseases may be organ-specific or generalized. At present, only a few diseases (e.g., Hashimoto’s thyroiditis, type 1 diabetes, SLE) fit this rigorous criterion.

An abnormal autoimmune response to self-antigens implies a loss of immune tolerance. Immune tolerance signifies a situation in which there is no measurable (or clinically consequential) immune response to specific (usually self) antigens. The reasons for loss of tolerance in autoimmune diseases is not understood. Experimental studies suggest that normal tolerance to self-antigens is an active process, and requires contact between self-antigens and immune cells. In the fetus, tolerance is readily established to antigens that cause vigorous immune responses in adults. There is extensive evidence that induction and maintenance of tolerance are active and ongoing immune activities that can be produced through a variety of mechanisms. Thus, tolerance is an active state in which an immune response is blocked or prevented. Induction of tolerance to an antigen is partly related to the dose of antigen to which cells are exposed.

Putative mechanisms of tolerance are divided into two categories: central and peripheral. Central tolerance is the processes by which self-reactive T and B lymphocytes are “deleted” during their maturation within the thymus and bone marrow, respectively. Developing self-reactive T cells recognize self peptides in the context of compatible MHC molecules and are induced to undergo apoptosis. These T cells are said to have been “negatively selected.” An analogous process occurs to B cells in the bone marrow. Peripheral tolerance is important in regulating T cells that escape intrathymic negative selection. These T lymphocytes are held in check in the periphery through anergy, suppression, and/or activation-induced cell death.

Theories of Autoimmunity

Inaccessible Self-Antigens

The simplest hypothesis to explain the loss of tolerance in autoimmune disease states that an immune reaction develops to a self-antigen not normally “accessible” to the immune system. Intracellular antigens are not exposed or released until some type of tissue injury releases them. At that time, an immune response develops. Examples of this type of response are antibody formation against spermatozoa, lens tissue, and myelin. Whether these autoantibodies can induce injury directly is another matter. In the context of compatible MHC molecules and are induced to undergo apoptosis. These T cells are said to have been “negatively selected.” An analogous process occurs to B cells in the bone marrow. Peripheral tolerance is important in regulating T cells that escape intrathymic negative selection. These T lymphocytes are held in check in the periphery through anergy, suppression, and/or activation-induced cell death.

Abnormal T Cell Function

Autoimmune reactions have been suggested to develop as a result of abnormalities in the T lymphocyte system. Most immune responses require T cell participation to activate antigen-specific
B cells. Thus, alterations in the number or functional activities of helper or suppressor T cells would be expected to influence one’s ability to mount an immune response. In fact, defects in T cells, particularly suppressor T cells, have been described in many autoimmune diseases. For example, there are reports of defective suppressor cell activity in human and experimental SLE. Lymphtocytotoxic antibodies have also been described in patients with lupus. Abnormalities in suppressor cell function characterize other autoimmune diseases, including primary biliary cirrhosis, thyroiditis, multiple sclerosis, myasthenia gravis, rheumatoid arthritis, and scleroderma. However, the critical question is whether these alterations in suppressor cell function cause these diseases or whether they merely represent an epiphenomenon. Defects in suppressor cell function have also been described in persons with no evidence of autoimmune disease.

There has also been interest in abnormalities in helper T cell function in autoimmune disease. Helper T cells are defined by their role in antigen-specific B cell activation. It is believed that these cells maintain the helper T cell tolerance induced by low doses of antigen. Recent evidence indicates that these cells become autoreactive in many autoimmune diseases. One key mechanism in autoimmunity is DNA hypomethylation caused by drugs and other agents. This effect leads to upregulation of leukocyte function antigen 1 (LFA-1) and B cell activation independent of antigen. An example of this T cell autoreactivity and loss of antigen specificity is drug-induced lupus. Experimentally, it is also possible to “break” this type of tolerance by altering an antigen so that the helper cell is activated and triggers the B cells. An example is when an antigen is modified by partial degradation or complexing with a carrier protein. Some rheumatic diseases are marked by autoantibodies to partially degraded connective tissue proteins, such as collagen or elastin. In some drug-induced hemolytic anemias, antibody against a drug causes hemolysis when the drug binds to erythrocyte membranes.

Molecular Mimicry
Another mechanism by which the helper T cell tolerance is overcome involves antibodies against foreign antigens that cross-react with self-antigens. Here helper T cells function “correctly” and do not induce autoantibody formation. Rather, the efferent limb of the immune response is abnormal. Thus, in rheumatic heart disease, antibodies against streptococcal bacterial antigens cross-react with antigens from cardiac muscle—a phenomenon known as molecular mimicry.

Polyclonal B-Cell Activation
Loss of tolerance may also involve polyclonal B cell activation, in which B lymphocytes are directly activated by complex substances that contain many antigenic sites (e.g., bacterial cell walls and viruses). Development of rheumatoid factor in rheumatoid arthritis, anti-DNA antibodies in lupus erythematosus, and other autoantibodies has been described after bacterial, viral, and parasitic infections.

Tissue Injury in Autoimmune Diseases
Autoimmune diseases have traditionally been considered to be prototypic of immune complex disease, which involves complexes that form either in the circulation or in tissues. Thus, type II (cytotoxic) and type III (immune complex) hypersensitivity reactions are implicated as the cause of tissue injury in most types of autoimmune diseases. Although it is probably true that these hypersensitivity reactions explain most autoimmune tissue injury, the story is more complicated. In some types of autoimmune diseases, T cells sensitized to self-antigens (such as thyroglobulin) may directly cause tissue injury (type IV reaction), but it is not clear to what extent.

Another mechanism of tissue injury is ADCC. Antibodies against an antigen expressed at the cell membrane lead to destruction of that cell. Thus, antibodies against parietal cell H+ / K+ -ATPase are important in the pathogenesis of atrophic gastritis. However, not all autoantibodies cause disease via cytotoxicity. In antireceptor antibody diseases, such as Graves disease and myasthenia gravis, antibody binds a receptor but the disease process reflects either activation or inactivation of the receptor, rather than cell loss. In Graves disease, autoantibody against TSH receptor acts as an agonist to stimulate thyroid hormone production, whereas in myasthenia gravis the autoantibody prevents acetylcholine binding to its receptor, thereby impairing neuromuscular synaptic transmission. Anti-insulin receptor antibodies have also been described in diseases such as acanthosis nigricans and ataxia telangiectasia, in which some patients exhibit a form of diabetes characterized by extreme insulin resistance.

Type III hypersensitivity reactions (immune complex disease) explain tissue injury in some types of autoimmune diseases. The prototypical disease in this category is SLE. In this disorder, DNA–anti-DNA complexes formed in the circulation (or at local sites) are deposited in tissues, where they induce inflammation and injury, such as occurs in vasculitis and glomerulonephritis. Other examples are rheumatoid arthritis, scleroderma, polymyositis/dermatomyositis, and Sjögren syndrome. All of these disorders are characterized by immune phenomena and are classified under the rubric “collagen vascular” diseases. The clinical manifestations are systemic and many organs and tissues are typically involved. By contrast, cytotoxic (type II-mediated) autoimmune reactions are, for the most part, organ specific.

Systemic Lupus Erythematosus Is a Prototypical Systemic Immune Complex Disease
SLE is a chronic, autoimmune, multisystem, inflammatory disease that may involve almost any organ but characteristically affects kidneys, joints, serous membranes, and skin. Autoantibodies are formed against a variety of self-antigens, including plasma proteins (complement components, clotting factors) and protein-phospholipid complexes that cell surface antigens (lymphocytes, neutrophils, platelets, erythrocytes), intracellular cytoplasmic components (microfilaments, microtubules, lysosomes, ribosomes, RNA) and nuclear DNA, ribonucleoproteins, and histones. The most important diagnostic autoantibodies are those against nuclear antigens—in particular, antibody to double-stranded DNA and to a soluble nuclear antigen complex that is part of the spliceosome and termed Sm (Smith) antigen. High titers of these two antinuclear antibodies (ANAs) are nearly pathognomonic of SLE but are not directly cytotoxic. Antigen–antibody complexes deposit in tissues, leading to the characteristic vasculitis, synovitis, and glomerulonephritis. For this reason, SLE is a prototype of type III hypersensitivity reactions. Occasionally, directly cytotoxic antibodies are present, particularly antibodies against cell surface antigens of leukocytes and erythrocytes.

