chapter 19

AIDS and Other Immunodeficiencies

Nude Mouse *(nu/nu)*

Like any complex multi-component system, the immune system is subject to failure of some or all of its parts. This failure can have dire consequences. When the system loses its sense of self and begins to attack host cells and tissues, the result is **autoimmunity,** which is described in Chapter 20. When the system errs by failing to protect the host from disease-causing agents or from malignant cells, the result is **immunodeficiency,** which is the subject of this chapter.

A condition resulting from a genetic or developmental defect in the immune system is called a primary immunodeficiency. In such a condition, the defect is present at birth although it may not manifest itself until later in life. Secondary immunodeficiency, or acquired immunodeficiency, is the loss of immune function and results from exposure to various agents. By far the most common secondary immunodeficiency is **acquired immunodeficiency syndrome,** or **AIDS,** which results from infection with the human immunodeficiency virus 1 (HIV-1). In the year 2000, AIDS killed approximately 3 million persons, and HIV infection continues to spread to an estimated 15,000 persons per day. AIDS patients, like other individuals with severe immunodeficiency, are at risk of infection with so-called opportunistic agents. These are microorganisms that healthy individuals can harbor with no ill consequences but that cause disease in those with impaired immune function.

The first part of this chapter describes the common primary immunodeficiencies, examines progress in identifying the genetic defects that underlie these disorders, and considers approaches to their treatment, including innovative uses of gene therapy. Animal models of primary immunodeficiency are also described. The rest of this chapter describes acquired immunodeficiency, with a strong focus on HIV infection, AIDS, and the current status of therapeutic and prevention strategies for combating this fatal acquired immunodeficiency.

Primary Immunodeficiencies

A primary immunodeficiency may affect either adaptive or innate immune functions. Deficiencies involving components of adaptive immunity, such as T or B cells, are thus differentiated from immunodeficiencies in which the nonspecific mediators of innate immunity, such as phagocytes or complement, are impaired. Immunodeficiencies are conveniently categorized by the type or the developmental stage of the cells involved. Figure 19-1 reviews the overall cellular development in the immune system, showing the locations of defects that give rise to primary immunodeficiencies. As Chapter 2 explained, the two main cell lineages important to immune function are lymphoid and myeloid. Most defects that lead to immunodeficiencies affect either one or the other. The lymphoid cell disorders may affect T cells, B cells, or, in combined immunodeficiencies, both B and T cells. The myeloid cell disorders affect phagocytic function. Most of the primary immunodeficiencies are inherited, and the precise molecular variations and the genetic defects that lead to many of these dysfunctions have been determined (Table 19-1 and Figure 19-2). In addition, there are immunodeficiencies that stem from developmental defects that impair proper function of an organ of the immune system.

The consequences of primary immunodeficiency depend on the number and type of immune system components involved. Defects in components early in the hematopoietic developmental scheme affect the entire immune system. In this category is reticular dysgenesis, a stem-cell defect that affects the maturation of all leukocytes; the resulting general failure of immunity leads to susceptibility to infection by a variety of microorganisms. Without aggressive treatment, the affected individual usually dies young from severe infection. In the

VISUALIZING CONCEPTS

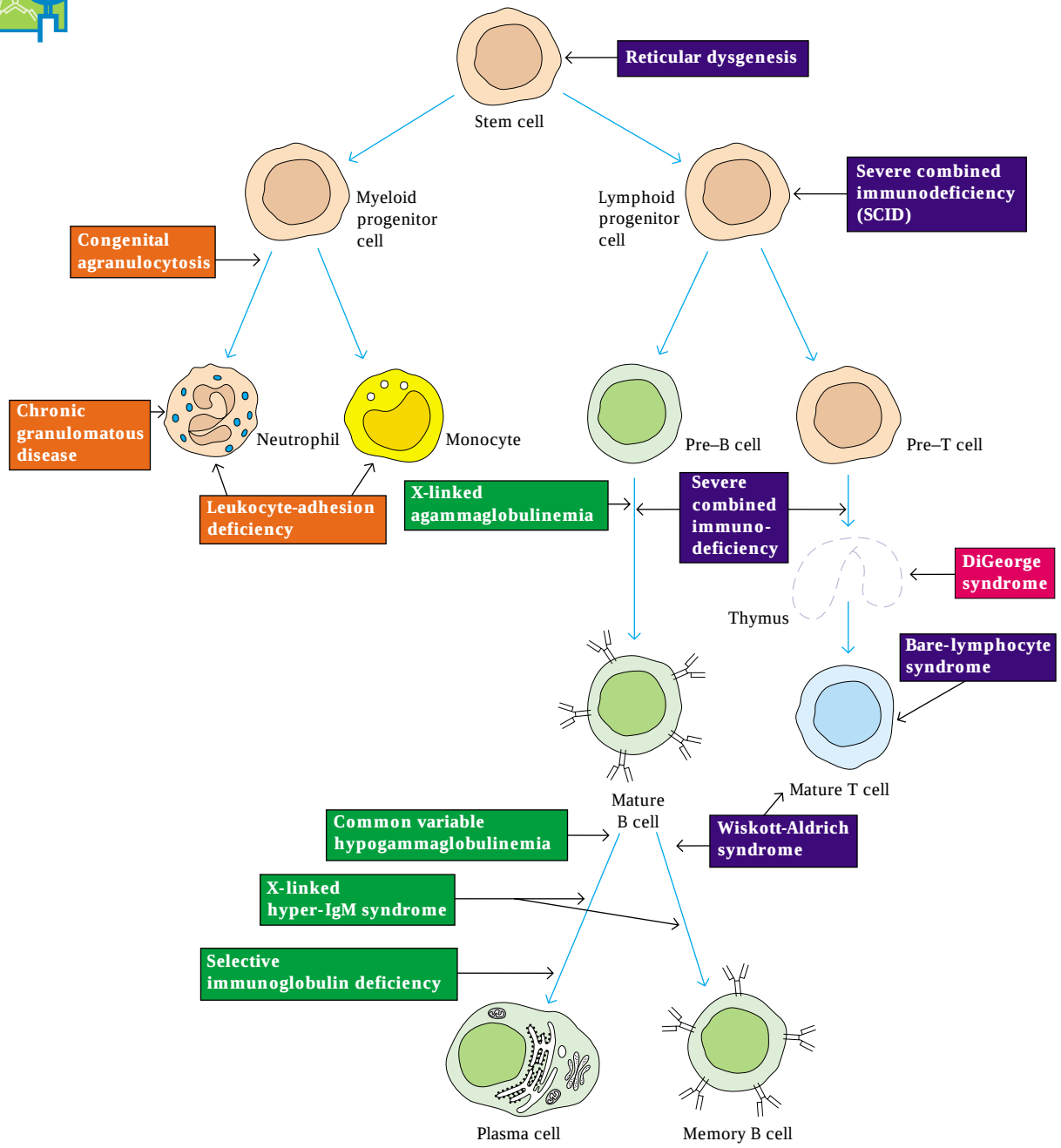


FIGURE 19-1 Congenital defects that interrupt hematopoiesis or impair functioning of immune-system cells result in various immunodeficiency diseases. (Orange boxes = phagocytic deficiencies, green = humoral deficiencies, red = cell-mediated deficiencies, and purple = combined immunodeficiencies, defects that affect more than one cell lineage.)

more restricted case of defective phagocytic function, the major consequence is susceptibility to bacterial infection. Defects in more highly differentiated compartments of the immune system have consequences that are more specific and usually less severe. For example, an individual with selective IgA deficiency may enjoy a full life span, troubled only by a greater than normal susceptibility to infections of the respiratory and genitourinary tracts.

TABLE 19-1 Some primary human immunodeficiency diseases and underlying genetic defects

Immunodeficiency disease	Specific defect	Impaired function	Inheritance mode*	Chromosomal defect
Severe combined immunodeficiency (SCID)	RAG-1/RAG-2 deficiency	No TCR or Ig gene rearrangement	AR	11p13
	ADA deficiency	Toxic metabolite in T and B cells	AR	20q13
	PNP deficiency		AR	14q13
	JAK-3 deficiency	Defective signals from IL-2, 4, 7, 9, 15,	AR	19p13
	IL-2Rγ-deficiency		XL	Xq13
	ZAP-70 deficiency	Defective signal from TCR	AR	2q12
Bare lymphocyte syndrome	Defect in MHC class II gene promoter	No class II MHC molecules	AR	16p13
Wiskott-Aldrich syndrome (WAS)	Cytoskeletal protein (CD43)	Defective T cells and platelets	XL	Xp11
Interferon gamma receptor	IFN-γ–receptor defect	Impaired immunity to mycobacteria	AR	6q23
DiGeorge syndrome	Thymic aplasia	T- and B-cell development	AD	22q11
Ataxia telangiectasia	Defective cell-cycle kinase	Low IgA, IgE	AR	11q22
Gammaglobulinemias	X-linked agammaglobulinemia	Bruton's tyrosine kinase (Btk); no mature B cells	XL	Xq21
	X-linked hyper-IgM syndrome	Defective CD40 ligand	XL	Xq26
	Common variable immunodeficiency	Low IgG, IgA; variable IgM	Complex	
	Selective IgA deficiency	Low or no IgA	Complex	
Chronic granulomatous disease	Cyt $p91^{phox}$	No oxidative burst for bacterial killing	XL	Xp21
	Cyt $p67^{phox}$		AR	1q25
	Cyt $p22^{phox}$		AR	16q24
Chediak-Higashi syndrome	Defective intracellular transport protein (LYST)	Inability to lyse bacteria	AR	1q42
Leukocyte-adhesion defect	Defective integrin β2 (CD18)	Leukocyte extravasation	AR	21q22

*AR = autosomal recessive; AD = autosomal dominant; XL = X linked; "Complex" indicates conditions for which precise genetic data are not available and that may involve several interacting loci.

Lymphoid Immunodeficiencies May Involve B Cells, T Cells, or Both

The combined forms of lymphoid immunodeficiency affect both lineages and are generally lethal within the first few years of life; these arise from defects early in developmental pathways. They are less common than conditions, usually less severe, that result from defects in more highly differentiated lymphoid cells.

B-cell immunodeficiency disorders make up a diverse spectrum of diseases ranging from the complete absence of mature recirculating B cells, plasma cells, and immunoglobulin to the selective absence of only certain classes of immunoglobulins. Patients with these disorders usually are subject to recurrent bacterial infections but display normal immunity to most viral and fungal infections, because the T-cell branch of the immune system is largely unaffected. Most common in patients with humoral immunodeficiencies are infections by such encapsulated bacteria as staphylococci, streptococci, and pneumococci, because antibody is critical for the opsonization and clearance of these organisms.

Because of the central role of T cells in the immune system, a T-cell deficiency can affect both the humoral and the cell-mediated responses. The impact on the cell-mediated system can be severe, with a reduction in both delayed-type hypersensitive responses and cell-mediated cytotoxicity.

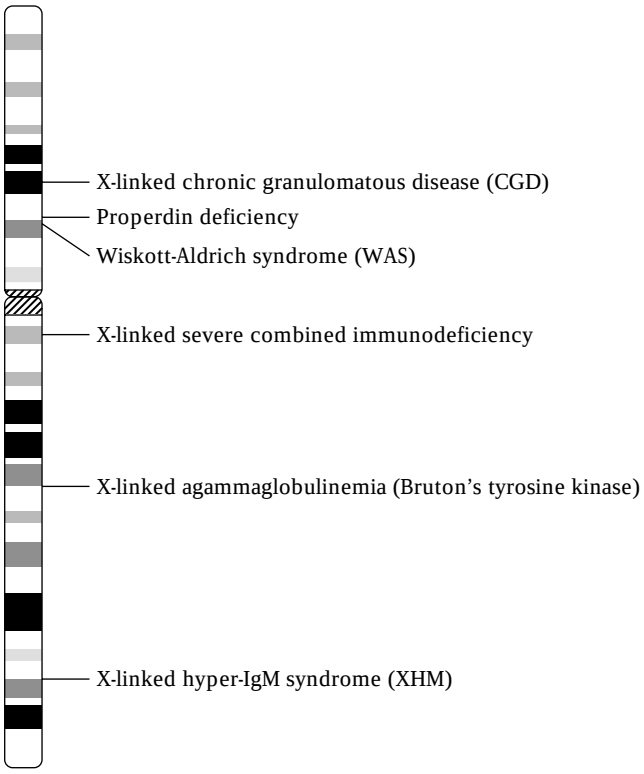


FIGURE 19-2 Several X-linked immunodeficiency diseases result from defects in loci on the X chromosome. *[Data from the Natl. Center for Biotechnology Information Web site.]*

Immunoglobulin deficiencies are associated primarily with recurrent infections by extracellular bacteria, but those affected have normal responses to intracellular bacteria, as well as viral and fungal infections. By contrast, defects in the cell-mediated system are associated with increased susceptibility to viral, protozoan, and fungal infections. Intracellular pathogens such as *Candida albicans, Pneumocystis carinii*, and *Mycobacteria* are often implicated, reflecting the importance of T cells in eliminating intracellular pathogens. Infections with viruses that are rarely pathogenic for the normal individual (such as cytomegalovirus or even an attenuated measles vaccine) may be life threatening for those with impaired cell-mediated immunity. Defects that cause decreased T-cell counts generally also affect the humoral system, because of the requirement for T_H cells in B-cell activation. Generally there is some decrease in antibody levels, particularly in the production of specific antibody after immunization.

As one might expect, combined deficiencies of the humoral and cell-mediated branches are the most serious of the immunodeficiency disorders. The onset of infections begins early in infancy, and the prognosis for these infants is early death unless therapeutic intervention reconstitutes their defective immune system. As described below, there are increasing numbers of options for the treatment of immunodeficiencies.

The immunodeficiencies that affect lymphoid function have in common the inability to mount or sustain a complete immune response against specific agents. A variety of failures can lead to such immunodeficiency. Defective intercellular communication may be rooted in deleterious mutations of genes that encode cell-surface receptors or signal-transduction molecules; defects in the mechanisms of gene rearrangement and other functions may prevent normal B- or T-cell responses. Figure 19-3 is an overview of the molecules involved in the more well-described interactions among T cells and B cells that give rise to specific responses, with a focus on proteins in which defects leading to immunodeficiency have been identified.

SEVERE COMBINED IMMUNODEFICIENCY (SCID)

The family of disorders termed SCID stems from defects in lymphoid development that affect either T cells or both T and B cells. All forms of SCID have common features despite differences in the underlying genetic defects. Clinically, SCID is characterized by a very low number of circulating lymphocytes. There is a failure to mount immune responses mediated by T cells. The thymus does not develop, and the few circulating T cells in the SCID patient do not respond to stimulation by mitogens, indicating that they cannot proliferate in response to antigens. Myeloid and erythroid (red-blood-cell precursors) cells appear normal in number and function, indicating that only lymphoid cells are depleted in SCID.

SCID results in severe recurrent infections and is usually fatal in the early years of life. Although both the T and B lineages may be affected, the initial manifestation of SCID in infants is almost always infection by agents, such as fungi or viruses, that are normally dealt with by T-cell immunity. The B-cell defect is not evident in the first few months of the affected infant's life because antibodies are passively obtained from transplacental circulation or from mother's milk. SCID infants suffer from chronic diarrhea, pneumonia, and skin, mouth, and throat lesions as well as a host of other opportunistic infections. The immune system is so compromised that even live attenuated vaccines (such as the Sabin polio vaccine) can cause infection and disease. The life span of a SCID patient can be prolonged by preventing contact with all potentially harmful microorganisms, for example by confinement in a sterile atmosphere. However, extraordinary effort is required to prevent direct contact with other persons and with unfiltered air; any object, including food, that comes in contact with the sequestered SCID patient must first be sterilized. Such isolation is feasible only as a temporary measure, pending treatment.