The prevalence of SLE varies worldwide and in North America and northern Europe is 40 / 100,000. In the United States, it appears to be more common and severe in African-Americans and Hispanics, although socioeconomic factors may in part be responsible. Over 80% of cases are in women of childbearing age, and SLE may strike as many as 1 in 700 women in this age group.
The etiology of SLE is unknown. The presence of numerous autoantibodies, particularly ANAs, suggests a breakdown in immune surveillance mechanisms that leads to a loss of tolerance. Many manifestations of SLE result from tissue injury caused by immune complex-mediated vasculitis. Other clinical manifestations (e.g., thrombocytopenia or the secondary antiphospholipid syndrome) are caused by autoantibodies against serum components or molecules on cell membranes. However, the diagnostically helpful ANAs are not incriminated in the pathogenesis of SLE. There appear to be many factors that predispose to the development of SLE (Fig. 4-20).

Although there was at one time interest in C-type viral particles in experimental murine models of SLE, most evidence argues against a viral etiology for human SLE. The clear female predisposition for SLE is true for many autoimmune diseases, and sex hormones may in part be the explanation. Immune responses in animals are strongly influenced by sex hormones. In mouse models of SLE, estrogens accelerate disease progression, while androgens have a moderating effect. Whether the course of human SLE is influenced in the same manner is controversial.

Experimentally, estrogens reportedly increase the likelihood of overcoming immune tolerance.

Some genetic predisposition to lupus is suggested by a higher prevalence in some ethnic groups, some families, and monozygotic twins. The latter exhibit a concordance of 20% to 30%, suggesting that both genetic and environmental factors play a role. The incidence of SLE (and other autoimmune diseases) is higher among persons who express certain MHC class II DR and DQ antigens. These gene products participate in two unlinked functions, namely, immunoregulation and the effector limb of the immune response. Thus, the HLA-B8 haplotype, which is often found in association with autoimmune diseases, is also associated with the DR antigens in certain immunoregulatory abnormalities. These disorders include abnormal lymphocyte responses to antigens, decreased numbers of circulating suppressor cells, and increased numbers of circulating B cells. Among the effector functions associated with these HLA haplotypes is a decrease in C3b receptors on cells that clear circulating immune complexes.

A critical role for the D/DR region in the pathogenesis of SLE is supported by the observation that inherited deficiencies of certain complement components, particularly C2, C4, and C1q are associated with an increased incidence of the disease. The genes that encode these early complement components are within the HLA region, close to the D/DR locus.

Production of autoantibodies against many antigens is characteristic of SLE, but the precise mechanisms underlying B cell hyperreactivity are unknown. Two general hypotheses have been advanced. One attributes the disease to a nonspecific, polyclonal B cell activation, although the nature of the stimulus is speculative. The second hypothesis holds that the antibodies formed in SLE represent a response to specific antigenic stimulation. Support for the latter supposition comes from the observation that with time the antibodies of SLE demonstrate gene rearrangements and mutations that are typical of an antigen-driven response. Moreover, a patient with SLE often has antibodies to more than one epitope on a single antigen, further suggesting a primary role for an antigen-driven process. Although inciting antigens have not been identified, a number of factors render normal body constituents more immunogenic, including infection, ultraviolet light exposure, and other environmental agents that damage cells. Foreign, e.g., viral, antigens might induce molecular mimicry, although direct evidence is lacking.

Whether or not the autoimmune response in SLE is primarily driven by antigens, the variety of autoantibodies strongly suggests a general disturbance of immune tolerance. CD4+ T cells become autoreactive secondary to DNA hypomethylation. These autoreactive CD4+ T cells over-express the cell adhesion molecule LFA-1 (CD11a), which stabilizes the interaction between T cells and APCs such as macrophages. These autoreactive CD4+ T cells have been best described in mouse models; no consistent defect in the T-suppressor cell population has been found in humans. Among other immunologic abnormalities described in SLE is an increase in circulating levels of IL-6, which in these patients is associated with B-cell differentiation.

The evidence for the hypothesis that SLE is predominantly mediated by type III hypersensitivity includes the occurrence of circulating immune complexes, which contain nuclear antigen; the presence of immune complexes in injured tissues, as identified by immunofluorescence; and the observation that immune complexes can be extracted from tissues that contain nuclear antigens. Thus, there is good reason to believe that the bulk of the injury in lupus is due to deposition of circulating immune complexes.
against self-antigens, particularly against DNA. Additional evidence suggests that under certain conditions immune complex formation also occurs in situ—that is, in tissues rather than in the circulation. Examples include antibody formed against connective tissue components and perhaps the membranous form of lupus glomerulonephritis. Type II hypersensitivity reactions also participate in lupus, since cytotoxic antibodies against leukocytes, erythrocytes, and platelets have been described.

**PATHOLOGY AND CLINICAL FEATURES**: Because circulating immune complexes deposit in almost all tissues, virtually every organ in the body can be involved.

**Skin involvement** (see Chapter 24) is common and is manifested by an erythematous rash in sun-exposed sites, a malar "butterfly" rash being the most characteristic. Microscopically, the skin exhibits a perivascular lymphoid infiltrate and liquefactive degeneration of the basal cells. Immunofluorescence studies reveal immunoglobulin and complement deposition at the dermal–epidermal junction ("lupus band").

**Joint disease** is the most common manifestation of SLE; over 90% of patients have polyarthralgia. An inflammatory synovitis occurs, but unlike rheumatoid arthritis, joint destruction is unusual.

**Renal disease**, in particular glomerulonephritis, afflicts three fourths of patients with SLE. Immune complexes between DNA and IgG antibodies to double-stranded DNA deposit in glomeruli and lead to glomerulonephritis (see Chapter 16). Although glomerulonephritis is the most common renal manifestation of SLE, interstitial nephritis or (rarely) vasculitis can also be seen. In many of these cases, immunoglobulins and complement are present in the interstitium and blood vessels of the kidney.

**Serous membranes** are commonly involved in SLE. More than one third of patients have pleuritis and pleural effusion. Pericarditis and peritonitis occur, but less frequently.

**Disorders of the respiratory system** in SLE occur frequently. The clinical manifestations are diverse, ranging from pleural disease to upper airway involvement and pulmonary parenchymal disease. Pneumonitis is thought to be caused by deposition of immune complexes in alveolar septa and is associated with patchy acute inflammation. Progressive interstitial fibrosis develops in some patients. An increased incidence of pulmonary hypertension has also been reported.

**Cardiac involvement** (see Chapter 11) is often encountered in SLE, although congestive heart failure is rare and is usually associated with myocarditis. All layers of the heart may be involved, with pericarditis being the most common finding. Libman-Sacks endocarditis, which is usually not clinically significant, is characterized by small nonbacterial vegetations on valve leaflets. These lesions should be differentiated from the larger, bulkier vegetations of bacterial endocarditis or the vegetations of rheumatic endocarditis, which are confined to the lines of valve closure.

**Disease of the CNS** is a life-threatening complication of lupus. Vasculitis is the common underlying lesion, leading to hemorrhage and infarction of the brain, which are often lethal.

**Antiphospholipid antibodies** are encountered in one third of patients with SLE. This autoimmune phenomenon predisposes patients to thromboembolic complications, including stroke, pulmonary embolism, deep venous thrombosis, portal vein thrombosis, and spontaneous abortions.

Other organ involvement is less frequent and is often due to vasculitis. Lesions in the spleen are characterized by thickening and concentric fibrosis of the penicillary arteries, the so-called "onion-skin" pattern.

The clinical course of SLE is highly variable, typically with exacerbations and remissions. Because of immunosuppressive therapies, better recognition of mild forms of the disease and improved antihypertensive medications, overall 10-year survival approaches 90%. The worst prognosis is in patients with severe renal or CNS disease and those with systolic hypertension.

### Lupus-like Diseases Feature Immune Complexes

#### Drug-Induced Lupus

A syndrome that resembles SLE can occur following use of certain drugs, most notably procainamide (for arrhythmias), hydralazine (for hypertension), and isoniazid (for tuberculosis). Drug-induced lupus ranges from asymptomatic laboratory abnormalities (positive ANA test result) to a syndrome that is clinically similar to SLE. Unlike SLE, drug-induced lupus shows no sex predominance and most patients are over 50 years old. Factors that predispose to this syndrome include large daily doses of the offending drug, slow drug-acetylator status and (in hydralazine-induced lupus) HLA-DR4 genotype. As in SLE, deposition of immune complexes is a feature of drug-induced lupus. Patients with drug-induced lupus typically exhibit constitutional signs, polyarthritis, pleuritis, and a positive ANA test result. In addition, they may develop rheumatoid factor, false-positive tests for syphilis, and a positive Coombs test. Unlike in SLE, renal and CNS involvement rarely occurs, and it is unusual to find antibodies to double-stranded DNA and Sm antigen. Autoantibodies to histones (which account for the positive ANA test result) are typical of drug-induced lupus. As in idiopathic SLE, autoreactive CD4⁺ T cells have been implicated in polyclonal B cell activation. Discontinuation of the offending drug is ordinarily curative.

#### Chronic Discoid Lupus

The most common variety of localized lupus erythematosus is a cutaneous disorder, although identical lesions can occur in some cases of SLE. Erythematous, depigmented, and telangiectatic plaques are found most commonly on the face and scalp. Deposition of immunoglobulins and complement at the dermal–epidermal interface in chronic discoid lupus is similar to that observed in SLE. However, unlike SLE, uninvolved skin contains no immune deposits. Although ANAs develop in about one third of patients, antibodies to double-stranded DNA and Sm antigen are not encountered. Most patients with discoid lupus are not otherwise ill, but up to 10% eventually manifest features of SLE.

#### Subacute Cutaneous Lupus

Subacute cutaneous lupus is characterized by papular and annular lesions, principally on the trunk. The disorder is aggravated by exposure to ultraviolet light (via sunlight), although lesions eventually resolve without scarring. Antibodies to a ribonucleoprotein complex (SS-A or Ro antigen) and an association with HLA-DR3 genotype are characteristic.

#### Sjögren Syndrome Targets the Salivary and Lacrimal Glands

Sjögren syndrome (SS) is an autoimmune disorder characterized by keratoconjunctivitis sicca (dry eyes) and xerostomia (dry mouth) in the absence of other connective tissue disease. This definition separates primary SS from secondary types that are occasionally associated with other disorders of connective tissue, such as SLE, rheumatoid arthritis, scleroderma, and polymyositis.
The primary type is also frequently associated with involvement of other organs, including the thyroid, lung, and kidney.

Primary SS is the second most common connective tissue disorder after SLE and affects up to 3% of the population. Like most autoimmune diseases, it occurs mostly in women, 30 to 65 years old. There are strong associations between primary SS and certain MHC types, notably HLA-B8, Dw3, HLA-DR3, DRw-52, and HLA-Dw2, as well as MT2, a B cell alloantigen. Familial clustering occurs, and these families also exhibit a high prevalence of other autoimmune diseases.

**PATHOGENESIS:** The cause of SS is unknown. The production of autoantibodies, particularly ANAs against DNA or nonhistone proteins, typically occurs in patients with SS. Autoantibodies to soluble nuclear nonhistone proteins, especially antigens SS-A (Ro) and SS-B (La), are found in half of patients with primary SS and are associated with more-severe glandular and extraglandular manifestations. Autoantibodies to DNA or histones are rare, and their presence suggests secondary SS associated with lupus. Organ-specific autoantibodies, e.g., against salivary gland antigens, are distinctly uncommon. As in SLE, it remains controversial whether the autoantibodies in SS mainly reflect polyclonal B cell activation or is essentially antigen-driven, although these processes are not mutually exclusive.

SS has become the prototype for investigation of a viral etiology for autoimmune disease. Particular attention has been paid to possible roles of EBV and human T cell leukemia virus-1 (HTLV-1). Although it is still difficult to assign a role for EBV in the pathogenesis of SS, there is evidence that reactivation of this virus may be involved in perpetuating SS, polyclonal B cell activation, and development of lymphoma. In Japan, the seroprevalence of HTLV-1 is four times as common as in many other countries. HTLV-I antibodies are more common and specific for the diffuse form of scleroderma, which is associated with the “CREST” variant of the disease (see below). The Scl-70 autoantibody is the most common and specific for the diffuse form of scleroderma, and is seen in 60% of these patients. However, there is no correlation between ANA titer and disease severity.

**PATHOLOGY AND CLINICAL FEATURES:** SS is characterized by an intense lymphocytic infiltrate in the salivary and lacrimal glands (Fig. 4-21). Focal lymphocytic infiltrates in these glands are initially observed in a periductal distribution. Most lobules are affected, especially the centers of the lobules. Well-defined germinal centers are rare. The lymphoid infiltrates destroy acini and ducts. The latter often become dilated and filled with cellular debris. The glandular stroma is preserved, which appearance helps to differentiate this disorder from lymphoma. The lymphocytic infiltrates in the glands are predominantly CD4+ T cells, but a few B cells are also present. In the late stage of the disease, the glands atrophy and may be replaced by hyalinized tissue and fibrosis. Owing to the absence of tears, the corneas become dry and fissured and may ulcerate. The lack of saliva causes atrophy, inflammation, and cracking of the oral mucosa. The pathology of the salivary and lacrimal glands is described in greater detail in Chapter 25.

Involvement of extraglandular sites is also common in SS. Pulmonary disease occurs in most patients, particularly bronchial gland atrophy in association with lymphoid infiltration. This causes thick tenacious secretions, focal atelectasis, recurrent infections, and bronchiectasis. The gastrointestinal tract is also affected, and many patients have difficulty swallowing (dysphagia). Esophageal submucosal glands are infiltrated by lymphocytes. In addition, atrophic gastritis occurs secondary to lymphoid infiltration of the gastric mucosa. Liver disease, especially primary biliary cirrhosis, is present in 5% to 10% of patients with SS and is associated with destruction of intrahepatic bile ducts and nodular lymphoid infiltrates. Interstitial nephritis and chronic thyroiditis occasionally accompany SS. SS is associated with a 40-fold increased risk of malignant lymphoma, probably through B-cell clonal expansion.

**Scleroderma (Progressive Systemic Sclerosis) Is an Autoimmune Disease of Connective Tissue**

Scleroderma is characterized by vasculopathy and excessive collagen deposition in the skin and internal organs, such as the lung, gastrointestinal tract, heart, and kidney. It is four times as common in women as in men, mostly in persons 25 to 50 years of age. Familial incidence has been reported. There is an association between HLA-DQβ1 and the formation of the autoantibodies characteristic of this disease.
Rheumatoid factor is commonly present in scleroderma and autoantibodies are occasionally directed against other issues, such as smooth muscle, thyroid gland, and salivary glands. Antibodies against collagen types I and IV have also been described.