The search for defects that underlie SCID has revealed several different causes for this general failure of immunity. A survey of 141 patients by Rebecca Buckley indicated that the most common cause (64 cases) was deficiency of the common gamma chain of the IL-2 receptor (IL-2Rγ; see Figure 12-7). Defects in this chain impede signaling through receptors for IL-4, -7, -9, and -15 as well as the IL-2 receptor, because the chain is present in receptors for all of these cytokines. Deficiency in the kinase JAK-3, which has a similar

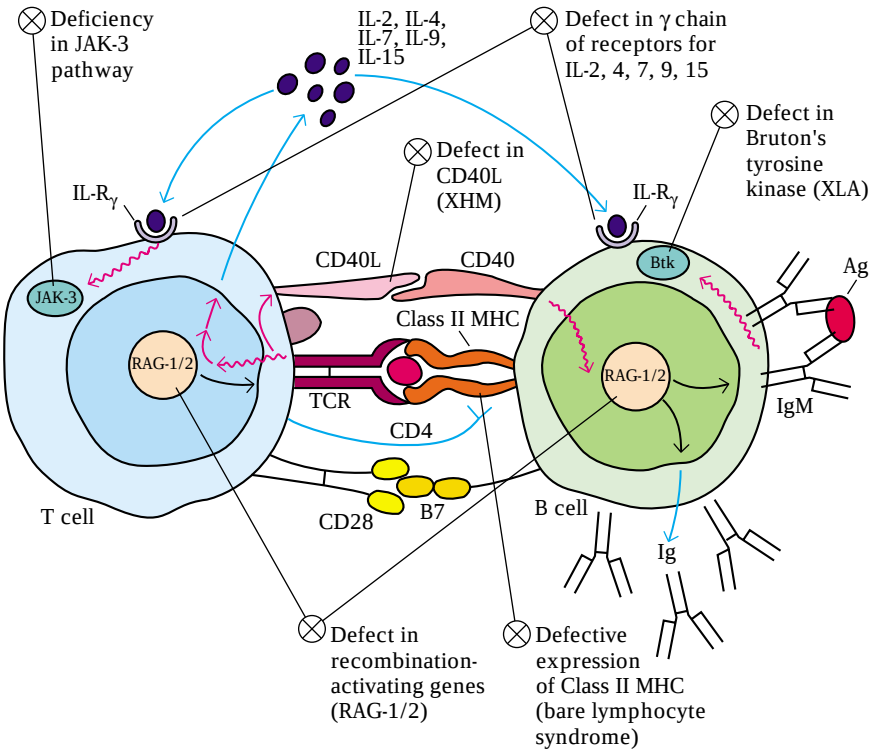


FIGURE 19-3 Defects in cell interaction and signaling can lead to severe immunodeficiency. The interaction of T cell and B cell is shown here with a number of the components important to the intra- and extracellular signaling pathways. A number of primary immunodeficiencies are rooted in defects in these interactions. SCID may result from defects in (1) the recombination-activating genes (*RAG-1* and *-2*) required for synthesis of the functional immunoglobulins and T-cell receptors that characterize mature B and T cells; (2) the γ chain of receptors for IL-2, 4, 7, 9, and 15 (IL-Rγ); (3) JAK-3, which transduces signals from the gamma chain of the cytokine receptor; or (4) expression of the class II MHC molecule (bare lymphocyte syndrome). XLA results from defective transduction of activating signals from the cell-surface IgM by Bruton's tyrosine kinase (Btk). XHM results from defects in CD40L that preclude normal maturation of B cells. *[Adapted from B. A. Smart and H. D. Ochs, 1997,* Curr. Opin. Pediatr. ***9:****570.]*

phenotype because the IL receptors signal through this molecule, accounted for 9 of the cases (see Figure 12-10). A rare defect found in only 2 of the patients involved the IL-7 receptor; these patients have impaired T and B cells but normal NK cells. Another common defect is the adenosine deaminase or ADA deficiency found in 22 patients. Adenosine deaminase catalyzes conversion of adenosine to inosine, and its deficiency results in accumulation of adenosine, which interferes with purine metabolism and DNA synthesis. The remaining cases included single instances of reticular dysgenesis and cartilage hair dysplasia or were classified as autosomal recessive defects not related to known IL-2Rγ or JAK-3 mutations. Thirteen of the 141 cases were of unknown origin, with no apparent genetic defect or family history of immunodeficiency.

There are other known defects that give rise to SCID. There is a defect characterized by depletion of $CD8^+$ T cells that involves the tyrosine kinase ZAP-70, an important element in T-cell signal transduction (see Figures 10-11 and 10-12). Infants with defects in ZAP-70 may have normal levels of immunoglobulin and $CD4^+$ lymphocytes, but their $CD4^+$ T cells are nonfunctional. A deficiency in the enzyme purine nucleoside phosphorylase (PNP) causes immunodeficiency by a mechanism similar to the ADA defect. As described in Chapters 5 and 9, both immunoglobulin and T-cell receptor genes undergo rearrangement to express the active forms of these molecules. A defect in the genes that encode mediators of the rearrangement processes (recombination-activating proteins RAG-1 and RAG-2) precludes development of B and T cells with functional receptors and leads to SCID.

A defect leading to general failure of immunity similar to SCID is failure to transcribe the genes that encode class II MHC molecules. Without these molecules, the patient's lymphocytes cannot participate in cellular interactions with T helper cells. This type of immunodeficiency is also called the *bare-lymphocyte syndrome*. Molecular studies of a class II MHC deficiency revealed a defective interaction between a 5′ promoter sequence of the gene for the class II MHC molecule and a DNA-binding protein necessary for gene transcription. Other patients with SCID-like symptoms lack class I MHC molecules. This rare variant of immunodeficiency was ascribed to mutation in the TAP genes that are vital to antigen processing by class I MHC molecules (see Clinical Focus Chapter 8). This defect causes a deficit in CD8-mediated

immunity, characterized by susceptibility to viral infection. A recent case of SCID uncovered a defect in the gene for the cell-surface phosphatase CD45. Interestingly, this defect caused lack of αβ T-cells but spared the γδ lineage.

WISKOTT-ALDRICH SYNDROME (WAS)

The severity of this X-linked disorder increases with age and usually results in fatal infection or lymphoid malignancy. Initially, T and B lymphocytes are present in normal numbers. WAS first manifests itself by defective responses to bacterial polysaccharides and by lower-than-average IgM levels. Other responses and effector mechanisms are normal in the early stages of the syndrome. As the WAS sufferer ages, there are recurrent bacterial infections and a gradual loss of humoral and cellular responses. The syndrome includes thrombocytopenia (lowered platelet count; the existing platelets are smaller than usual and have a short half-life), which may lead to fatal bleeding. Eczema (skin rashes) in varying degrees of severity may also occur, usually beginning around one year of age. The defect in WAS has been mapped to the short arm of the X chromosome (see Table 19-1 and Figure 19-2) and involves a cytoskeletal glycoprotein present in lymphoid cells called sialophorin (CD43). The WAS protein is required for assembly of actin filaments required for the formation of microvesicles.

INTERFERON-GAMMA–RECEPTOR DEFECT

A recently described immunodeficiency that falls into the mixed-cell category involves a defect in the receptor for interferon gamma (IFN-γ, see Chapter 12). This deficiency was found in patients suffering from infection with atypical mycobacteria (intracellular organisms related to the bacteria that cause tuberculosis and leprosy). Most of those carrying this autosomal recessive trait are from families with a history of inbreeding. The susceptibility to infection with mycobacteria is selective in that those who survive these infections are not unusually susceptible to other agents, including other intracellular bacteria. This immunodeficiency points to a specific role for IFN-γ and its receptor in protection from infection with mycobacteria.

Whereas SCID and the related combined immunodeficiencies affect T cells or all lymphoid cells, other primary immunodeficiencies affect B-cell function and result in the reduction or absence of some or all classes of immunoglobulins. While the underlying defects have been identified for some of these, little information exists concerning the exact cause of some of the more common deficiencies, such as common variable immunodeficiency and selective IgA deficiency.

X-LINKED AGAMMAGLOBULINEMIA

A B-cell defect called X-linked agammaglobulinemia (XLA) or Bruton's hypogammaglobulinemia is characterized by extremely low IgG levels and by the absence of other immunoglobulin classes. Individuals with XLA have no peripheral B cells and suffer from recurrent bacterial infections, beginning at about nine months of age. A palliative treatment for this condition is periodic administration of immunoglobulin, but patients seldom survive past their teens. There is a defect in B-cell signal transduction in this disorder, due to a defect in a transduction molecule called Bruton's tyrosine kinase (Btk), after the investigator who described the syndrome. B cells in the XLA patient remain in the pre-B stage with H chains rearranged but L chains in their germ-line configuration. (The Clinical Focus in Chapter 11 describes the discovery of this immunodeficiency and its underlying defect in detail.)

X-LINKED HYPER-IgM SYNDROME

A peculiar immunoglobulin deficiency first thought to result from a B-cell defect has recently been shown to result instead from a defect in a T-cell surface molecule. X-linked hyper-IgM (XHM) syndrome is characterized by a deficiency of IgG, IgA, and IgE, and elevated levels of IgM, sometimes as high as 10 mg/ml (normal IgM concentration is 1.5 mg/ml). Although individuals with XHM have normal numbers of B cells expressing membrane-bound IgM or IgD, they appear to lack B cells expressing membrane-bound IgG, IgA, or IgE. XHM syndrome is generally inherited as an X-linked recessive disorder (see Figure 19-2), but some forms appear to be acquired and affect both men and women. Affected individuals have high counts of IgM-secreting plasma cells in their peripheral blood and lymphoid tissue. In addition, XHM patients often have high levels of autoantibodies to neutrophils, platelets, and red blood cells. Children with XHM suffer recurrent infections, especially respiratory infections; these are more severe than expected for a deficiency characterized by low levels of immunoglobulins.

The defect in XHM is in the gene encoding the CD40 ligand (CD40L), which maps to the X chromosome. T_H cells from patients with XHM fail to express functional CD40L on their membrane. Since an interaction between CD40 on the B cell and CD40L on the T_H cell is required for B-cell activation, the absence of this co-stimulatory signal inhibits the B-cell response to T-dependent antigens (see Figures 19-3 and 11-10). The B-cell response to T-independent antigens, however, is unaffected by this defect, accounting for the production of IgM antibodies. As described in Chapter 11, class switching and formation of memory B cells both require contact with T_H cells by a CD40–CD40L interaction. The absence of this interaction in XHM results in the loss of class switching to IgG, IgA, or IgE isotypes and in a failure to produce memory B cells. In addition, XHM individuals fail to produce germinal centers during a humoral response, which highlights the role of the CD40–CD40L interaction in the generation of germinal centers.

COMMON VARIABLE IMMUNODEFICIENCY (CVI)

CVI is characterized by a profound decrease in numbers of antibody-producing plasma cells, low levels of most immunoglobulin isotypes (hypogammaglobulinemia), and recurrent infections. The condition is usually manifested later

in life than other deficiencies and is sometimes called late-onset hypogammaglobulinemia or, incorrectly, acquired hypogammaglobulinemia. However, CVI has a genetic component and is considered a primary immunodeficiency, although the exact pattern of inheritance is not known. Because the manifestations are very similar to those of acquired hypogammaglobulinemia, there is some confusion between the two forms (see below). Infections in CVI sufferers are most frequently bacterial and can be controlled by administration of immunoglobulin. In CVI patients, B cells fail to mature into plasma cells; however in vitro studies show that CVI B cells are capable of maturing in response to appropriate differentiation signals. The underlying defect in CVI is not known, but must involve either an in vivo blockage of the maturation of B cells to the plasma-cell stage or their inability to produce the secreted form of immunoglobulins.

HYPER-IgE SYNDROME (JOB SYNDROME)

A primary immunodeficiency characterized by skin abcesses, recurrent pneumonia, eczema, and elevated levels of IgE accompanies facial abnormalities and bone fragility. This multi-system disorder is autosomal dominant and has variable expressivity. The gene for hyper IgE syndrome, or HIES, maps to chromosome 4. HIES immunologic signs include recurrent infection and eosinophilia in addition to elevated IgE levels.

SELECTIVE DEFICIENCIES OF IMMUNOGLOBULIN CLASSES

A number of immunodeficiency states are characterized by significantly lowered amounts of specific immunoglobulin isotypes. Of these, IgA deficiency is by far the most common. There are family-association data showing that IgA deficiency prevails in the same families as CVI, suggesting a relationship between these conditions. The spectrum of clinical symptoms of IgA deficiency is broad; many of those affected are asymptomatic, while others suffer from an assortment of serious problems. Recurrent respiratory and genitourinary tract infections resulting from lack of secreted IgA on mucosal surfaces are common. In addition, problems such as intestinal malabsorption, allergic disease, and autoimmune disorders may also be associated with low IgA levels. The reasons for this variability in the clinical profile of IgA deficiency are not clear but may relate to the ability of some, but not all, patients to substitute IgM for IgA as a mucosal antibody. The defect in IgA deficiency is related to the inability of IgA B cells to undergo normal differentiation to the plasma-cell stage. IgG2 and IgG4 may also be deficient in IgA-deficient patients. No causative defect in IgA genes has been identified, and the surface IgA molecules on these patients' B cells appear to be expressed normally. A gene outside of the immunoglobulin gene complex is suspected to be responsible for this fairly common syndrome.

Other immunoglobulin deficiencies have been reported, but these are rarer. An IgM deficiency has been identified as an autosomal recessive trait. Victims of this condition are subject to severe infection by agents such as meningococcus, which causes fatal disease. IgM deficiency may be accompanied by various malignancies or by autoimmune disease. IgG deficiencies are also rare. These are often not noticed until adulthood and can be effectively treated by administration of immunoglobulin.

ATAXIA TELANGIECTASIA

Although not classified primarily as an immunodeficiency, ataxia telangiectasia is a disease syndrome that includes deficiency of IgA and sometimes of IgE. The syndrome is characterized by difficulty in maintaining balance (ataxia) and by the appearance of broken capillaries (telangiectasia) in the eyes. The primary defect appears to be in a kinase involved in regulation of the cell cycle. The relationship between the immune deficiency and the other defects in ataxia telangiectasia remains obscure.

IMMUNE DISORDERS INVOLVING THE THYMUS

Several immunodeficiency syndromes are grounded in failure of the thymus to undergo normal development. Thymic malfunction has a profound effect on T-cell function; all populations of T cells, including helper, cytolytic, and regulatory varieties, are affected. Immunity to viruses and fungi is especially compromised in those suffering from these conditions.

DiGeorge syndrome, or congenital thymic aplasia, in its most severe form is the complete absence of a thymus. This developmental defect, which is associated with the deletion in the embryo of a region on chromosome 22, causes immunodeficiency along with characteristic facial abnormalities, hypoparathyroidism, and congenital heart disease (Figure 19-4). The stage at which the causative developmental defect occurs has been determined, and the syndrome is sometimes called the *third and fourth pharyngeal pouch syndrome* to reflect its precise embryonic origin. The immune defect includes a profound depression of T-cell numbers and absence of T-cell responses. Although B cells are present in normal numbers, affected individuals do not produce antibody in response to immunization with specific antigens. Thymic transplantation is of some value for correcting the T-cell defects, but many DiGeorge patients have such severe heart disease that their chances for long-term survival are poor, even if the immune defects are corrected.

Whereas the DiGeorge syndrome results from an intrauterine or developmental anomaly, thymic hypoplasia, or the Nezelof syndrome, is an inherited disorder. The mode of inheritance for this rare disease is not known and its presentation varies, making it somewhat difficult to diagnose. As the name implies, thymic hypoplasia is a defect in which a vestigial thymus is unable to serve its function in T-cell development. In some patients, B cells are normal, whereas in others a B-cell deficiency is secondary to the T-cell defect. Affected individuals suffer from chronic diarrhea, viral and fungal infections, and a general failure to thrive.

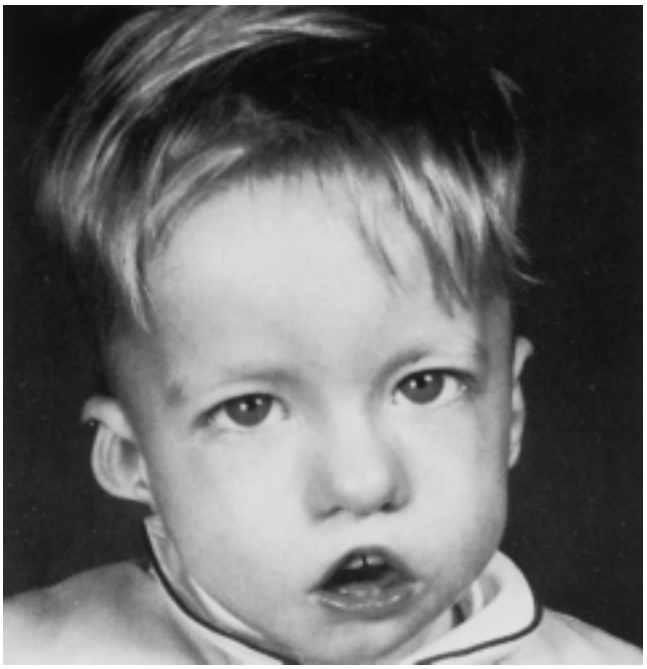


FIGURE 19-4 A child with DiGeorge syndrome showing characteristic dysplasia of ears and mouth and abnormally long distance between the eyes. *[R. Kretschmer et al., 1968,* New Engl. J. Med. ***279:****1295; photograph courtesy of F. S. Rosen.]*

Immunodeficiencies of the Myeloid Lineage Affect Innate Immunity

Immunodeficiencies of the lymphoid lineage affect adaptive immunity. By contrast, defects in the myeloid cell lineage affect the innate immune functions (see Figure 19-1). Most of these defects result in impaired phagocytic processes that are manifested by recurrent microbial infection of greater or lesser severity. There are several stages at which the phagocytic processes may be faulty; these include cell motility, adherence to and phagocytosis of organisms, and killing by macrophages.

REDUCTION IN NEUTROPHIL COUNT

As described in Chapter 2, neutrophils are circulating granulocytes with phagocytic function. Quantitative deficiencies in neutrophils can range from an almost complete absence of cells, called agranulocytosis, to a reduction in the concentration of peripheral blood neutrophils below 1500/mm^3, called granulocytopenia or neutropenia. These quantitative deficiencies may result from congenital defects or may be acquired through extrinsic factors. Acquired neutropenias are much more common than congenital ones.

Congenital neutropenia is often due to a genetic defect that affects the myeloid progenitor stem cell; it results in reduced production of neutrophils during hematopoiesis. In congenital agranulocytosis, myeloid stem cells are present in the bone marrow but rarely differentiate beyond the promyelocyte stage. As a result, children born with this condition show severe neutropenia, with counts of less than 200 neutrophils/mm^3. These children suffer from frequent bacterial infections beginning as early as the first month of life; normal infants are protected at this age by maternal antibody as well as by innate immune mechanisms, including neutrophils. Experimental evidence suggests that this genetic defect results in decreased production of granulocyte colony-stimulating factor (G-CSF) and thus in a failure of the myeloid stem cell to differentiate along the granulocytic lineage (see Figure 2-1).

Neutrophils have a short life span, and their precursors must divide rapidly in the bone marrow to maintain levels of these cells in the circulation. For this reason, agents such as radiation and certain drugs (e.g., chemotherapeutic drugs) that specifically damage rapidly dividing cells are likely to cause neutropenia. Occasionally, neutropenia develops in such autoimmune diseases as Sjögren's syndrome or systemic lupus erythematosus; in these conditions, autoantibodies destroy the neutrophils. Transient neutropenia often develops after certain bacterial or viral infections, but neutrophil counts return to normal as the infection is cleared.

CHRONIC GRANULOMATOUS DISEASE (CGD)

CGD is a genetic disease that has at least two distinct forms: an X-linked form that occurs in about 70% of patients and an autosomal recessive form found in the rest. This disease is rooted in a defect in the oxidative pathway by which phagocytes generate hydrogen peroxide and the resulting reactive products, such as hypochlorous acid, that kill phagocytosed bacteria. CGD sufferers undergo excessive inflammatory reactions that result in gingivitis, swollen lymph nodes, and nonmalignant granulomas (lumpy subcutaneous cell masses); they are also susceptible to bacterial and fungal infection. CGD patients are not subject to infection by those bacteria, such as pneumococcus, that generate their own hydrogen peroxide. In this case, the myeloperoxidase in the host cell can use the bacterial hydrogen peroxide to generate enough hypochlorous acid to thwart infection. Several related defects may lead to CGD; these include a missing or defective cytochrome (cyt b_{558}) that functions in an oxidative pathway and defects in proteins (phagocyte oxidases, or phox) that stabilize the cytochrome. In addition to the general defect in the killer function of phagocytes, there is also a decrease in the ability of mononuclear cells to serve as APCs. Both processing and presentation of antigen are impaired. Increased amounts of antigen are required to trigger T-cell help when mononuclear cells from CGD patients are used as APCs.

The addition of IFN-γ has been shown to restore function to CGD granulocytes and monocytes in vitro. This observation prompted clinical trials of IFN-γ for CGD patients. Encouraging increases in oxidative function and restoration of cytoplasmic cytochrome have been reported in these

patients. In addition, knowledge of the precise gene defects underlying CGD makes it a candidate for gene therapy, and replacement of the defective cytochrome has had promising results (see below).

CHEDIAK-HIGASHI SYNDROME

This autosomal recessive disease is characterized by recurrent bacterial infections, partial oculo-cutaneous albinism (lack of skin and eye pigment), and aggressive but nonmalignant infiltration of organs by lymphoid cells. Phagocytes from patients with this immune defect contain giant granules but do not have the ability to kill bacteria. The molecular basis of the defect is a mutation in a protein (LYST) involved in the regulation of intracellular trafficking. The mutation impairs the targeting of proteins to secretory lysosomes, which makes them unable to lyse bacteria.

LEUKOCYTE ADHESION DEFICIENCY (LAD)

As described in Chapter 15, cell-surface molecules belonging to the integrin family of proteins function as adhesion molecules and are required to facilitate cellular interaction. Three of these, LFA-1, Mac-1, and gp150/95 (CD11a, b, and c, respectively) have a common β chain (CD18) and are variably present on different monocytic cells; CD11a is also expressed on B cells (Table 19-2). An immunodeficiency related to dysfunction of the adhesion molecules is rooted in a defect localized to the common β chain and affects expression of all three of the molecules that use this chain. This defect, called leukocyte adhesion deficiency (LAD), causes susceptibility to infection with both gram-positive and gram-negative bacteria as well as various fungi. Impairment of adhesion of leukocytes to vascular endothelium limits recruitment of cells to sites of inflammation. Viral immunity is somewhat impaired, as would be predicted from the defective T-B cell cooperation arising from the adhesion defect. LAD varies in its severity; some affected individuals die within a few years, others survive into their forties. The reason for the variable disease phenotype in this disorder is not known. LAD is the subject of a Clinical Focus in Chapter 15.

Complement Defects Result in Immunodeficiency or Immune-Complex Disease

Immunodeficiency diseases resulting from defects in the complement system are described in Chapter 13. Many complement deficiencies are associated with increased susceptibility to bacterial infections and/or immune-complex diseases. One of these complement disorders, a deficiency in properdin, which stabilizes the C3 convertase in the alternative complement pathway, is caused by a defect in a gene located on the X chromosome (see Figure 19-2).

TABLE 19-2 Properties of integrin molecules that are absent in leukocyte-adhesion deficiency

	INTEGRIN MOLECULES*		
Property	LFA-1	CR3	CR4
CD designation	CD11a/CD18	CD11b/CD18	CD11c/CD18
Subunit composition	αLβ2	αMβ2	αXβ2
Subunit molecular mass (kDa)			
α chain	175,000	165,000	150,000
β chain	95,000	95,000	95,000
Cellular expression	Lymphocytes	Monocytes	Monocytes
	Monocytes	Macrophages	Macrophages
	Macrophages	Granulocytes	Granulocytes
	Granulocytes	Natural killer cells	
	Natural killer cells		
Ligand	ICAM-1	C3bi	C3bi
	ICAM-2		
Functions inhibited with monoclonal antibody	Extravasation CTL killing T-B conjugate formation ADCC	Opsonization Granulocyte adherence, aggregation, and chemotaxis ADCC	Granulocyte adherence and aggregation

*CR3 = type 3 complement receptor, also known as Mac-1; CR4 = type 4 complement receptor, also known as gp150/95; LFA-1, CR3, and CR4 are heterodimers containing a common β chain but different α chains designated L, M, and X, respectively.

Immunodeficiency Disorders Are Treated by Replacement of the Defective Element

Although there are no cures for immunodeficiency disorders, there are several treatment possibilities. In addition to the drastic option of total isolation from exposure to any microbial agent, treatment options for the immunodeficiencies include:

- replacement of a missing protein
- replacement of a missing cell type or lineage
- replacement of a missing or defective gene

For disorders that impair antibody production, the classic course of treatment is administration of the missing protein immunoglobulin. Pooled human gamma globulin given either intravenously or subcutaneously protects against recurrent infection in many types of immunodeficiency. Maintenance of reasonably high levels of serum immunoglobulin (5 mg/ml serum) will prevent most common infections in the agammaglobulinemic patient. This is generally accomplished by the administration of immunoglobulin that has been selected for antibodies directed against a particular organism. Recent advances in the preparation of human monoclonal antibodies and in the ability to genetically engineer chimeric antibodies with mouse V regions and human-derived C regions make it possible to prepare antibodies specific for important pathogens (see Chapter 5).

Advances in molecular biology make it possible to clone the genes that encode other immunologically important proteins, such as cytokines, and to express these genes in vitro, using bacterial or eukaryotic expression systems. The availability of such proteins allows new modes of therapy in which immunologically important proteins may be replaced or their concentrations increased in the patient. For example, the administration of recombinant IFN-γ has proven effective for patients with CGD, and the use of recombinant IL-2 may help to restore immune function in AIDS patients. Recombinant adenosine deaminase has been successfully administered to ADA deficient SCID patients.

Cell replacement as therapy for immunodeficiencies has been made possible by recent progress in bone-marrow transplantation (see Chapter 21). Replacement of stem cells with those from an immunocompetent donor allows development of a functional immune system (see Clinical Focus Chapter 2). High rates of success have been reported for those who are fortunate enough to have an HLA-identical donor. Careful matching of patients with donors and the ability to manipulate stem-cell populations to select $CD34^+$ precursor cells continues to minimize the risk in this procedure, even when no ideal donor exists. These procedures have been highly successful with SCID infants when haploidentical (complete match of one HLA gene set or haplotype) donor marrow is used. T cells are depleted and $CD34^+$ stem cells are enriched before introducing the donor bone marrow into the SCID infant. Because this therapy has been used only in recent years, it is not known whether transplantation cures the immunodeficiency permanently. A variation of bone-marrow transplantation is the injection of paternal $CD34^+$ cells in utero when the birth of an infant with SCID is expected. Two infants born after this procedure had normal T-cell function and did not develop the infections that characterize SCID.

If a single gene defect has been identified, as in adenosine deaminase deficiency or chronic granulomatous disease, replacement of the defective gene may be a treatment option. Clinical tests of such therapy are underway for SCID caused by ADA deficiency and for chronic granulomatous disease with defective $p67^{phox}$, with promising initial results. Disease remission for up to 18 months was seen in the SCID patients and up to 6 months in the CGD patients. A similar procedure was used in both trials. It begins with obtaining cells ($CD34^+$ stem cells are usually selected for these procedures) from the patient and transfecting them with a normal copy of the defective gene. The transfected cells are then returned to the patient. As this treatment improves, it will become applicable to a number of immunodeficiencies for which a genetic defect is well defined. As mentioned above, these include defects in genes that encode the γ chain of the IL-2 receptor, JAK-3, and ZAP-70, all of which give rise to SCID.

Experimental Models of Immunodeficiency Include Genetically Altered Animals

Immunologists use two well-studied animal models of primary immunodeficiency for a variety of experimental purposes. One of these is the athymic, or nude, mouse; the other is the severe combined immunodeficiency, or SCID, mouse.

NUDE (ATHYMIC) MICE

A genetic trait designated *nu*, which is controlled by a recessive gene on chromosome 11, was discovered in certain mice. Mice homozygous for this trait (*nu/nu*) are hairless and have a vestigial thymus (Figure 19-5). Heterozygotic, *nu*/+, litter mates have hair and a normal thymus. It is not known whether the hairlessness and the thymus defect are caused by the same gene. It is possible that two very closely linked genes control these defects, which, although unrelated, appear together in this mutant mouse. A gene that controls development may be involved, since the pathway that leads to the differential development of the thymus is related to the one that controls the skin epithelial cells. The *nu/nu* mouse cannot easily survive; under normal conditions, the mortality is 100% within 25 weeks and 50% die within the first two weeks after birth. Therefore, when these animals are to be used for experimental purposes, they must be maintained under conditions that protect them from infection. Precautions include use of sterilized food, water, cages, and bedding. The cages are protected from dust by placing them in a laminar flow rack or by the use of air filters fitted over the individual cages.

Nude mice lack cell-mediated immune responses, and they are unable to make antibodies to most antigens. The

FIGURE 19-5 A nude mouse *(nu/nu).* This defect leads to absence of a thymus or a vestigial thymus and cell-mediated immunodeficiency. *[Courtesy of the Jackson Laboratory, Bar Harbor, Maine.]*

immunodeficiency in the nude mouse can be reversed by a thymic transplant. Because they can permanently tolerate both allografts and xenografts, they have a number of practical experimental uses. For example, hybridomas or solid tumors from any origin may be grown as ascites or as implanted tumors in a nude mouse. It is known that the nude mouse does not completely lack T cells; rather, it has a limited population that increases with age. The source of these T cells is not known; an intriguing possibility is that there is an extrathymic source of mature T cells. However, it is more likely that the T cells arise from the vestigial thymus. The majority of cells in the circulation of a nude mouse carry T-cell receptors of the $\gamma\delta$ type instead of the $\alpha\beta$ type that prevails in the circulation of a normal mouse.

THE SCID MOUSE

In 1983, Melvin and Gayle Bosma and their colleagues described an autosomal recessive mutation in mice that gave rise to a severe deficiency in mature lymphocytes. They designated the trait SCID because of its similarity to human severe combined immunodeficiency. The SCID mouse was shown to have early B- and T-lineage cells, but there was a virtual absence of lymphoid cells in the thymus, spleen, lymph nodes, and gut tissue, the usual locations of functional T and B cells. The precursor T and B cells in the SCID mouse appeared to be unable to differentiate into mature functional B and T lymphocytes. Inbred mouse lines carrying the SCID defect have been derived and studied in great detail. The SCID mouse can neither make antibody nor carry out delayed-type hypersensitivity (DTH) or graft-rejection reactions. If the animals are not kept in an extremely clean environment, they succumb to infection early in life. Cells other than lymphocytes develop normally in the SCID mouse; red blood cells, monocytes, and granulocytes are present and functional. SCID mice may be rendered immunologically competent by transplantation of stem cells from normal mice.