Cellular immune derangements are also seen in patients with progressive systemic sclerosis. Reduced circulating CD8⁺ T suppressor cells, evidence of T cell activation, alterations in functions mediated by IL-1 and elevated IL-2, and soluble IL-2 receptor occur in active disease. Increased levels of IL-4 and IL-6 have also been described. Tissues exhibit active mononuclear inflammation, which precedes the development of the vasculopathy and fibrosis characteristic of this disease. In these infiltrates, increased numbers of CD4⁺ and γδ⁺ T cells (which adhere to fibroblasts) are present, as well as macrophages. Mast cells (degranulated) are also present in skin of these patients. The incidence of other autoimmune disorders, such as thyroiditis and primary biliary cirrhosis, is increased in patients with progressive systemic sclerosis. Circulating male fetal cells have been demonstrated in blood and blood vessel walls of many women with scleroderma who bore male children many years before the disease began. It has been suggested that scleroderma in these patients is similar to graft-versus-host disease (GVHD).

Progressive systemic sclerosis is characterized by widespread excessive collagen deposition. Although the cause remains unclear, there is emerging evidence that there is expansion and activation of fibrogenic clones of fibroblasts. These clones behave autonomously and display augmented procollagen synthesis, including increased circulating levels of type III collagen aminopropeptide. Several factors may be responsible for this fibroblast activation. The γδ⁺ T cells adhere to fibroblasts and may induce activation via cytokine generation. TGF-β is elevated in tissues of these patients, as are IL-1 and IL-4, all of which stimulate fibroblast proliferation and collagen biosynthesis. IL-6—which is upregulated matrix metalloproteinase and is important in modulation of collagen metabolism—is also elevated. Activated fibroblasts themselves produce cytokines and growth factors, such as IL-1, prostaglandin E (PGE), TGF-β, and PDGF, which may in turn serve to activate other fibroblasts. Finally, activated fibroblasts also express the adhesion molecule ICAM-1 on their surface, which may be important in adherence of T cells and macrophages and their subsequent activation.

**PATHOLOGY:** The skin in scleroderma initially shows edema and then induration. The thickened skin exhibits a striking increase in collagen fibers in the reticular dermis; thinning of the epidermis with loss of rete pegs; atrophy of dermal appendages; hyalinization and obliteration of arterioles; and variable mononuclear infiltrates, consisting primarily of T cells. The stage of induration may progress to atrophy or revert to normal. Increases in collagen deposition can also occur in synovia, lungs, gastrointestinal tract, heart, and kidneys.

Lesions in the arteries, arterioles, and capillaries are typical, and in some cases may be the first demonstrable pathologic finding in the disease. Initial subintimal edema with fibrin deposition is followed by thickening and fibrosis of the vessel and reduplication or fraying of the internal elastic lamina. The involved vessels can become severely restricted in terms of blood flow and may become occluded by thrombus.

The kidneys are involved in more than half of patients with scleroderma. They show marked vascular changes, often with focal hemorrhage and cortical infarcts (see Chapter 16). Among the most severely affected vessels are the interlobular arteries and afferent arterioles. Early fibromuscular thickening of the subintima causes luminal narrowing, which is followed by fibrosis (Fig. 4-22). Fibrinoid necrosis is commonly seen in afferent arterioles. Glomerular alterations are nonspecific and focal changes range from necrosis extending from the afferent arterioles to fibrosis. There is diffuse deposition of immunoglobulin, complement, and fibrin in affected vessels early in the disease, probably because of increased vascular permeability.

Diffuse interstitial fibrosis is the primary abnormality in lungs. The disease can progress to end-stage pulmonary fibrosis, so-called honeycomb lung.

Most patients with scleroderma have patchy myocardial fibrosis and in about one fourth of cases, more than 10% of the myocardium is involved. These lesions result from focal myocardial necrosis, which may reflect focal ischemia secondary to a Raynaud-like reactivity of coronary microvasculature.

Progressive systemic sclerosis can involve any portion of the gastrointestinal tract. Esophageal dysfunction is the most common and troublesome gastrointestinal complication. Atrophy of smooth muscle and fibrous replacement are seen in the lower esophagus. The small bowel is often involved, with patchy fibrosis, principally of the muscular layers.

**CLINICAL FEATURES:** Scleroderma presents as two distinct clinical categories, a generalized (progressive systemic) form and a limited variant. Progressive systemic sclerosis (diffuse scleroderma) is characterized by severe and progressive disease of skin and early onset of all or most of the associated abnormalities of visceral organs. Symptoms
usually begin with Raynaud phenomenon, namely, intermittent episodes of ischemia of fingers, marked by pallor, paresthesias, and pain. These symptoms are accompanied or followed by edema of fingers and hands, tightening and thickening of skin, polyarthralgia, and complaints referable to involvement of specific internal organs. The typical patient with generalized scleroderma exhibits “stone facies,” owing to tightening of facial skin and restricted motion of the mouth. Progression of vascular lesions in fingers leads to ischemic ulcerations of fingertips, with subsequent shortening and atrophy of digits. Many patients suffer from painful tendinitis and joint pain is common. Esophageal involvement causes hypomotility and dysphagia. Fibrosis in the small bowel interferes with intestinal mobility, with consequent bacterial overgrowth and secondary malabsorption. Dyspnea on exertion is the initial symptom of pulmonary fibrosis in scleroderma, occurring in more than half of patients. The lung disease progresses to dyspnea at rest and eventually to respiratory failure. Patients with long-standing disease are at risk for development of pulmonary hypertension and cor pulmonale. Although most patients with scleroderma have some myocardial fibrosis, congestive heart failure is uncommon. However, ventricular arrhythmias can cause sudden death.

The vascular involvement of the kidneys in generalized scleroderma is responsible for so-called scleroderma renal crisis the sudden onset of malignant hypertension, progressive renal insufficiency, and frequently, microangiopathic hemolytic anemia. The syndrome, which reflects ischemic injury to the kidneys, usually occurs in the first few years of the disease and is marked by conspicuously elevated levels of circulating renin.

The so-called limited form of scleroderma is a milder disease than generalized scleroderma. Typically, such patients exhibit skin involvement, particularly the face and fingers. A variant within the spectrum of limited scleroderma is CREST syndrome. CREST is characterized by calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia. The limited variant usually does not entail severe systemic involvement early in disease but later can progress, primarily in the form of diffuse interstitial lung fibrosis. Patients with limited scleroderma often possess circulating anticitrulline antibodies.

### Mixed Connective Tissue Disease Combines Features of SLE, Scleroderma, and Dermatomyositis

The incidence of mixed connective tissue disease (MCTD) is unknown. Between 80% and 90% of patients are female, and most are adults (mean age, 37 years). Those symptoms that are characteristic of SLE include rash, Raynaud phenomenon, arthritis, and arthralgias. The characteristics of scleroderma are swollen hands, esophageal hypomotility, and pulmonary interstitial disease. Some patients also develop symptoms suggestive of rheumatoid arthritis. Patients with MCTD have been reported to respond well to corticosteroid therapy, although some studies have challenged this assertion.

### Immune Reactions to Transplanted Tissues

Antigens encoded by the MHC on chromosome 6 are critical immunogenic molecules that can stimulate rejection of transplanted tissues. Thus, optimal graft survival occurs when recipient and donor are closely matched with regard to histocompatibility antigens. In practice, an exact HLA match is obtained infrequently, except in the case of transplantation between monozygotic twins. Vigilant monitoring of the functional status of the graft and immunosuppressive therapy is thus required after transplantation. In recent years, therapeutic advances (e.g., cyclosporine and tacrolimus) have greatly improved transplant success rates, even when there is a degree of histo-incompatibility. When host-versus-graft immune reactions (rejection) occur, any combination of immune responses may injure the graft.