The mutation in a DNA protein kinase that causes mouse SCID is a so-called "leaky" mutation, because a certain number of SCID mice do produce immunoglobulin. About half of these leaky SCID mice can also reject skin allografts. This finding suggests that the defective enzyme can function partly in T- and B-cell development, allowing normal differentiation of a small percentage of precursor cells. More recently, immunodeficient SCID-like mice have been developed by deletion of the recombination-activating enzymes (RAG-1 and RAG-2) responsible for the rearrangement of immunoglobulin or T-cell–receptor genes in both B- and T-cell precursors (RAG knockout mice). This gives rise to a defect in both B and T cells of the mouse; neither can rearrange the genes for their receptor and thus neither proceeds along a normal developmental path. Because cells with abnormal rearrangements are eliminated in vivo, both B and T cells are absent from the lymphoid organs of the RAG knockout mouse. In addition to providing a window into possible causes of combined T- and B-cell immunodeficiency, the SCID mouse has proven extremely useful in studies of cellular immunology. Because its rejection mechanisms do not operate, the SCID mouse can be used for studies on cells or organs from various sources. For example, immune precursor cells from human sources may be used to reestablish the SCID mouse's immune system. These human cells can develop in a normal fashion and, as a result, the SCID mouse circulation will contain immunoglobulin of human origin. In one important application, these SCID mice are infected with HIV-1. Although normal mice are not susceptible to HIV-1 infection, the SCID mouse reconstituted with human lymphoid tissue (SCID-Hu mouse) provides an animal model in which to test therapeutic or prophylactic strategies against HIV infection of the transplanted human lymphoid tissue.

AIDS and Other Acquired or Secondary Immunodeficiencies

As described above, a variety of defects in the immune system give rise to immunodeficiency. In addition to the primary immunodeficiencies, there are also acquired, or secondary, immunodeficiencies. One that has been known for some time is called acquired hypogammaglobulinemia.

(As mentioned above, this condition is sometimes confused with common variable immunodeficiency, a condition that shows genetic predisposition.) The origin of acquired hypogammaglobulinemia is unknown, and its major symptom, recurrent infection, manifests itself in young adults. The patients generally have very low but detectable levels of total immunoglobulin. T-cell numbers and function may be normal, but there are some cases with T-cell defects and these may grow more severe as the disease progresses. The disease is generally treated by immunoglobulin therapy, allowing patients to survive into their seventh and eighth decades. Unlike similar deficiencies described above, there is no evidence for genetic transmission of this disease. Mothers with acquired hypogammaglobulinemia deliver normal infants. However, at birth the infants will be deficient in circulating immunoglobulin, because the deficiency in maternal circulation is reflected in the infant.

Another form of secondary immunodeficiency, known as agent-induced immunodeficiency, results from exposure to any of a number of chemical and biological agents that induce an immunodeficient state. Certain of these are drugs used to combat autoimmune diseases such as rheumatoid arthritis or lupus erythematosis. Corticosteroids, which are commonly used for autoimmune disorders, interfere with the immune response in order to relieve disease symptoms. Similarly, a state of immunodeficiency is deliberately induced in transplantation patients who are given immunosuppressive drugs, such as cyclosporin A, in order to blunt the attack of the immune system on transplanted organs. As will be described in Chapter 21, there are recent efforts to use more specific means of inducing tolerance to allografts to circumvent the unwanted side effects of general immunosuppression. The mechanism of action of the immunosuppressive agents varies, although T cells are a common target. In addition, cytotoxic drugs or radiation treatments given to treat various forms of cancer frequently damage the dividing cells in the body, including those of the immune system, and induce a state of immunodeficiency as an unwanted consequence. Patients undergoing such therapy must be monitored closely and treated with antibiotics or immunoglobulin if infection appears.

HIV/AIDS Has Claimed Millions of Lives Worldwide

In recent years, all other forms of immunodeficiency have been overshadowed by an epidemic of severe immunodeficiency caused by the infectious agent called human immunodeficiency virus 1, or HIV-1. The disease that HIV-1 causes, acquired immunodeficiency syndrome (AIDS) was first reported in the United States in 1981 in Los Angeles, New York, and San Francisco. A group of patients displayed unusual infections, including the opportunistic fungal pathogen *Pneumocystis carinii*, which causes a pneumonia called PCP (*P. carinii* pneumonia) in persons with immunodeficiency. In addition to PCP, some patients had Kaposi's sarcoma, an extremely rare skin tumor, as well as other, rarely encountered opportunistic infections. More complete evaluation of the patients showed that they had in common a marked deficiency in cellular immune responses and a significant decrease in the subpopulation of T cells that carry the CD4 marker (T helper cells.) When epidemiologists examined the background of the first patients with this new syndrome, it was found that the majority of those afflicted were homosexual males. As the number of AIDS cases increased and the disease was recognized throughout the world, persons found to be at high risk for AIDS were homosexual males, promiscuous heterosexual individuals of either sex and their partners, intravenous drug users, persons who received blood or blood products prior to 1985, and infants born to HIV-infected mothers.

Since its discovery in 1981, AIDS has increased to epidemic proportions throughout the world. As of December 2000, the cumulative total number of persons in the United States reported to have AIDS was 688,200, and of these approximately 420,000 have died. Although reporting of AIDS cases is mandatory, many states do not require reporting of cases of HIV infection that have not yet progressed to AIDS. Therefore, there is no official count of the number of HIV-infected individuals; as many as 1 million Americans are estimated to be infected. Although the death rate from AIDS has decreased in recent years because of improved treatments, AIDS remains among the leading killers of persons in the 25–44-year-old age range in this country (Figure 19-6). The fact that the number of yearly AIDS deaths has leveled off is encouraging, but does not indicate an end to the epidemic in this country; there were an estimated 45,000 persons newly infected in 2000.

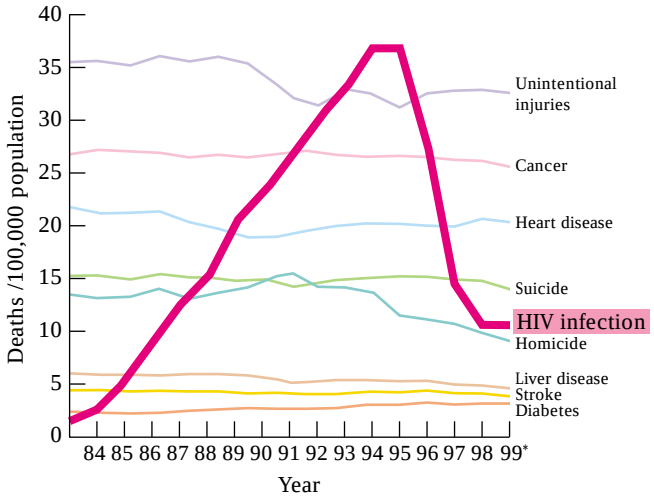


FIGURE 19-6 Death rates of the leading causes of death in persons aged 25–44 years in the United States for the years 1982–99 (* = preliminary data). The heavy line shows that the death rate per 100,000 persons caused by AIDS surpassed any other single cause of death in this age range during the period 1993 to 1995. The recent decrease in AIDS deaths in the United States is attributed to improvements in anti-HIV drug therapy, which prolongs the lives of patients. *[National Vital Statistics Report.]*

The magnitude of the AIDS epidemic in the United States is dwarfed by figures for other parts of the world. The global distribution of those afflicted with AIDS is shown in Figure 19-7. In sub-Saharan Africa an estimated 25.3 million persons were living with AIDS at the end of 2000, and in South and Southeast Asia there were another 5.8 million. There are an estimated 36.1 million persons worldwide with AIDS, including over 5 million children. In addition, there are over 8 million children who have been orphaned by the death of their parents from AIDS. Recent estimates from the World Health Organization indicate that there were 5.3 million new HIV infections in 2000, or an average of almost 15,000 persons infected each day during that year. This number includes a daily infection toll of 1700 children under 15 years of age.

The initial group of AIDS patients in the United States and Western Europe was predominantly white and male. Although this remains the group predominantly affected in these areas, more recently the distribution in the United States has shifted to include a larger proportion of women (20% in 2000 versus 6% in 1985) and an increasing proportion of minorities (39% black and Hispanic in 1996 versus 11% in 1985). Worldwide, the number of AIDS patients distributes more equally between males and females, and in sub-Saharan Africa, which has the highest incidence of AIDS, about 50% of those afflicted are females.

HIV-1 Spreads by Sexual Contact, Infected Blood, and from Mother to Infant

Although the precise mechanism by which HIV-1 infects an individual is not known, epidemiological data indicate that common means of transmission include homosexual and heterosexual intercourse, receipt of infected blood or blood products, and passage from mothers to infants. Before tests for HIV in the blood supply were routinely used, patients who received blood transfusions and hemophiliacs who received blood products were at risk for HIV-1 infection. Exposure to infected blood accounts for the high incidence of AIDS among intravenous drug users who normally share hypodermic needles. Infants born to mothers who are infected with HIV-1 are at high risk of infection. Unless infected mothers are treated with anti-viral agents before delivery, approximately

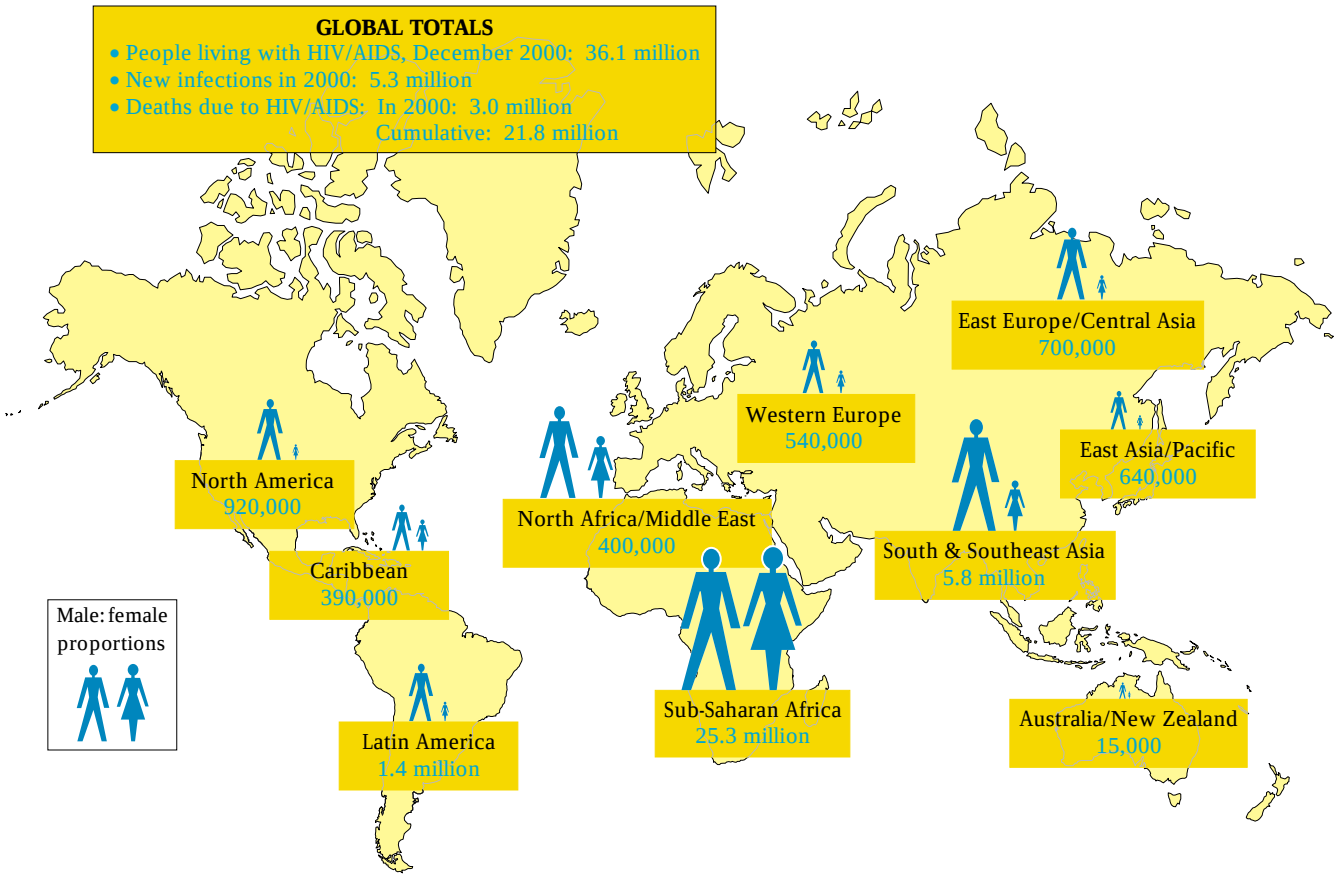


FIGURE 19-7 The global AIDS epidemic. The estimated worldwide distribution of AIDS cases as of December 2000. There were approximately 36.1 million persons living with AIDS as of December 2000; most of these were in sub-Saharan Africa and Southeast Asia. In North America and Western Europe, about 80% of those affected were men, whereas in Africa nearly equal numbers of women and men have AIDS. *[HIV/AIDS UNAIDS: Report on the Global Epidemic, 2000.]*

30% of infants born to them will become infected with the virus (see Clinical Focus). Possible vehicles of passage from mother to infant include blood transferred in the birth process and milk in the nursing period. Transmission from an infected to an uninfected individual is most likely by transmission of HIV-infected cells—in particular, macrophages, dendritic cells, and lymphocytes.

In the worldwide epidemic, it is estimated that 75% of the cases of HIV transmission are attributable to heterosexual contact. While the probability of transmission by vaginal intercourse is lower than by other means, such as IV drug use or receptive anal intercourse, the likelihood of infection is greatly enhanced by the presence of other sexually transmitted diseases (STDs). In populations where prostitution is rampant, STDs flourish and provide a powerful cofactor for the heterosexual transmission of HIV-1. Reasons for this increased infection rate include the lesions and open sores present in many STDs, which favor the transfer of HIV-infected blood during intercourse.

While the AIDS epidemic has engendered an understandable fear of infection among most informed individuals, there are also exaggerated claims of the ease with which HIV infection may be passed on. At present, there is no evidence that casual contact with or touching an infected person can spread HIV-1 infection. Airborne transmission has never been observed to cause infection. In virtually every well-documented case of HIV-1 infection, there is evidence for contact with blood, milk, semen, or vaginal fluid from an infected individual. Research workers and medical professionals who take reasonable precautions have a very low incidence of AIDS, despite repeated contact with infected materials. The risk of transmitting HIV infection can be minimized by simple precautionary measures, including the avoidance of any practice that could allow exposure of broken or abraded skin or any mucosal membrane to blood from a potentially infected person. The use of condoms when having sex with individuals of unknown infection status is highly recommended. One factor contributing to the spread of HIV is the long period after infection during which no clinical signs may appear but during which the infected individual may infect others. Thus, universal use of precautionary measures is important whenever and wherever infection status is uncertain.