Both T-cell-mediated and antibody-mediated reactions are important in the pathophysiology of transplant rejection. Antigen-presenting cells, specifically those bearing foreign MHC molecules in the graft, are recognized by host CD8+ cytotoxic T lymphocytes which mediate tissue injury; and host CD4+ T helper cells which augment antibody production, induce IFN-γ production, and activate macrophages. Induction of IFN-γ leads to enhanced MHC expression with amplification of tissue injury. Host APCs also process foreign donor antigens leading to CD4+ T-mediated delayed type hypersensitivity and CD4+ T-mediated antibody production.

Transplant rejection reactions have been traditionally categorized as “hyperacute, acute, and chronic” rejection, based on the clinical tempo of the response and on the pathophysiologic mechanisms involved. However, in practice, there can be overlap of features and ambiguity in diagnosis. The diagnosis of transplant rejection is further complicated by toxic effects of immunosup-
pressive drugs and by the potential for either mechanical problems (e.g., vascular thrombosis) or recurrence of original disease (e.g., some types of glomerulonephritis). The next sections illustrate rejection in the context of renal transplantation. Similar responses occur in other transplanted tissues, although each transplanted tissue type exhibits its own unique problems.

**Hyperacute Rejection Occurs Within Minutes to Hours after Transplantation**

Hyperacute rejection is manifested clinically as a sudden cessation of urine output, along with fever and pain in the area of the graft site. This immediate rejection is catastrophic and necessitates prompt surgical removal of the kidney. The histologic features of hyperacute rejection within the transplanted kidney are vascular congestion, fibrin–platelet thrombi within capillaries, neutrophilic vasculitis with fibrinoid necrosis, prominent interstitial edema, and neutrophilic infiltrates (Fig. 4-23A). This form of rejection is mediated by preformed anti-HLA antibodies and complement activation products, including chemotactic and other inflammatory mediators. Fortunately, hyperacute rejection is not common when appropriate pretransplantation antibody screening is performed.

**Acute Rejection Is Seen within the First Few Weeks or Months after Transplantation**

Acute rejection is characterized by abrupt onset of azotemia and oliguria, which may be associated with fever and graft tenderness. A needle biopsy is often used to differentiate between acute rejection and acute tubular necrosis or toxicity from immunosuppressive agents. Findings vary depending whether the rejection is primarily cellular or humoral. In the former case, microscopic findings include interstitial infiltrates of lymphocytes, and macrophages, edema, lymphocytic tubulitis and tubular necrosis (see Fig. 4-23B). The acute humoral form, sometimes called rejection vasculitis, shows vascular damage manifested as arteritis, fibrinoid necrosis, and thrombosis. Vascular involvement is an ominous sign because it usually means the rejection episode will be refractory to therapy. Acute rejection most typically involves both cell-mediated and humoral mechanisms of tissue damage. If detected in its early stages, acute rejection can be reversed with immunosuppressive therapy.

**Chronic Rejection Appears Months to Years after Transplantation**

Chronic rejection typically develops progressive azotemia, oliguria, hypertension, and weight gain over a period of months. The dominant histologic features are arterial and arteriolar intimal thickening causing vascular stenosis or obstruction, thickened glomerular capillary walls, tubular atrophy, and interstitial fibrosis (see Fig. 4-23C). The interstitium often exhibits scattered mononuclear infiltrates and tubules contain proteinaceous casts. Chronic rejection may be the end-result of repeated episodes of cellular rejection, either asymptomatic or clinically apparent. This advanced state of damage does not respond to therapy. As in the clinical diagnosis, histologic features of acute and chronic rejection may overlap and vary in degree, so that clear distinction may not be possible on renal biopsy.

**Graft-Versus-Host Disease Occurs When Donor Lymphocytes Recognize and React to the Recipient**

The advent of transplantation of allogenic (donor) bone marrow or HSCs into patients with hematogenous malignancies or severe connective tissue disorder, has allowed treatment of previously terminal conditions or conditions which were refractory to standard treatment. To allow engraftment of the new bone marrow to the host, the patient’s native bone marrow and...
immune system must be “conditioned” (ablated) usually by cytotoxic drugs, sometimes plus radiation. Immunocompetent lymphocytes, if present in the grafted marrow, may react to—“reject”—host tissues, leading to GVHD. GVHD can also occur when a profoundly immunodeficient patient is transfused with blood products containing HLA-incompatible lymphocytes.

The major organs affected in GVHD are skin, gastrointestinal tract, and liver. The skin and intestine exhibit mononuclear cell infiltrates and epithelial cell necrosis. The liver displays periportal inflammation, damaged bile ducts and liver cell injury. Clinically, acute GVHD manifests as rash, diarrhea, abdominal cramps, anemia, and liver dysfunction. The chronic form of GVHD is characterized by dermal sclerosis, sicca syndrome (dry eyes and mouth due to chronic inflammation of lacrimal and salivary glands), and immunodeficiency. Treatment of GVHD requires immunosuppressive therapy. Patients, especially those with chronic GVHD, may be at a higher risk for opportunistic infections, e.g., fungal infection such as invasive aspergillosis are often life-threatening.

**Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome**

AIDS is the most common immunodeficiency state worldwide. It is mainly caused by HIV-1, although a small minority of patients are infected with HIV-2, primarily in western Africa. Persons infected with HIV-1 exhibit a variety of immunologic defects, the most devastating of which is a complete eventual loss of cellular immunity, which is progressive if not treated with appropriate HAART. As a result, catastrophic opportunistic infections are virtually inevitable if left untreated. The relentless progression of HIV infection is now recognized as a continuum that extends from an initial asymptomatic stage to the immune depletion that characterizes patients with overt AIDS, and the continuum is often referred to as HIV/AIDS. The basic lesion is infection of CD4+ (helper) T lymphocytes by HIV, which leads to depletion of this cell population and consequent impaired immune function and dysregulation. As a result, rather than dying of HIV infection itself, patients with AIDS usually die of opportunistic infections. There is also a high incidence of malignant tumors, principally B-cell lymphomas and Kaposi sarcoma. Finally, infection of the CNS with HIV often leads to an array of syndromes ranging from minor cognitive or motor neuron disorders to frank dementia.

**EPIDEMIOLOGY:** AIDS was first reported in the United States in 1981, with a report of *Pneumocystis carinii* pneumonia in homosexual men. The starting time for this human epidemic is uncertain: although antibodies to HIV have been found in stored blood from the Congo Republic dating to 1959, sporadic cases of diseases that can retrospectively be attributed to HIV certainly occurred in Africa during the 1960s. By the late 1970s, clusters of strange infectious diseases in New York and Miami among homosexual men, intravenous drug users, and Haitians are now recognized as having been secondary to HIV. By 1982, these unusual infections were associated with Kaposi sarcoma and considered to reflect an underlying immune deficiency. Thus, the acronym “AIDS” was coined. At the same time, it became clear that AIDS was spread by contact with blood of persons suspected of bearing an infectious agent. In addition to homosexual men and intravenous drug users who shared needles, persons at risk were identified among recipients of whole blood and blood products, especially hemophiliacs, heterosexual contacts, and infants born to female drug users. In 1983, the responsible virus, now called HIV-1, was identified. Development of a first-generation serologic test to detect antibodies to HIV-1 in 1985 permitted accurate diagnosis and allowed for improved public health measures. Thus, donations of blood and plasma have been screened for HIV-1 antibodies, and clotting factor concentrates used to treat hemophilia are processed to inactivate HIV.

Although AIDS is believed to have originated in sub-Saharan Africa, it is now a worldwide pandemic. The spread of HIV is attributable to the ease of international travel and enhanced population mobility, which in many societies have coincided with a rapid increase in sexual promiscuity and sexually transmitted diseases. Presently, over 40 million people are infected with HIV.

By the mid-1990s more than 1 million HIV-positive persons were reported in the United States. Originally, homosexual men represented two-thirds of these cases, and 30% were accounted for by intravenous drug users and their sexual partners. However, because of behavioral changes, the prevalence of infection among homosexuals has decreased. Men account for the majority of AIDS cases in the United States, although the prevalence in women continues to increase.

Inhabitants of sub-Saharan Africa suffer more from the ravages of AIDS than persons in other regions. Although accurate statistics from this area are not as readily available as in industrialized countries, in parts of sub-Saharan Africa it is estimated that 25% of the population is HIV-positive. The epidemiologic pattern differs from that in the United States, in that African patients rarely report homosexuality or intravenous drug use. The sex ratio for AIDS in Africa shows only a slight male predominance, pointing to a predominance of heterosexual spread of the infection.

Many cases of AIDS have been reported in western Europe. As in the United States, most have been in homosexual men, intravenous drug users and their sexual partners, and prostitutes. AIDS is being reported increasingly in Asia, and some countries on that continent (Thailand, India, and China) have described an exponential increase in the numbers of HIV infections.

**HIV is Transmitted by Contact with Blood and Certain Body Fluids, and Through Sexual Activity**

Save for intravenous drug users and transfusion recipients, AIDS is transmitted principally as a venereal disease, both homosexually and heterosexually. Transmission to newborns via breast milk is a concern in the developing world. Significant amounts of HIV have been isolated from blood, semen, vaginal secretions, breast milk, and cerebrospinal fluid. Except for the latter, HIV in these fluids is not inactivated. 

Transmission to newborns via breast milk is a concern in the developing world. Significant amounts of HIV have been isolated from blood, semen, vaginal secretions, breast milk, and cerebrospinal fluid. Except for the latter, HIV in these fluids is not inactivated. 

Among homosexual men, the receptive partner in unprotected anal intercourse is at particularly high risk of becoming infected with HIV. The virus is transmitted from semen through tears in the rectal mucosa and it can infect epithelial cells of the rectum directly. In heterosexual contact, transmission from male to female is more likely than the reverse, perhaps reflecting the greater concentration of HIV in semen than in vaginal fluids. The risk of infecting a woman with HIV is evidenced by the demonstration that 8% to 50% of women artificially inseminated with semen from donors later shown to be HIV-positive became infected with the AIDS virus. Additionally, genital lesions, usually caused by other sexually transmit-
AIDS is not transmissible by nonsexual, casual exposure to infected persons. A particular concern of health care workers is the possibility of HIV infection from accidental exposure to the virus. In prospective studies of hundreds of health care workers who sustained “needle sticks” or other accidental exposures to blood from patients with AIDS, fewer than 1% actually seroconverted and became infected with HIV-1. Immediate postexposure prophylaxis with antiretroviral therapy is indicated in such accidental exposures, with the goal of preventing HIV-1 infection. (Specific recommendations are available online at the Centers for Disease Control and Prevention [CDC].)

The Etiologic Agent of AIDS is HIV-1

HIV-1 is an enveloped member of the retrovirus family, specifically the subfamily of lentiviruses. Animal lentiviruses have been recognized for a century, but human lentiviruses are known for less than 3 decades.

Two identical 9.7-kb single copies of the virus’ RNA genome plus some key enzymes needed early in the infectious cycle (see below), such as reverse transcriptase (RNA-dependent DNA polymerase) and integrase, are encased within a core of viral proteins. This core is in turn enveloped by a phospholipid bilayer derived from the host cell membrane, in which are found virally encoded glycoproteins (gp120 and gp41). In addition to the gag, pol, and env genes characteristic of all replication-competent RNA viruses, HIV-1 contains six other genes that code for proteins involved in regulation of viral replication. Specific target cells for HIV-1 are CD4+ helper T lymphocytes and mononuclear phagocytes, although infection of other cells can occur, such as in B lymphocytes, glial cells, and intestinal epithelial cells.

The replicative cycle of HIV-1 is depicted in Figure 4-24.

1. Binding: Free HIV or an infected lymphocyte can transmit the virus to an uninfected cell. The HIV envelope glycoprotein gp120, either on the free virus or on the surface of an infected cell, binds the CD4 molecule on the surface of helper T lymphocytes and other cells, as well as one of a family of β-chemokine receptors. The most important of these chemokine receptors are CXCR4 (on T lymphocytes) and CCR-5 (on many phagocytic cells). Binding of both receptors is necessary for HIV entry.

About 1% of Caucasians are homozygous for major deletions in the CCR-5 gene and remain uninfected with HIV even with extensive exposure to the agent. Even heterozygosity for the mutant CCR-5 allele provides partial protection against HIV infection and if infection does occur they usually progress at a slower pace. Interestingly, the mutant allele is found in up to 20% of Caucasians but is absent in blacks and Asians. Some persons who have been multiply exposed to HIV-1 and who do not seroconvert and possibly some persons with long-term HIV infection who do not progress to AIDS have high levels of chemokines, which may block the coreceptors for HIV.

2. Internalization: The binding of gp120 allows gp41 to insert into the target cell’s plasma membrane, leading to its fusion with the viral envelope and virus entry.

3. DNA synthesis: The virus uncoats in the cytoplasm, and its RNA is copied into double-stranded DNA—complementary DNA (cDNA)—by retroviral reverse transcriptase.

4. Integration: Virus cDNA integrates into the host genome using a viral integrase protein, generating the latent proviral form of HIV-1. Viral genes are replicated along with host chromosomes and therefore persist for the life of the cell. As memory T cells have a long life span, some experts estimate that even if total suppression of HIV-1 replication were achieved, over 60 years would be needed for infected T cells to die off. Also, even with the most effective HAART regimens some replication occurs.

5. Replication: Viral RNA is reproduced by transcriptional activation of the integrated HIV provirus, a process that, e.g., for T cells, requires “activation” of the infected cell plus certain inducible host transcription factors.

6. Dissemination: To complete its cycle, nascent virus is assembled in the cytoplasm just beneath the cell membrane and disseminated to other target cells. This is accomplished either by fusion of an infected cell with an uninfected one or by the budding of virions from the plasma membrane of the infected cell (Fig. 4-25).

The mechanism by which HIV kills infected T lymphocytes is still incompletely understood. Potential mechanisms for depletion of CD4+ lymphocytes include direct viral cytopathicity, immune clearance of infected cells, and the actions of secondary mediators such as cytokines. Whatever the mechanism(s), there is a clear association between increasing viral burden and declining CD4+ lymphocyte counts.

The long interval between HIV-1 entry and the appearance of clinical symptoms of AIDS is related to the small number of infected T lymphocytes and viral latency and, it is now becoming clear, extensive virus replication in the gut-associated lymphoid tissue (GALT), away from the circulation. During this asymptomatic period, only 0.01–0.001% of circulation T cells actively transcribe the HIV-1 genome, even though 1% contain integrated proviral DNA. Moreover, virus replication continues apace in the GALT, consuming certain CD4+ T cell populations, particularly memory T cells. When this depletion eventually exceeds the body’s ability to replenish these cells, systemic HIV-1 replication supervenes.

In latent infection, the virus can exist in three forms: untranscribed viral RNA in the cytoplasm of resting T cells; unintegrated, and thus untranscribed, viral DNA in the cytoplasm; and integrated proviral DNA, which may remain untranscribed in a resting T cell. The mechanisms underlying latency and conversion of latent to lytic infection are incompletely understood.

Initiation of viral replication in latent HIV-1 infection depends on induction of host proteins during T-cell activation. Viral transcription may be activated by many T-cell mitogens and cytokines produced by monocyte/macrophages, including TNF-α and IL-1, and in addition, by proteins produced by other viruses that infect patients with AIDS, such as herpesvirus, EBV, adenosivirus, and CMV. Thus, immune system activation by a variety of infectious agents may promote HIV replication.