It is a sobering thought that the epidemic of AIDS came at a time when many believed that infectious diseases no longer posed a serious threat to people in the United States and other industrialized nations. Vaccines and antibiotics controlled most serious infectious agents. The eradication of smallpox in the world had recently been celebrated, and polio was yielding to widespread vaccination efforts; these were considered milestones on the road to elimination of most infectious diseases. The outbreak of AIDS shattered this complacency and triggered a massive effort to combat this disease. In addition, the immunodeficiency that characterizes AIDS has allowed re-emergence of other infectious diseases, such as tuberculosis, which have the potential to spread into populations not infected with HIV.

A Retrovirus, HIV-1, Is the Causative Agent of AIDS

Within a few years after recognition of AIDS as an infectious disease, the causative agent was discovered and characterized by efforts in the laboratories of Luc Montagnier in Paris and Robert Gallo in Bethesda (Figure 19-8). This immunodeficiency syndrome was novel at the time in that the type of virus causing it was a **retrovirus.** Retroviruses carry their genetic information in the form of RNA. When the virus enters a cell, the RNA is reverse transcribed to DNA by a virally encoded enzyme, reverse transcriptase (RT). As the name implies, RT reverses the normal transcription process and makes a DNA copy of the viral RNA genome. This copy, which is called a **provirus,** is integrated into the cell genome and is replicated along with the cell DNA. When the provirus is expressed to form new virions, the cell lyses. Alternatively, the provirus may remain latent in the cell until some regulatory signal starts the expression process.

Only one other human retrovirus, human T-cell lymphotropic virus I, or HTLV-I, had been described before HIV-1. This retrovirus is endemic in the southern part of Japan and in the Caribbean. Although most individuals infected with HTLV-I display no clinical signs of disease, a small percentage develop serious illness, either adult T-cell leukemia, which is aggressive and usually fatal, or a disabling progressive neurologic disorder called HTLV-I–associated myelopathy (called tropical spastic paraparesis in early reports). Although comparisons of their genomic sequences revealed that HIV-1 is not a close relative of HTLV-I, similarities in overall characteristics led to use of the name HTLV-III for the AIDS virus in early reports. There is also a related human virus called HIV-2, which is less pathogenic in humans than HIV-1. HIV-2 is similar to viruses isolated from monkeys; it infects certain nonhuman primates that are not infected by HIV-1.

Viruses related to HIV-1 have been found in nonhuman primates. These viruses, variants of simian immunodeficiency virus, or SIV, cause immunodeficiency disease in certain infected monkeys. Normally, SIV strains cause no disease in their normal host but produce immunodeficiency similar to AIDS when injected into another species. For example, the virus from African green monkeys (SIV_{agm}) is present in a high percentage of normal healthy African green monkeys in the wild. However, when SIV_{agm} is injected into macaques, it causes a severe, often lethal, immunodeficiency.

A number of other animal retroviruses more or less similar to HIV-1 have been reported. These include the feline and bovine immunodeficiency viruses and the mouse leukemia virus. Study of these animal viruses has yielded information concerning the general nature of retrovirus action, but specific information about HIV-1 cannot be gained by infecting ani-

VISUALIZING CONCEPTS

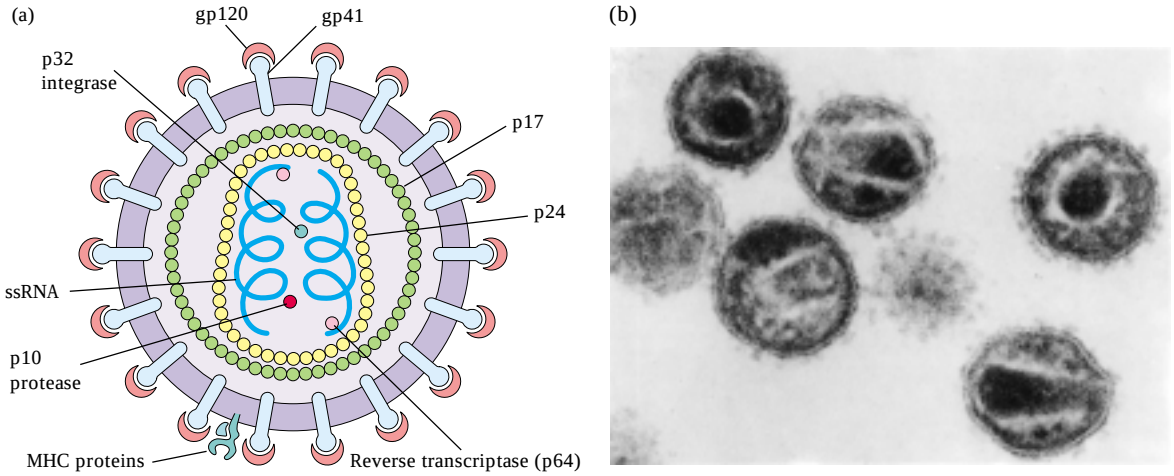


FIGURE 19-8 Structure of HIV. (a) Cross-sectional schematic diagram of HIV virion. Each virion expresses 72 glycoprotein projections composed of gp120 and gp41. The gp41 molecule is a transmembrane molecule that crosses the lipid bilayer of the viral envelope. Gp120 is associated with gp41 and serves as the viral receptor for CD4 on host cells. The viral envelope derives from the host cell and contains some host-cell membrane proteins, including class I and class II MHC molecules. Within the envelope is the viral core, or nucleocapsid, which includes a layer of a protein called p17 and an inner layer of a protein called p24. The HIV genome consists of two copies of single-stranded RNA, which are associated with two molecules of reverse transcriptase (p64) and nucleoid proteins p10, a protease, and p32, an integrase. (b) Electron micrograph of HIV virions magnified 200,000 times. The glycoprotein projections are faintly visible as "knobs" extending from the periphery of each virion. *[Part (a) adapted from B. M. Peterlin and P. A. Luciw, 1988,* AIDS ***2:****S29; part (b) from a micrograph by Hans Geldenblom of the Robert Koch Institute (Berlin), in R. C. Gallo and L. Montagnier, 1988,* Sci. Am. ***259****(6):41.]*

mals because HIV-1 does not replicate in them. Only the chimpanzee supports infection with HIV-1 at a level sufficient to be useful in vaccine trials, but infected chimpanzees only rarely develop AIDS, which limits the value of this model in the study of viral pathogenesis. In addition, the number of chimpanzees available for such studies is low and both the expense and the ethical issues involved in experiments with chimpanzees preclude widespread use of this infection model. The SCID mouse (see above) reconstituted with human lymphoid tissue for infection with HIV-1 has been useful for certain studies of HIV-1 infection, especially in the development of drugs to combat viral replication.

Reasons for the limited host range of HIV-1 include not only the cell-surface receptors required for entry of the virus into the host cell but dependence of the virus on host-cell factors for early events in its replication process, such as transcription and splicing of viral messages. For example, mouse cells transfected with genes that mediate expression of the human receptors for HIV-1 will not support HIV-1 replication because they lack other host factors. By contrast, cells from hamsters or rabbits transfected to express the human receptors support levels of virus replication similar to those seen in human cells. Despite some progress in understanding the factors needed for HIV-1 infection, no clear candidate for an animal model of HIV-1 infection exists. This lack of a suitable infection model hampers efforts to develop both drugs and vaccines to combat AIDS.

Recent publicity focused on activists claiming that there is no connection between HIV and AIDS and that antiretroviral drugs are useless to combat the disease. The so-called AIDS denialists believe that precautions against infection are not necessary, and that testing for HIV infection has no value because treatment is worthless or harmful. Some even deny the existence of an epidemic or that AIDS is an actual disease. While science requires that all ideas should be tested, denial of medical care to infected individuals based on this fringe group's notions is not an option. All relevant studies support a near perfect correlation between HIV infection and disease; drugs that lower the amount of virus in a patient (viral load) prevent opportunistic infections.

CLINICAL FOCUS

Prevention of Infant HIV Infection by Anti-Retroviral Treatment

Approximately 500,000 infants become infected with HIV each year. The majority of these infections result from transmission of virus from HIV-infected mothers during childbirth or by transfer of virus from milk during breast-feeding. The incidence of maternal acquired infection can be reduced as much as 67% by treatment of the infected mother with a course of Zidovudine (AZT) for several months prior to delivery, and treatment of her infant for 6 weeks after birth. This treatment regimen is widely used in the U.S. However, the majority of worldwide HIV infection of infants occurs in sub-Saharan Africa and other less developed areas, where the cost and timing of the Zidovudine regimen render it an impractical solution to the problem of maternal-infant HIV transmission.

A 1999 clinical trial of the anti-retroviral Nevirapine (viramune) brings hope for a practical way to combat infant HIV infection under less than ideal conditions of clinical care. The trial took place at Mulago Hospital in Kampala, Uganda, and enrolled 645 mothers who tested positive for HIV infection. About half of the mothers were given a single dose of Nevirapine at the onset of labor and their infants were given a single dose 24–30 hours after birth. The dose and timing were dictated by the customary rapid discharge at the hospital. The control arm of the study involved a more extensive course of Zidovudine, but in-country conditions did not allow exact replication of the full course administered to infected mothers in the U.S.

The overall rate of infection for infants born to untreated mothers is estimated to be about 37%. When the full course of Zidovudine is used, the rate drops to 20%. The highly encouraging results of the Uganda study revealed infection in only 13.1% of the babies in the Nevirapine group when tested at 16 weeks of age. Of those given a short course of Zidovudine, 25.1% were infected at this age compared to 40.2% in a small group given placebo. From this study it appears that the single dose of Nevirapine is the most effective means found thus far to prevent maternal-infant transmission of HIV infection—even better than the more extensive and costly regimen currently used in developed countries. These results must be verified and the possibility of unexpected side effects must be explored. However, this result gives hope for reduction of infant infection in parts of the world where access to medical care is limited.

As mentioned above, the study was designed to conform to the reality of maternal health care in Kampala; it fits this system perfectly. The use of Nevirapine has other significant advantages, including stability of the drug at room temperature and reasonable cost. The dose of Nevirapine administered to the mother and infant costs about 200 times less than the Zidovudine regimen in current use in the U.S. In fact, the treatment is sufficiently inexpensive to suggest that it may be cost-effective to treat all mothers at the time of delivery in those areas where rates of infection are high, because the Nevirapine treatment costs less than the tests used to determine HIV infection. Obviously, such a strategy must be embarked upon cautiously, given the danger of long-term side effects and other unexpected problems.

Mural showing mother and child on an outside wall of Mulago Hospital Complex in Kampala, Uganda, site of the clinical trial demonstrating that maternal-infant HIV-1 transmission was greatly reduced by Nevirapine. *[Courtesy of Thomas Quinn, Johns Hopkins University.]*

In Vitro Studies Revealed the HIV-1 Replication Cycle

The AIDS virus can infect human T cells in culture, replicating itself and in many cases causing the lysis of the cell host (Figure 19-9). Much has been learned about the life cycle of HIV-1 from in vitro studies. The various proteins encoded by the viral genome have been characterized and the functions of most of them are known (Figure 19-10).

The first step in HIV infection is viral attachment and entry into the target cell. HIV-1 infects T cells that carry the CD4 antigen on their surface; in addition, certain HIV strains will infect monocytes and other cells that have CD4 on their surface. The preference for $CD4^+$ cells is due to a high-affinity interaction between a coat (envelope or env) protein of HIV-1 and cell-surface CD4. Although the virus binds to CD4 on the cell surface, this interaction alone is not sufficient for entry and productive infection. Expression of other cell-surface molecules, coreceptors present on T cells and monocytes, is required for HIV-1 infection. The infection of a T cell, depicted in Figure 19-11a, is assisted by the T-cell coreceptor CXCR4 (in initial reports, this molecule was called fusin). An analogous receptor called CCR5 functions for the monocyte or macrophage.

After the virus has entered the cell, the RNA genome of the virus is reverse transcribed and a cDNA copy (provirus) integrates into the host genome. The integrated provirus is transcribed and the various viral RNA messages spliced and translated into proteins, which along with a complete new copy of the RNA genome are used to form new viral particles (Figure 19-11b). The gag proteins of the virus are cleaved by the viral protease into the forms that make up the nuclear capsid (see Figure 19-10) in a mature infectious viral particle. As will be described below, different stages in this viral replication process can be targeted by antiviral drugs.

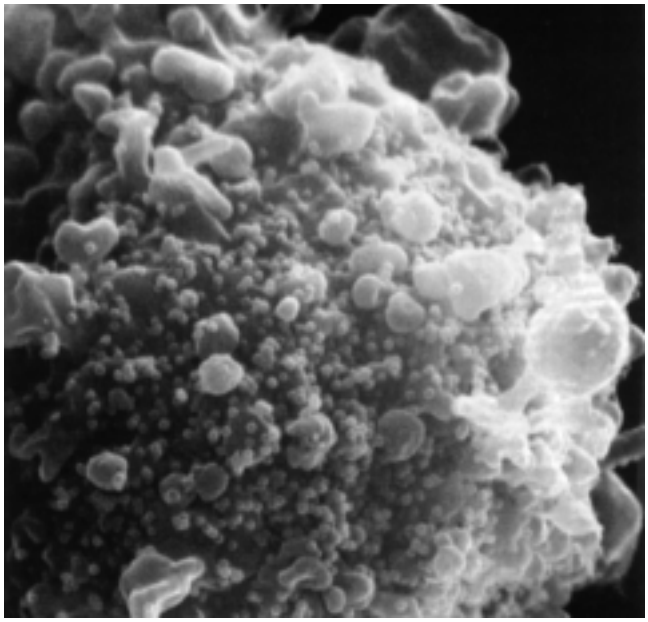


FIGURE 19-9 Once the HIV provirus has been activated, buds representing newly formed viral particles can be observed on the surface of an infected T cell. The extensive cell damage resulting from budding and release of virions leads to the death of infected cells. *[Courtesy of R. C. Gallo, 1988,* J. Acquired Immune Deficiency Syndromes ***1****:521.]*

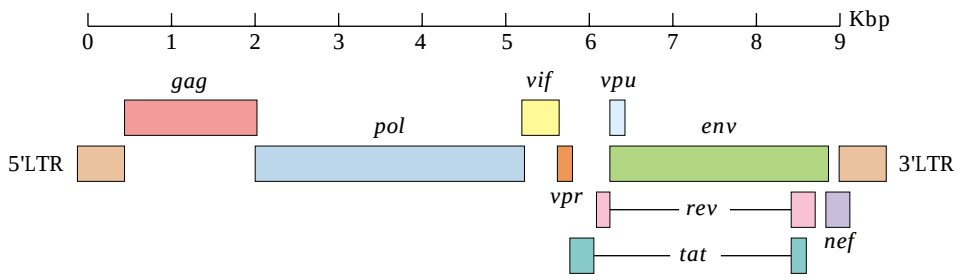
The discovery that CXCR4 and CCR5 serve as coreceptors for HIV-1 on T cells and macrophages, respectively, explained why some strains of HIV-1 preferentially infect T cells (T-tropic strains) while others prefer macrophages (M-tropic strains). A T-tropic strain uses CXCR4, while the M-tropic strains use CCR5. This use of different coreceptors also helped to explain the different roles of cytokines and chemokines in virus replication. It was known from in vitro studies that certain chemokines had a negative effect on virus replication while certain pro-inflammatory cytokines had a positive effect. Both of the HIV coreceptors, CCR5 and CXCR4, function as receptors for chemokines (see Table 15-2). Because the receptors cannot bind simultaneously to HIV-1 and to their chemokine ligand, there is competition for the receptor between the virus and the normal ligand (Figure 19-11c), and the chemokine can block viral entry into the host cell. Whereas the chemokines compete with HIV for usage of the coreceptor and thus inhibit viral entry, the pro-inflammatory cytokines induce greater expression of the chemokine receptors on the cell surface, making the cells more susceptible to viral entry.