**IMMUNOLOGY OF AIDS:** The destruction of CD4+ T cells by HIV-1 can essentially disable the entire immune system because this subset of lymphocytes exerts critical regulatory and effector functions that involve both cellular and humoral immunity. Thus, in typical AIDS patients all elements of the immune system are eventually perturbed, including T cells, B cells, NK cells, the monocyte/macrophages lineage of cells, and immunoglobulin production.
1. HIV BINDS TO CD4

2. (a) INTERNALIZATION
   (b) UNCOATING
   (c) REVERSE
   TRANSCRIPTION
   (RNA→DNA)

3. LATENT HIV INFECTION

4. PRODUCTIVE HIV INFECTION

5. VIRAL DISSEMINATION

   CELL-CELL FUSION

   BUDDING

   FIGURE 4-24. The life cycle of human immunodeficiency virus-1 (HIV-1) is a multistep process. mRNA = messenger RNA.
Pathology

To as little as 0.5. Numbers of CD8\(^+\) helper-to-suppressor T-cell ratios decline from a normal of 2.0

togens and antigens in vitro. Moreover, the deficiency of

responses to skin testing with a variety of antigens (delayed

To be of the cytotoxic variety.

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activity is related both to a decrease in NK cell number and to

suppression of NK cell activity is severely decreased in AIDS as well. Since these cells kill both virus-infected cells and tumor cells, this defect may contribute to the malignant tumors and viral infections that plague these patients. Suppression of NK cell activity is related both to a decrease in NK cell number and to reduction in IL-2 levels, owing to a loss of CD4\(^+\) cells.

Lentiviruses tend to target monocyte/macrophages, and infected macrophages may serve as reservoirs for dissemination of the virus. Interestingly, some macrophages express CD4 on their surfaces. Unlike T lymphocytes, which are killed by HIV, infected macrophages generally survive. Macrophages from patients with AIDS display impaired phagocytosis of immune complexes and opsonized particles, decreased chemotaxis, and impaired responses to antigenic challenges.

Of the two functional types of CD4\(^+\) T lymphocytes, i.e., helper and amplifier (or inducer) cells, those affected first in HIV infection are the amplifier subset. Eventually, total CD4\(^+\) lymphocyte counts fall to less than 500 cells/\(\mu\)L, and helper-to-suppressor T-cell ratios decline from a normal of 2.0 to as little as 0.5. Numbers of CD8\(^+\) (cytotoxic/suppressor) cells are variable, although in AIDS, most of these cells seem to be of the cytotoxic variety.

Defects in T-cell function are manifested by defective responses to skin testing with a variety of antigens (delayed hypersensitivity) and impaired proliferative responses to mitogens and antigens in vitro. Moreover, the deficiency of CD4\(^+\) cells reduces levels of IL-2, the cytokine produced in response to antigens that stimulate cytotoxic T cell killing. Thus, patients with AIDS cannot generate the antigen-specific cytotoxic T cells that are required to clear viruses and other infectious agents.

Humoral immunity is also abnormal. Production of antibodies in response to specific antigenic stimulation is markedly decreased, often to under 10\% of normal. B cells also show poor proliferative responses in vitro to mitogens and antigens. Yet, sera of patients with AIDS usually show high levels of polyclonal immunoglobulins, autoantibodies, and immune complexes. This apparent paradox is probably explained by the concurrent infection with polyclonal B cell-activating viruses (e.g., EBV or CMV) which constantly stimulate B cells nonspecifically to produce immunoglobulins. Lack of CD4\(^+\) lymphocytes impairs the cytotoxic T cell proliferation that normally would eliminate B cells infected with EBV.

NK cell activity is severely decreased in AIDS as well. Since these cells kill both virus-infected cells and tumor cells, this defect may contribute to the malignant tumors and viral infections that plague these patients. Suppression of NK cell activity is related both to a decrease in NK cell number and to reduction in IL-2 levels, owing to a loss of CD4\(^+\) cells.

Lentiviruses tend to target monocyte/macrophages, and infected macrophages may serve as reservoirs for dissemination of the virus. Interestingly, some macrophages express CD4 on their surfaces. Unlike T lymphocytes, which are killed by HIV, infected macrophages generally survive. Macrophages from patients with AIDS display impaired phagocytosis of immune complexes and opsonized particles, decreased chemotaxis, and impaired responses to antigenic challenges.

PATHOLOGY AND CLINICAL FEATURES OF AIDS: Patients recently infected with HIV-1 may have an acute, usually self-limited flu-like illness called the acute retroviral syndrome that resembles infectious mononucleosis. This occurs 2 to 3 weeks after exposure to HIV, before appearance of antibodies against the virus. Less commonly, they present with neurologic symptoms that suggest encephalitis, aseptic meningitis, or a neuropathy. Fever, myalgia, lymphadenopathy, sore throat, and a macular rash are common. Most of these symptoms resolve within 2 to 3 weeks, although lymphadenopathy, fever, and myalgia may persist for a few months. Seroconversion occurs 1 to 10 weeks after the onset of this acute illness. Thus the standard HIV-1 enzyme immunoassay (EIA) and Western Blot testing, which depends on the presence of anti-HIV-1 gag antibodies, is negative during the initial stage of the infection. Most patients recover from this initial illness as their immune system mounts a cytotoxic T-cell counterattack, although a small percentage progress rapidly to frank AIDS within a few months.

After the initial acute syndrome, most newly infected individuals enter a period of latency and slow immune system decline that averages approximately ten years before they reach a state of serious immune compromise. If unrecognized or untreated, the outcome will eventually be fulminating immunodeficiency and its fatal complications (Fig. 4-26).

Persistent generalized lymphadenopathy is palpable lymph node enlargement at two or more extraginal sites, persisting for more than 3 months in a person infected with HIV. The disorder develops either as part of the acute HIV syndrome or within a few months of seroconversion. The most common sites of involvement are the axillary, inguinal, and posterior cervical nodes, although almost any group of lymph nodes can be affected. Many cells within the affected lymph nodes, especially follicular dendritic cells, harbor actively replicating virus. Biopsy reveals reactive changes with follicular hyperplasia, but are not diagnostic. Persistent generalized lymphadenopathy does not have any prognostic significance with respect to progression of HIV infection to AIDS.

Most patients infected with HIV express detectable viral antigens and antibodies within 6 months. Patients will generally experience an initial period of intense viremia with very high viral loads during the acute retroviral syndrome with a corresponding sharp drop in their absolute number of CD4\(^+\) T cells. As a patient’s immune system begins to recognize the new infection,
viral load drops and CD4+ T cell count begins to climb. This control of HIV-1 infection occurs via a vigorous cytotoxic T cell response. Viral replication continues but is constrained by the immune response. The immune system and the HIV-1 load eventually enter into a sort of uneasy equilibrium, during which the HIV-1 viral RNA load stays fairly constant at the “viral set point.” During this time infected persons are generally asymptomatic. However, virus replication virtually always begins to increase. At some time the number of CD4+ T cells starts to decrease. Patients generally remain asymptomatic until the CD4+ lymphocyte count falls below 500/μL. Then, nonspecific constitutional symptoms may appear, along with opportunistic infections. As CD4+ T cells fall below 350/μL, patients become much more susceptible to primary or reactivation Mycobacterium tuberculosis, which may progress rapidly to severe disease or death. Once CD4+ levels are under 150/μL and CD4:CD8 ratios less than 0.8, the disease progresses rapidly. A variety of bacteria, viruses, fungi, and protozoa attack the immunocompromised patient. Kaposi sarcoma and lymphoproliferative disorders may appear, and neurologic disease is common.

Symptoms of CNS dysfunction occur in one-third of AIDS patients and postmortem studies of patients who have died of AIDS reveal CNS pathology in more than three-fourths of the case. HIV is thought to enter the brain via infected blood monocytes and then to reside there in glial cells. Although HIV infection of neurons is not common, HIV gene products cause neuron apoptosis via several mechanisms.