HIV-1 infection of T cells with certain strains of virus leads to the formation of giant cells or syncytia. These are formed by the fusion of a group of cells caused by the interaction of the viral envelope protein gp120 on the surface of infected cells with CD4 and the coreceptors on the surface of other cells, infected or not. After the initial binding, the action of other cell-adhesion molecules welds the cells together in a large multinuclear mass with a characteristic fused ballooning membrane which eventually bursts. Formation of syncytia may be blocked by antibodies to some of the epitopes of the CD4 molecule, by soluble forms of the CD4 molecule (prepared by in vitro expression of a CD4 gene genetically engineered to lack the transmembrane portion), and by antibodies to cell-adhesion molecules. Individual isolates of HIV-1 differ in their ability to induce syncytia formation.

Isolates of HIV-1 from different sources were formerly classified as syncytia-inducing (SI) or non–syncytium-inducing (NSI). In most cases, these differences correlated with the ability of the virus to infect T cells or macrophages: T-tropic strains were SI, whereas M-tropic strains were NSI. More recent classifications of HIV-1 are based on which coreceptor the virus uses; there is good but not absolute correlation between the use of CXCR4, which is present on T cells, and syncytia-inducing ability. The NSI strains use

Go to www.whfreeman.com/immunology Molecular Visualization
Viral Antigens *See Introduction and HIV gp120.*

(a)



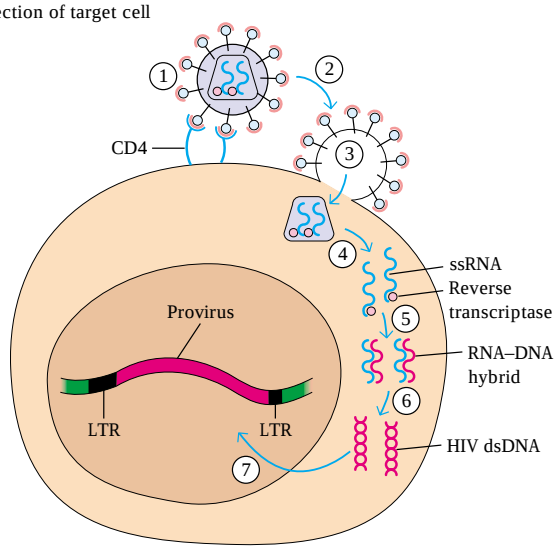
(b)

Gene	Protein product	Function of encoded proteins
gag	53-kDa precursor	*Nucleocapsid proteins*
	↓	
	p17	Forms outer core-protein layer
	p24	Forms inner core-protein layer
	p9	Is component of nucleoid core
	p7	Binds directly to genomic RNA
env	160-kDa precursor	*Envelope glycoproteins*
	↓	
	gp41	Is transmembrane protein associated with gp120 and required for fusion
	gp120	Protrudes from envelope and binds CD4
pol	Precursor	*Enzymes*
	↓	
	p64	Has reverse transcriptase and RNase activity
	p51	Has reverse transcriptase activity
	p10	Is protease that cleaves *gag* precursor
	p32	Is integrase
		Regulatory proteins
tat	p14	Strongly activates transcription of proviral DNA
rev	p19	Allows export of unspliced and singly spliced mRNAs from nucleus
		Auxiliary proteins
nef	p27	Down-regulates host-cell class I MHC and CD4
vpu	p16	Is required for efficient viral assembly and budding. Promotes extracellular release of viral particles, degrades CD4 in ER
vif	p23	Promotes maturation and infectivity of viral particle
vpr	p15	Promotes nuclear localization of preintegration complex, inhibits cell division

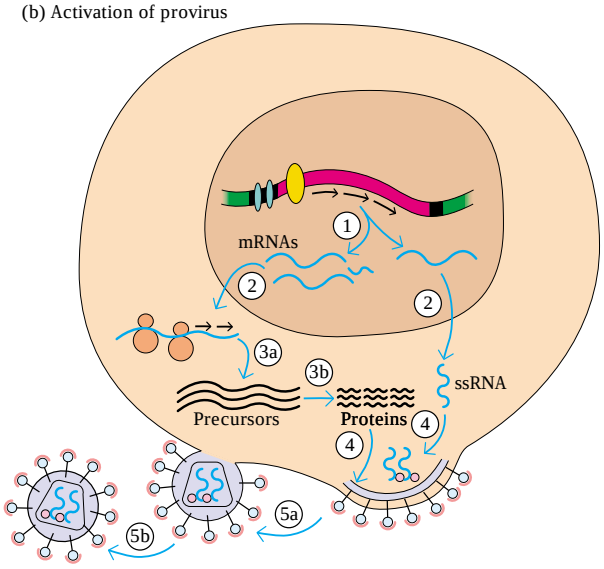
FIGURE 19-10 Genetic organization of HIV-1 (a) and functions of encoded proteins (b). The three major genes—*gag, pol,* and *env*—encode polyprotein precursors that are cleaved to yield the nucleocapsid core proteins, enzymes required for replication, and envelope core proteins. Of the remaining six genes, three (*tat, rev,* and *nef*) encode regulatory proteins that play a major role in controlling expression; two (*vif* and *vpu*) encode proteins required for virion maturation; and one (*vpr*) encodes a weak transcriptional activator. The 5′ long terminal repeat (LTR) contains sequences to which various regulatory proteins bind. The organization of the HIV-2 and SIV genomes are very similar, except that the *vpu* gene is replaced by *vpx* in both of these.

VISUALIZING CONCEPTS

(a) Infection of target cell



(b) Activation of provirus



1. HIV gp120 binds to CD4 on target cell.
2. Fusogenic domain in gp41 and CXCR4, a G-protein–linked receptor in the target-cell membrane, mediate fusion.
3. Nucleocapsid containing viral genome and enzymes enters cells.
4. Viral genome and enzymes are released following removal of core proteins.
5. Viral reverse transcriptase catalyzes reverse transcription of ssRNA, forming RNA–DNA hybrids.
6. Original RNA template is partially degraded by ribonuclease H, followed by synthesis of second DNA strand to yield HIV dsDNA.
7. The viral dsDNA is then translocated to the nucleus and integrated into the host chromosomal DNA by the viral integrase enzyme.

1. Transcription factors stimulate transcription of proviral DNA into genomic ssRNA and, after processing, several mRNAs.
2. Viral RNA is exported to cytoplasm.
3a. Host-cell ribosomes catalyze synthesis of viral precursor proteins.
3b. Viral protease cleaves precursors into viral proteins.
4. HIV ssRNA and proteins assemble beneath the host-cell membrane, into which gp41 and gp120 are inserted.
5a. The membrane buds out, forming the viral envelope.
5b. Released viral particles complete maturation; incorporated precursor proteins are cleaved by viral protease present in viral particles.

(c)

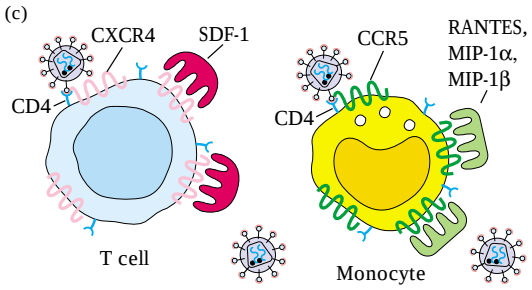


FIGURE 19-11 Overview of HIV infection of target cells and activation of provirus. (a) Following entry of HIV into cells and formation of dsDNA, integration of the viral DNA into the host-cell genome creates the provirus. (b) The provirus remains latent until events in the infected cell trigger its activation, leading to formation and release of viral particles. (c) Although CD4 binds to the envelope glycoprotein of HIV-1, a second receptor is necessary for entry and infection. The T-cell–tropic strains of HIV-1 use the coreceptor CXCR4, while the macrophage-tropic strains use CCR5. Both are receptors for chemokines, and their normal ligands can block HIV infection of the cell.

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Retrovirus

CCR5, which is present on monocytes. Studies of the viral envelope protein gp120 identified a region called the V3 loop, which plays a role in the choice of receptors used by the virus. A study by Mark Goldsmith and Bruce Chesebro and their colleagues indicates that a single amino acid difference in this region of gp120 may be sufficient to determine which receptor is used.

HIV-1 Infection Leads to Opportunistic Infections

Isolation of HIV-1 and its growth in culture has allowed purification of viral proteins and the development of tests for infection with the virus. The most commonly used test is for the presence of antibodies directed against proteins of HIV-1. These generally appear in the serum of infected individuals by three months after the infection has occurred. When the antibodies appear, the individual is said to have seroconverted or to be seropositive for HIV-1. Although the precise course of HIV-1 infection and disease onset varies considerably in different patients, a general scheme for the progression of AIDS can be constructed (Figure 19-12). The course of HIV-1 infection begins with no detectable anti-HIV-1 antibodies or virus and progresses to the full AIDS syndrome. Diagnosis of AIDS includes evidence for infection with HIV-1 (presence of antibodies or virus in blood), greatly diminished numbers of $CD4^+$ T cells (< 200 cells/mm^3), impaired or absent delayed-hypersensitivity reactions, and the occurrence of opportunistic infections (Table 19-3). Patients with AIDS generally succumb to tuberculosis, pneumonia, severe wasting diarrhea, or various malignancies. The time between acquisition of the virus and death from the immunodeficiency averages nine to twelve years. In the period between infection and severe disease, there may be few symptoms. Primary infection in a minority of patients may be symptomatic with fever, lymphadenopathy (swollen lymph nodes), and a rash, but these symptoms generally do not persist more than a few weeks. Most commonly, primary infection goes unnoticed and is followed by a long chronic phase, during which the infected individual shows little or no overt sign of HIV-1 infection.

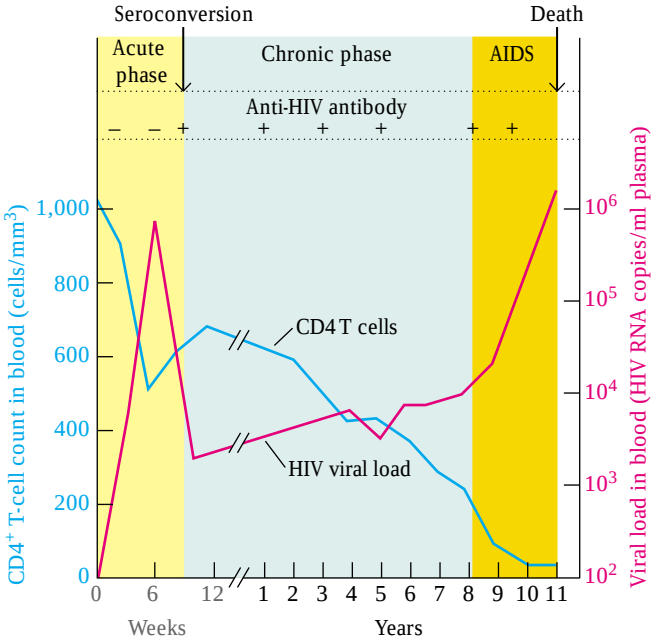

FIGURE 19-12 Serologic profile of HIV infection showing three stages in the infection process. Soon after infection, viral RNA is detectable in the serum. However, HIV infection is most commonly detected by the presence of anti-HIV antibodies after seroconversion, which normally occurs within a few months after infection. Clinical symptoms indicative of AIDS generally do not appear for at least 8 years after infection, but this interval is variable. The onset of clinical AIDS is usually signaled by a decrease in T-cell numbers and an increase in viral load. *[Adapted from A. Fauci et al., 1996,* Annals Int. Med. ***124****:654.]*

The first overt indication of AIDS may be opportunistic infection with the fungus *Candida albicans*, which causes the appearance of sores in the mouth (thrush) and, in women, a vulvovaginal yeast infection that does not respond to treatment. A persistent hacking cough caused by *P. carinii* infection of the lungs may also be an early indicator. A rise in the level of circulating HIV-1 (viral load) in the plasma and concomitant drop in the number of $CD4^+$ T cells generally previews this first appearance of symptoms. Some relation between the $CD4^+$ T-cell number and the type of infection experienced by the patient has been established (see Table 19-3). Of intense interest to immunologists are the events that take place between the initial confrontation with HIV-1 and the takeover and collapse of the host immune system. Understanding how the immune system holds HIV-1 in check during this chronic phase can lead to the design of effective therapeutic and preventive strategies.

Research into the process that underlies the progression of HIV infection to AIDS has revealed a dynamic interplay between the virus and the immune system. The initial infection event causes dissemination of virus to lymphoid organs and a resultant strong immune response. This response, which involves both antibody and cytotoxic $CD8^+$ T lymphocytes, keeps viral replication in check; after the initial burst of viremia (high levels of virus in the circulation), the viral level in the circulation achieves a steady state. Although the infected individual normally has no clinical signs of disease at this stage, viral replication continues and virus can be detected in circulation by sensitive PCR assays for viral RNA. These PCR-based assays, which measure **viral load** (the number of copies of viral genome in the plasma), have assumed a major role in determination of the patient's status and prognosis. Even when the level of virus in the circulation is stable, large amounts of virus are produced in infected $CD4^+$ T cells; as many as 10^9 virions are released every day and continually infect and destroy additional host T cells (Figure 19-13a). Despite this high rate of replication, the virus is kept in check by the immune system throughout the

TABLE 19-3 Clinical diagnosis of HIV-infected individuals

	CLINICAL CATEGORIES*		
$CD4^+$ T-cell count	A	B	C
≥ 500/μl	A1	B1	**C1**
200–499/μl	A2	B2	**C2**
< 200μl	**A3**	**B3**	**C3**

CLASSIFICATION OF AIDS INDICATOR DISEASE

Category A

- Asymptomatic: no symptoms at the time of HIV infection
- Acute primary infection: glandular fever-like illness lasting a few weeks at the time of infection
- Persistent generalized lymphadenopathy (PGL): lymph-node enlargement persisting for 3 or more months with no evidence of infection

Category B

- Bacillary angiomatosis
- Candidiasis, oropharyngeal (thrush)
- Candidiasis, vulvovaginal: persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Constitutional symptoms such as fever (> 38.5°C) or diarrhea lasting > 1 month
- Hairy leukoplakia, oral
- Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly by tubo-ovarian abscess
- Peripheral neuropathy

Category C

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

*All categories shown in bold type are considered AIDS. For Category A diagnosis, no condition in categories B or C can be present; for category B, no category C condition can be present.

SOURCE: CDC guidelines for AIDS diagnosis, 1993 revision.

chronic phase of infection, and the level of virus in circulation from about six months after infection is a good predictor of the course of disease. Low levels of virus in this period correlate with a longer time in which the infected individual remains free of opportunistic infection. But the virus eventually breaks through host immune defenses, resulting in an increase in viral load, a decrease in $CD4^+$ T cell numbers, increased opportunistic infection, and death of the patient.

While the viral load in plasma remains fairly stable throughout the period of chronic HIV infection, examination of the lymph nodes has revealed a different story. Fragments of nodes obtained by biopsy from infected subjects

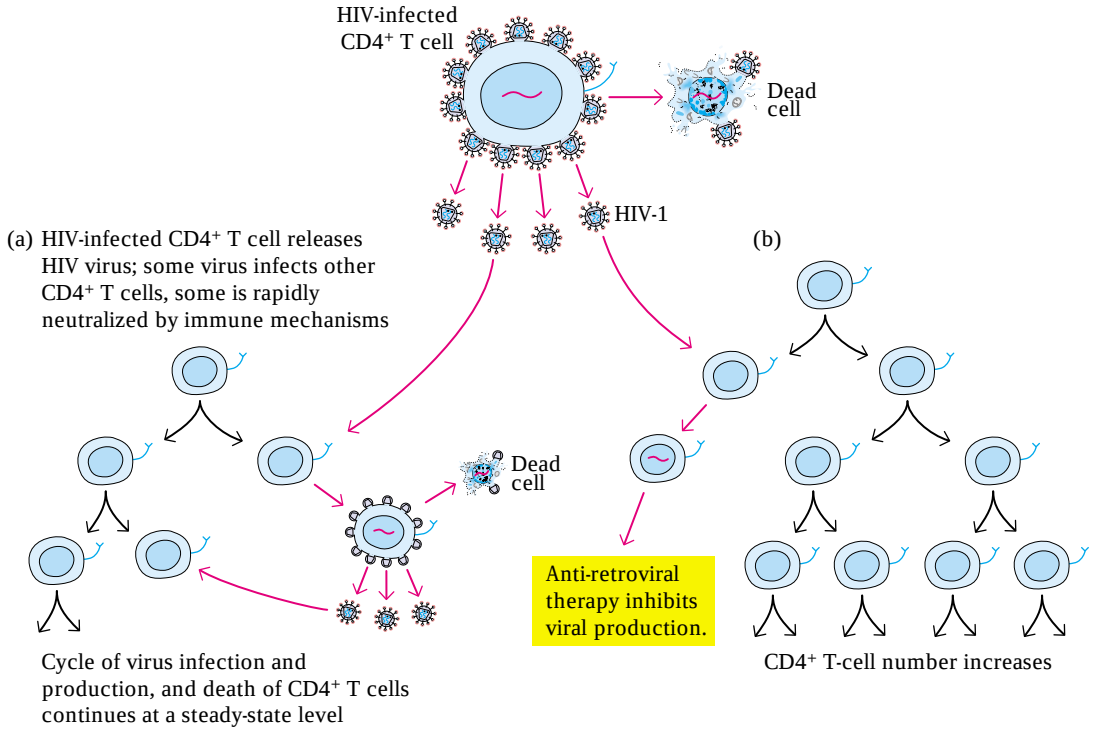

FIGURE 19-13 Production of virus by $CD4^+$ T cells and maintenance of a steady state of viral load and T-cell number. (a) A dynamic relationship exists between the number of $CD4^+$ cells and the amount of virus produced. As virus is produced, new $CD4^+$ cells are infected, and these infected cells have a half-life of 1.5 days. In progression to full AIDS, the viral load increases and the $CD4^+$ T-cell count decreases before onset of opportunistic infections. (b) If the viral load is decreased by anti-retroviral treatment, the $CD4^+$ T-cell number increases almost immediately.

showed high levels of infected cells at all stages of infection; in many cases, the structure of the lymph node had been completely destroyed by virus long before plasma viral load increased above the steady-state level.

The decrease in $CD4^+$ T cells is the hallmark of AIDS. Several explanations have been advanced for the depletion of these cells in patients. In early studies, direct viral infection and destruction of $CD4^+$ T cells was discounted as the primary cause, because the large numbers of circulating HIV-infected T cells predicted by the model were not found. More recent studies indicate that the reason for the difficulty in finding the infected cells is that they are so rapidly killed by HIV; the half-life of an actively infected $CD4^+$ T cell is less than 1.5 days. There are smaller numbers of $CD4^+$ T cells that become infected but do not actively replicate virus. These latently infected cells persist for long periods, and the integrated proviral DNA replicates in cell division along with cell DNA. Studies in which viral load is decreased by anti-retroviral therapy show a concurrent increase in $CD4^+$ T cell numbers (Figure 19-13b). These data support a model of dynamic interaction between virus and T cells, with simultaneous high levels of viral production and rapid depletion of infected $CD4^+$ T cells. While other mechanisms for depletion of $CD4^+$ T cells may be envisioned, infection with HIV remains the prime suspect.

Not only depletion of $CD4^+$ T cells but other immunologic consequences can be measured in HIV-infected individuals during the progression to AIDS. These include a decrease or absence of delayed hypersensitivity to antigens to which the individual normally reacts. Serum levels of immunoglobulins, especially IgG and IgA, show a sharp increase in the AIDS patient. This increase may be due to increased levels in HIV-infected individuals of a B-cell subpopulation with low CD21 expression and enhanced immunoglobulin secretion. This population proliferates poorly in response to B-cell mitogens. Cellular parameters of immunologic response, such as the proliferative response to mitogens, to antigens, or to alloantigens, all show a marked decrease. Generally, the HIV-infected individual loses the ability to mount T-cell responses in a predictable sequence: responses to specific antigens (for example, influenza virus) are first lost, then response to alloantigens declines, and lastly, the response to mitogens such as concanavalin A or phytohemagglutinin can no longer be detected. Table 19-4 lists some immune abnormalities in AIDS.

HIV-1 infected individuals often display dysfunction of the central and peripheral nervous systems. Specific viral DNA and RNA sequences have been detected by HIV-1 probes in the brains of children and adults with AIDS, suggesting that viral replication occurs there. Quantitative comparison of speci-

TABLE 19-4 Immunologic abnormalities associated with HIV infection

Stage of infection	Typical abnormalities observed
	LYMPH NODE STRUCTURE
Early	Infection and destruction of dendritic cells; some structural disruption
Late	Extensive damage and tissue necrosis; loss of folicular dendritic cells and germinal centers; inability to trap antigens or support activation of T and B cells
	T HELPER (T_H) CELLS
Early	No in vitro proliferative response to specific antigen
Late	Decrease in T_H-cell numbers and corresponding helper activities; no response to T-cell mitogens or alloantigens
	ANTIBODY PRODUCTION
Early	Enhanced nonspecific IgG and IgA production but reduced IgM synthesis
Late	No proliferation of B cells specific for HIV-1: no detectable anti-HIV antibodies in some patients; increased numbers of B cells with low CD21 and enhanced Ig secretion.
	CYTOKINE PRODUCTION
Early	Increased levels of some cytokines
Late	Shift in cytokine production from T_H1 subset to T_H2 subset
	DELAYED-TYPE HYPERSENSITIVITY
Early	Highly significant reduction in proliferative capacity of T_{DTH} cells and reduction in skin-test reactivity
Late	Elimination of DTH response; complete absence of skin-test reactivity
	T CYTOTOXIC (T_C) CELLS
Early	Normal reactivity
Late	Reduction but not elimination of CTL activity due to impaired ability to generate CTLs from T_C cells

mens from brain, lymph node, spleen, and lung of AIDS patients with progressive encephalopathy indicated that the brain was heavily infected. A frequent complication in later stages of HIV infection is AIDS dementia complex, a neurological syndrome characterized by abnormalities in cognition, motor performance, and behavior. Whether AIDS dementia and other clinical and histopathological effects observed in the central nervous systems of HIV-infected individuals are a direct effect of viral antigens on the brain, a consequence of immune responses to the virus, or a result of infection by opportunistic agents remains unknown.

Therapeutic Agents Inhibit Retrovirus Replication

Development of a vaccine to prevent the spread of AIDS is the highest priority for immunologists, but it is also critical to develop drugs and therapies that can reverse the effects of HIV-1 in infected individuals. The number of HIV-infected persons is estimated to be close to 1 million in the United States alone; for all of these individuals to develop AIDS would be an enormous tragedy. There are several strategies for development of effective anti-viral drugs. The life cycle of HIV shows several susceptible points that might be blocked by pharmaceutical agents (Figure 19-14). The key to success of such therapies is that they must be specific for HIV-1 and interfere minimally with normal cell processes. Thus far, two types of antiviral agents have found their way into common usage. The first success in treatment was with drugs that interfere with the reverse transcription of viral RNA to cDNA; several drugs in common use operate at this step. A second stage of viral replication that has proved amenable to blockade is the step at which precursor proteins are cleaved into the units needed for construction of a new mature virion. This step requires the action of a specific viral protease, which can be inhibited by chemical agents; this precludes the formation of infectious viral particles.

Several antiretroviral drugs are now in widespread use (Table 19-5) that either interfere with reverse transcription or inhibit the viral protease. The prototype of the drugs that

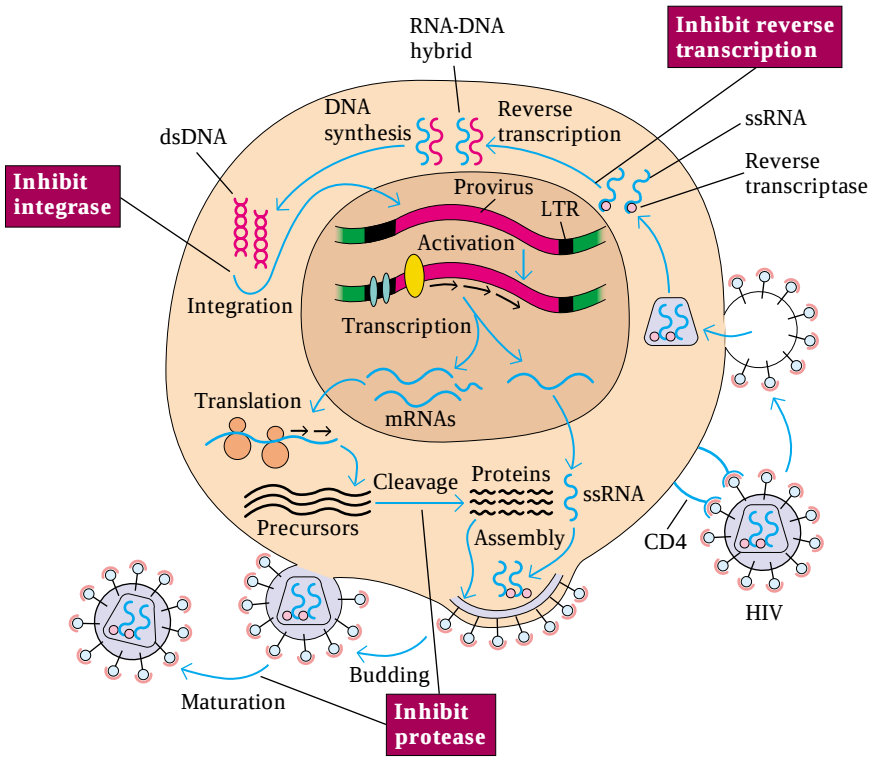

FIGURE 19-14 Stages in the viral replication cycle that provide targets for therapeutic antiretroviral drugs. At present, the licensed drugs with anti-HIV activity block the step of reverse transcription of viral RNA to cDNA or inhibit the viral protease necessary to cleave viral precursor proteins into the proteins needed to assemble a new virion and complete its maturation to infectious virus.

interfere with reverse transcription is zidovudine, or AZT (azidothymidine). The introduction of AZT, a nucleoside analog, into the growing cDNA chain of the retrovirus causes termination of the chain. AZT is effective in some but not all patients, and its efficacy is further limited because long-term use has several adverse side effects and because resistant viral mutants develop in treated patients. The administered AZT is used not only by the HIV-1 reverse transcriptase but also by human DNA polymerase. The incorporation of AZT into the DNA of host cells kills them. Precursors of red blood cells are especially sensitive to AZT, which thus causes anemia in addition to other side effects. A different approach to blocking reverse transcription employs drugs such as Nevirapine, which inhibit the action of the reverse transcriptase enzyme (see Table 19-5).

A second class of drugs called protease inhibitors has proven effective when used in conjunction with AZT and/or other nucleoside analogs. Current treatment for AIDS is a combination therapy, using regimens designated HAART (highly active anti-retroviral therapy). In most cases, this combines the use of two nucleoside analogs and one protease inhibitor. The combination strategy appears to overcome the ability of the virus to rapidly produce mutants that are drug resistant. In many cases, HAART has lowered viral load to levels that are not detectable by current methods and has improved the health of AIDS patients to the point that they can again function at a normal level. The decrease in the number of AIDS deaths in the United States in recent years (see Figure 19-6) is attributed to this advance in therapy. Despite the optimism engendered by success with HAART, present drawbacks include a strict time schedule of administration and the large number of pills to be taken every day. In addition, there may be serious side effects (see Table 19-5) that, in some patients, may be too severe to allow use of HAART.

The success of HAART in treating AIDS has opened discussion of whether it might be possible to eradicate all virus from an infected individual and thus actually cure AIDS. Most AIDS experts are not convinced that this is possible, mainly because of the persistence of latently infected $CD4^+$ T cells and macrophages, which can serve as a reservoir of infectious virus if the provirus should be activated. Even with a viral load beneath the level of detection by PCR assays, the immune system may not recover sufficiently to clear virus should it begin to replicate in response to some activation signal. In addition, virus may persist in sites such as the brain, not readily penetrated by the antiretroviral drugs, even though the virus in circulation is undetectable. The use of immune modulators, such as recombinant IL-2, in conjunction with HAART is be-

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HIV-1 *Reverse Transcriptase.*

TABLE 19-5 Some anti-HIV drugs in clinical use

Generic name (other names)	Typical dosage	Some potential side effects
REVERSE TRANSCRIPTASE INHIBITORS: NUCLEOSIDE ANALOG		
Didanosine (Videx, ddI)	2 pills, 2 times a day on empty stomach	Nausea, diarrhea, pancreatic inflammation, peripheral neuropathy
Lamivudine (Epivir, 3TC)	1 pill, 2 times a day	Usually none
Stavudine (Zerit, d4T)	1 pill, 2 times a day	Peripheral neuropathy
Zalcitabine (HIVID, ddC)	1 pill, 3 times a day	Peripheral neuropathy, mouth inflammation, pancreatic inflammation
Zidovudine (Retrovir, AZT)	1 pill, 2 times a day	Nausea, headache, anemia, neutropenia (reduced levels of neutrophil white blood cells), weakness, insomnia
Pill containing lamivudine and zidovudine (Combivir)	1 pill, 2 times a day	Same as for zidovudine
REVERSE TRANSCRIPTASE INHIBITORS: NONNUCLEOSIDE ANALOGUES		
Delavirdine (Rescriptor)	4 pills, 3 times a day (mixed into water); not within an hour of antacids or didanosine	Rash, headache, hepatitis
Nevirapine (Viramune)	1 pill, 2 times a day	Rash, hepatitis
PROTEASE INHIBITORS		
Indinavir (Crixivan)	2 pills, 3 times a day on empty stomach or with a low-fat snack and not within 2 hours of didanosine	Kidney stones, nausea, headache, blurred vision, dizziness, rash, metallic taste in mouth, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance
Nelfinavir (Viracept)	3 pills, 3 times a day with some food	Diarrhea, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance
Ritonavir (Norvir)	6 pills, 2 times a day (or 4 pills, 2 times a day if taken with saquinavir) with food and not within 2 hours of didanosine	Nausea, vomiting, diarrhea, abdominal pain, headache, prickling sensation in skin, hepatitis, weakness, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance
Saquinavir (Invirase, a hard-gel capsule; Fortovase, a soft-gel capsule)	6 pills, 3 times a day (or 2 pills, 2 times a day if taken with ritonavir) with a large meal	Nausea, diarrhea, headache, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance

SOURCE: J. G. Bartlett and R. D. Moore, 1998, Improving HIV therapy, *Sci. Am.* **279**(1):87.

ing examined as a strategy to help reconstitute the immune system and restore normal immune function.