Discussion of the diversity of infectious agents that ravage patients with AIDS is beyond the scope of this chapter, and only a few representative examples are mentioned. It is important to recognize that while most non-immunocompromised patients will have only one infection at a time, HIV-1-infected patients can develop multiple severe infections simultaneously.

Opportunistic Infections, Particularly Polymicrobial Infections are Common in Patients With AIDS

The majority of patients with HIV-1/AIDS suffer from opportunistic pulmonary infections, although this has been greatly reduced through the use of prophylactic antibiotics. Pneumocystis jiroveci (formerly P. carinii) pneumonia may occur in patients with advanced HIV-1 disease. Lung infection with CMV and Mycobacterium avium-intracellulare are less common. Patients with AIDS are also susceptible to Legionella infections.

Diarrhea occurs in over 75% of patients, often representing simultaneous infections with more than one organism. The most frequent pathogens are protozoans, including Cryptosporidium, Isospora belli, and Giardia lamblia. M. avium-intracellulare and Salmonella species are the most common bacterial causes of diarrhea in AIDS patients. CMV infection of the gastrointestinal tract can manifest as a colitis associated with watery diarrhea in patients whose CD4 counts are under 50 cells/mm3.

Cryptococcal meningitis is a devastating complication, and represents 5% to 8% of all opportunistic infections in patients with AIDS.
with AIDS. CNS complications include cerebral toxoplasmosis; primary CNS lymphoma; encephalitis caused by herpes simplex, varicella, or CMV; and progressive multifocal leukoencephalopathy, which is caused by the JC virus.

Virtually all patients with AIDS develop some form of skin disease, infections being the most prominent. *Staphylococcus aureus* is the most common, causing bullous impetigo, deeper purulent lesions (ecthyma) and folliculitis. Many of these *S. aureus* isolates carry virulence factors such as the Panton Valentine leukocidin, which may increase the risk of bacterial invasion and severe disease. Chronic mucocutaneous herpes simplex infection is so characteristic of AIDS that it is considered an index infection in establishing the diagnosis. Skin lesions produced by *Molluscum contagiosum* and HIV are also common, as are scabies and infections with *Candida* species. A varicella zoster outbreak in someone under the age of 50 should raise the question of a possible occult HIV-1 infection.

Among the most common causes of death in patients with HIV/AIDS is hepatitis C virus (HCV) infection (see Chapter 14). In some studies, over a quarter of deaths among HIV-positive individuals are from hepatitis C. A very high percentage of HIV-positive intravenous drug abusers are also infected with HCV. There is evidence suggesting that coinfection with HIV and HCV accelerates the course of disease with both viruses.

*Kaposi sarcoma (KS)* is an otherwise rare, multicentric, malignant neoplasm. It is characterized by cutaneous and (less commonly) visceral nodules, in which endothelium-lined channels and vascular spaces are admixed with spindle-shaped cells (see Chapter 24). Patients with AIDS, especially homosexual men rather than intravenous drug users, are at very high risk for KS. In fact, occurrence of KS in an otherwise healthy person under 60 years is strong evidence of AIDS. Unlike the classic indolent variety of KS, the tumor in AIDS is usually aggressive, often involving viscera such as the gastrointestinal tract or lungs. Lung involvement frequently leads to death.

A strain of herpesvirus—human herpes virus 8 (HHV8)—is implicated in all forms of KS, including that associated with AIDS. HHV8 is also thought to be the cause of a peculiar lymphoma associated with AIDS (*primary effusion lymphoma*) and of AIDS-associated Castleman disease. The virus has been detected in both KS spindle cells and endothelial cells. The finding of HHV8 in the blood strongly predicts later development of KS. In fact, 75% of HIV-infected persons with HHV8 in the blood developed KS within 3 years. It is thought that HHV8 is sexually transmitted, as almost all homosexual HIV carriers are infected, but only a quarter of heterosexual drug users with HIV infection harbor HHV8.

B cell lymphoproliferative diseases are common in patients with AIDS. Congenital and acquired immunodeficiency states are associated with B-cell hyperplasia, usually manifested as generalized lymphadenopathy. This lymphoproliferative syndrome may be followed by appearance of high-grade B-cell lymphomas. In fact, patients who have been subjected to immunosuppressive therapy for renal transplants are at a 35-times-greater risk of developing lymphoma, and in one third of these cases the disease is confined to the CNS. The lymphomas in chronically immunodeficient patients may manifest as an invasive polyclonal B-cell proliferation or as a monoclonal B-cell lymphoma. Many patients exhibit serologic evidence of infection with EBV and the EBV genome has been demonstrated in the lymphoma cells.

B-cell hyperplasia and generalized lymphadenopathy precede malignant lymphoproliferative disease. HIV-associated lymphomas are usually the large cell variety, as in other immunodeficiency conditions, although small cell lymphomas are sometimes seen. A conspicuous feature of lymphomas associated with AIDS is their predilection for extranodal disease, particularly primary lymphomas of the brain. In addition, lymphomas of the gastrointestinal tract, liver, and bone marrow are frequent. The EBV genome has also been demonstrated in many AIDS-related lymphomas, especially in the CNS.

**Therapy for HIV/AIDS**

HIV infection represents a novel challenge in treatment. Human lentivirus infections have not been therapeutic targets in the past. Thus, new strategies have had to be developed to treat patients with HIV/AIDS. Therapy focuses on HIV proteins that are obligatory for HIV replication and sufficiently different from normal cellular proteins to offer clear targets for pharmacotherapy. Initial agents were designed to inhibit the function of HIV reverse transcriptase (RT) and protease (PR). Combining compounds that inhibit RT and drugs that inhibit PR is the mainstay of highly active anti-retroviral therapy (HAART) today. Introduction of HAART revolutionized AIDS treatment, reducing AIDS-related mortality and increasing all indices of health in HIV-1–infected patients.

Unlike most retroviral reverse transcriptases, HIV RT lacks an editing function. Thus, virus genome replication is highly error-prone, and HIV mutates much more often than most other viruses. This high mutation rate facilitates avoidance of immune attack, and enhances its ability to generate functional mutations that are resistant to HAART. Although combining three or more drugs in most HAART regimens depresses viral replication, HIV mutants resistant to multiple chemotherapeutic agents contribute now a high percentage of HIV isolates in the United States. Further, HAART drugs do not cross the blood–brain barrier well, and the CNS may be a sanctuary for the virus.

Quantitation of HIV-positive cells in the body has led to the conclusion that eradication of the virus from the body is not a realistic expectation with the types of chemotherapy currently available. Even HAART patient with no detectable blood HIV-1 continue to deplete their memory CD4+ T cells. Finally, although HAART may eliminate HIV positive cells from the blood, even temporary cessation of therapy leads to rebound, i.e., reactivation of HIV from reservoirs outside the circulation and subsequent viral rebound.

**HIV-2 Causes a Clinical Syndrome Similar to that Caused by HIV-1**

In 1985, otherwise healthy prostitutes in Senegal were discovered to harbor antibodies that cross-reacted with a monkey retrovirus, now termed simian immunodeficiency virus (SIV). A year later, a retrovirus similar to HIV-1 was isolated from West African patients with AIDS who were negative for antibodies against HIV-1. Antibodies to this new retrovirus, now termed HIV-2, also cross-reacted with SIV antigens. Frozen sera from West Africa dating to the 1960s have been shown to contain antibodies to HIV-2. In Guinea-Bissau, infection with HIV-2 has been shown in 8% of pregnant women, 10% of male blood donors, and more than one third of prostitutes. The infection has now also been reported from other parts of Africa, Europe, and the United States.

HIV-2 is morphologically similar to HIV-1, and the immunodeficiency state associated with HIV-2 infection is indistinguishable from AIDS caused by HIV-1. The risk factors for infection in both diseases seem to be similar. However, HIV-2 is more difficult to transmit than HIV-1, and persons infected with the former progress at a slower rate to AIDS.