New drugs are in various stages of development. One promising class of drugs interferes with integration of the viral DNA into the host genome (see Figure 19-14). Others drugs being considered act at the stage of viral attachment to the host cell. It should be stressed that the development of any drug to the point at which it can be used for patients is a long and arduous procedure. The drugs that pass the rigorous tests for safety and efficacy represent a small fraction of those that receive initial consideration.

A Vaccine May Be the Only Way to Stop the HIV/AIDS Epidemic

The AIDS epidemic continues to rage despite the advances in therapeutic approaches outlined above. The present expense of HAART (as much as $15,000 per year), the strict regimen

TABLE 19-6 Why AIDS does not fit the paradigm for classic vaccine development

Classic vaccines mimic natural immunity against reinfection generally seen in individuals recovered from infection; there are no recovered AIDS patients.
Most vaccines protect against disease, not against infection; HIV infection may remain latent for long periods before causing AIDS.
Most vaccines protect for years against viruses that change very little over time; HIV-1 mutates at a rapid rate and efficiently selects mutant forms that evade immunity.
Most effective vaccines are whole-killed or live-attenuated organisms; killed HIV-1 does not retain antigenicity and the use of a live retrovirus vaccine raises safety issues.
Most vaccines protect against infections that are infrequently encountered; HIV may be encountered daily by individuals at high risk.
Most vaccines protect against infections through mucosal surfaces of the respiratory or gastrointestinal tract; the great majority of HIV infection is through the genital tract.
Most vaccines are tested for safety and efficacy in an animal model before trials with human volunteers; there is no suitable animal model for HIV/AIDS at present.

SOURCE: Adapted from A. S. Fauci, 1996, An HIV vaccine: breaking the paradigms, *Proc. Am. Assoc. Phys.* **108**:6.

required, and the possibility of side effects precludes universal application. Even if eradication of the virus in individuals treated with combination therapy becomes possible, it will not greatly influence the epidemic in the developing countries, which include the majority of AIDS victims. It is likely that effective, inexpensive, and well-tolerated drugs will be developed in the future, but at present it appears that the best option to stop the spread of AIDS is a safe, effective vaccine that prevents infection and progression to disease. Why do we not have an AIDS vaccine? The best answer to this question is to examine the special conditions that must be addressed in developing a safe, effective vaccine for this disease (Table 19-6).

Most effective vaccines mimic the natural state of infection. Individuals who recover from most diseases are immune from subsequent attacks. The infection by HIV-1 and progression to immunodeficiency syndrome flourishes even in the presence of circulating antibodies directed against proteins of the virus. Immunity may hold the virus in check for a time, but as mentioned above, it rarely exceeds 12 years. In a rare subset of infected individuals called long-term nonprogressors, the period of infection without disease is longer and even indefinite. Another group for whom immunity seems to function are those who are persistently exposed but who remain seronegative. In this category are a low percentage of commercial sex workers in areas of high endemic infection, such as Nairobi, who have not become infected despite multiple daily exposures to infected individuals. Because the state of immunity (which antibodies are present and what type of cellular immunity is active) in these individuals is not clear or consistent, it is difficult to duplicate for vaccine development. Certain of the long-term nonprogressors or exposed and noninfected individuals have mutations and deletions in genes encoding cell coreceptors that slow the progress of viral attack on their immune system, rather than an immune response that is holding HIV replication in check.

Most vaccines prevent disease, not infection. Polio and influenza vaccines hold the virus produced by infected cells in check so that it does not cause harm to the host, and it is then cleared. HIV-1 does not fit this model, because it integrates into the host genome and may remain latent for long periods. As described above in the context of treatment strategies, eradication of a retrovirus is not a simple matter. Clearance of a retrovirus is a difficult goal for a vaccine; every copy of the virus and every infected cell, including those latently infected, must be eradicated from the host. However even without complete eradication, an HIV vaccine may benefit the infected individual; furthermore, a vaccine that caused a lowered viral load would help to control the spread of infection. A recent study in Uganda of sexual partners unmatched for infection showed that low viral load in the infected partner inhibited spread to the uninfected mate.

Most vaccines prevent infection by viruses that show little variation. The instability of its genome differentiates HIV-1 from most viruses for which successful vaccines have been developed. With the exception of influenza, for which the vaccines must be changed periodically, most viruses that can be controlled by immunization show only minor variability in structure. For comparison, consider that the rhinoviruses that cause the common cold have more than 100 subtypes; therefore no effective vaccine has been developed. HIV-1 shows variation in most viral antigens; and the rate of replication may be as high as 10^9 viruses per day. This variability along with the high rate of replication allows the production of viruses with multiple mutations; some of these allow escape from immunity. The fact that significant differences in viral-envelope protein sequences have been seen in viral iso-

lates taken from the same patient at different times indicates that variation occurs and that some of the variants replicate, presumably because they have learned to evade host immune defenses. Data showing that antibody from advanced AIDS patients will not neutralize virus isolated from that patient, but will kill other strains of HIV-1, argues that HIV-1 does evade the immune system by mutation of proteins targeted by antibody.

The majority of successful vaccines are live-attenuated or heat-killed organisms. While there are exceptions to this, notably the recombinant protein used for hepatitis B vaccine and the conjugate used for *Haemophilus influenzae* B vaccine (see Chapter 18), most of the widely used vaccines are attenuated organisms. The development of a live-attenuated retrovirus vaccine from animal viruses engineered to include HIV antigens is a possible route. However, the use of live vaccines is predicated on the supposition that the immunity raised will clear the vaccine virus from the host. This is not easily done for a retrovirus, which integrates into the host genome. A massive testing effort would be required to assure that a live retroviral vaccine was safe and did not cause chronic host infection. On the positive side, clinical studies using other viruses such as attenuated vaccinia or canarypox as carriers for genes encoding HIV proteins have passed phase I (safety) trials and have advanced to phase II (efficacy) trials.

For most viruses, the frequency of exposure to infection is rare or seasonal. In many high-risk individuals, such as commercial sex workers, monogamous sexual partners of HIV-infected subjects, and intravenous drug users, the virus is encountered frequently and, potentially, in large doses. An AIDS vaccine is thus asked to prevent infection against a constant attack by the virus and/or massive doses of virus; this is not normally the case with other viruses for which immunization has proved successful.

Most vaccines protect against respiratory or gastrointestinal infection. In addition to the frequency of exposure to HIV, which may be extraordinarily high for some high-risk individuals, there is also the question of route. The majority of successful vaccines protect against viruses that are encountered in the respiratory and gastrointestinal tracts; the most common route of HIV-1 infection is by the genital tract. It is not known whether the immunity established by conventional vaccination procedures will protect against infection by this route. Although the lack of a completely relevant animal model precludes an in-depth test of protection, preliminary vaccine studies using rectal or vaginal challenge of immunized primates with HIV-SIV chimeric viruses (SHIV) show protection to this challenge route.

Development of most vaccines through to clinical trials relies upon animal experiments. Testing a vaccine for safety and efficacy normally involves challenge of an animal with the virus under conditions similar to those encountered in the human. In this way, the correlates of protective immunity are established. For example, if high titers of $CD8^+$ T cells and neutralizing antibody are necessary for protection in an animal, then $CD8^+$ T-cell immunity and antibody should be measured in human trials of the vaccine. Thus far, animal studies of HIV infection and disease have yielded only a few hard facts about immune responses that are protective against infection or that prevent progression to disease. Many results involve a specific virus in a particular host and are not easily extrapolated to universal concepts, because they depend upon host factors as well the relationships between the immunizing and challenge strains of virus. However, experiments have shown that passive immunization with antibodies taken from HIV-infected chimpanzees protect macaques from challenge with SHIV strains bearing HIV-envelope glycoprotein. Further indication that antibodies can prevent infection is given by studies in which monoclonal antibodies protected macaques from vaginal challenge with SHIV. In all cases the antibodies needed to be present at the time of challenge. Post-challenge administration of antibodies was not effective in preventing infection.

Although there are no reports of great success in human HIV vaccine trials, research in this difficult area continues to be active. At the end of the year 2000, there were 60 phase I trials in progress involving recombinant proteins, peptides, DNA vaccines, and poxvirus/recombinant protein combination trials. At the same time, only 6 phase II trials were in progress and only 2 candidates advanced to phase III—the 3rd, or final, phase of clinical trials—the test of efficacy. Despite a massive effort, progress remains slow. There is now hope that a vaccine can emerge from the accumulating knowledge on human responses to the vaccine candidates.

In addition to developing a scientific rationale, behavioral and social issues influence the development and testing of candidate AIDS vaccines. Counseling concerning safe sexual practice must be part of the care given to volunteers in a vaccine trial. Will this influence the results? Would a lowering of the infection rate in all groups taking part in the trial preclude seeing a meaningful difference in the infection rate between the vaccine and the placebo groups? A further consideration is the fact that anyone successfully immunized against the AIDS virus will become seropositive and will test positive in the standard screening assays for infection. What ramifications will this have? Will the more complex viral-load assays be needed to ascertain whether an immunized individual is actually infected?

It is clear that development of an AIDS vaccine is not a simple exercise in classic vaccinology. More research is needed to understand how this viral attack against the immune system can be thwarted. While much has been written about the subject and large-scale initiatives are proposed, the path to an effective vaccine is not obvious. It is certain only that all data must be carefully analyzed and that all possible means of creating immunity must be tested. This is one of the greatest public health challenges of our time. An intense and cooperative effort must be launched to devise, test, and deliver a safe and effective vaccine for AIDS. The status of current efforts in AIDS vaccine development is summarized in Table 19-7.

TABLE 19-7 Vaccine strategies under study

Vaccine constituents	Status	Advantages	Disadvantages
		VACCINES ELICITING ANTI-HIV ANTIBODIES	
Viral surface proteins, such as gp120	In phase I and II trials, which examine safety	Safe and simple to prepare	Vaccine-elicited antibodies have failed to recognize HIV from patients
Whole, killed HIV	Not under study in humans	Should present HIV surface proteins in a relatively natural conformation; simple to prepare	Slight risk that preparations might include some active virus; inactivated virus might shed its proteins and become ineffective
Pseudovirions (artificial viruses containing HIV surface proteins)	Close to phase I trials	Present HIV surface proteins in a relatively natural conformation	Difficult to produce and to ensure long-term stability
		VACCINES ELICITING CELLULAR RESPONSES	
Live vector viruses (non-HIV viruses engineered to carry genes encoding HIV proteins)	In phase II trials	Makers can control amount and kinds of viral proteins produced	Complicated to prepare; current vaccines elicit modest immune response
Naked DNA containing one or more HIV genes	In phase I trials	Simple and inexpensive to prepare	Some worry that integration of HIV genes into human cells could harm patients
HIV peptides (protein fragments)	In phase I trials	Simple to prepare	Do not elicit strong immune response
		VACCINES ELICITING ANTIBODY AND CELLULAR RESPONSES	
Combinations of elements, such as pure gp120 protein plus canarypox vector	In phase II trials	Should stimulate both arms of the immune response at once	Complicated to prepare
Live, attenuated HIV	Not under study in humans; being assessed in nonhuman primates	Most closely mimics HIV; may interfere with ability of infectious HIV to replicate	Vaccine virus could potentially cause AIDS

SOURCE: D. Baltimore and C. Heilman, HIV vaccines: prospects and challenges, 1998, *Sci. Am.* **279**(1):101.

SUMMARY

- Immunodeficiency results from the failure of one or more components of the immune system. Primary immunodeficiencies are present at birth, secondary or acquired immunodeficiencies arise from a variety of causes.
- Immunodeficiencies may be classified by the cell types involved and may affect either the lymphoid or the myeloid cell lineage or both.
- The gene defects that underlie primary immunodeficiency allow precise classification. Genetic defects in molecules involved in signal transduction or in cellular communication are found in many immunodeficiencies.
- Lymphoid immunodeficiencies affect T cells, B cells, or both. Failure of thymic development results in severe immunodeficiency and can hinder normal development of B cells, because of the lack of cellular cooperation.
- Myeloid immunodeficiency causes impaired phagocytic function. Those affected suffer from increased susceptibility to bacterial infection.

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Review and quiz of key terms

- Severe combined immunodeficiency, or SCID, may result from a number of different defects in the lymphoid lineage and is usually fatal.
- Selective immunoglobulin deficiencies are a less severe form of immunodeficiency and result from defects in more highly differentiated cell types.
- Immunodeficiency may be treated by replacement of the defective or missing protein, cells, or gene. Administration of human immunoglobulin is a common treatment.
- Animal models for immunodeficiency include nude and SCID mice. Gene knockout mice provide a means to study the role of specific genes on immune function.
- Secondary immunodeficiency results from injury or infection; the most common form is HIV/AIDS caused by a retrovirus, human immunodeficiency virus-1.
- HIV-1 infection is spread mainly by sexual contact, passage of blood, and from HIV-infected mother to infant.
- Infection with HIV-1 results in severe impairment of immune function marked by depletion of $CD4^+$ T cells and death from opportunistic infection, usually within 10 years of infection.
- Treatment of HIV infection with anti-retroviral drugs can cause lowering of viral load and relief from infection, but this is temporary and no cures have been documented.
- Efforts to develop a vaccine for HIV/AIDS have not yet been successful. The millions of new infections in the year 2000 emphasize the need for an effective vaccine.

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USEFUL WEB SITES

http://www.scid.net/

The SCID home page contains links to periodicals and databases with information about SCID.

http://www.nhgri.nih.gov/DIR/LGT/SCID/

This site from the National Insitute for Human Genome Research includes a database of mutations in X-linked SCID.

http://hivinsite.ucsf.edu

Information about the global AIDS epidemic can be accessed from this site.

http://www.cdc.gov

Up-to-date information concerning AIDS epidemiology in the United States can be obtained at this site.

http://hiv-web.lanl.gov

Web site maintained by the Los Alamos National laboratories containing all available sequence data on HIV and SIV along with up-to-date reviews on topics of current interest to AIDS research.

ftp://nlmpubs.nlm.nih.gov/aids/adatabases/drugs.txt

A listing with detailed information for several hundred drugs under development for HIV infection and opportunistic infections associated with AIDS; maintained by the National Library of Medicine.

http://www.niaid.nih.gov/daids/vaccine/abtvaccines.htm

Information about AIDS vaccines from the National Institute of Allergy and Infectious Diseases, NIH. Includes links to documents about vaccines in general.

Study Questions

CLINICAL FOCUS QUESTION The spread of HIV/AIDS from infected mothers to infants can be reduced by single-dose regimens of the reverse transcriptase inhibitor Nevirapine. What would you want to know before giving this drug to all mothers and infants (without checking infection status) at delivery in areas of high endemic infection?

1. Indicate whether each of the following statements is true or false. If you think a statement is false, explain why.

a. DiGeorge syndrome is a congenital birth defect resulting in absence of the thymus.
b. X-linked agammaglobulinemia (XLA) is a combined B-cell and T-cell immunodeficiency disease.
c. The hallmark of a phagocytic deficiency is increased susceptibility to viral infections.
d. In chronic granulomatous disease, the underlying defect is in a cytochrome or an associated protein.
e. Injections of immunoglobulins are given to treat individuals with X-linked agammaglobulinemia.
f. Multiple defects have been identified in human SCID.
g. Mice with the SCID defect lack functional B and T lymphocytes.
h. Mice with SCID-like phenotype can be produced by knockout of *RAG* genes.
i. Children born with SCID often manifest increased infections by encapsulated bacteria in the first months of life.
j. Failure to express class II MHC molecules in bare-lymphocyte syndrome affects cell-mediated immunity only.

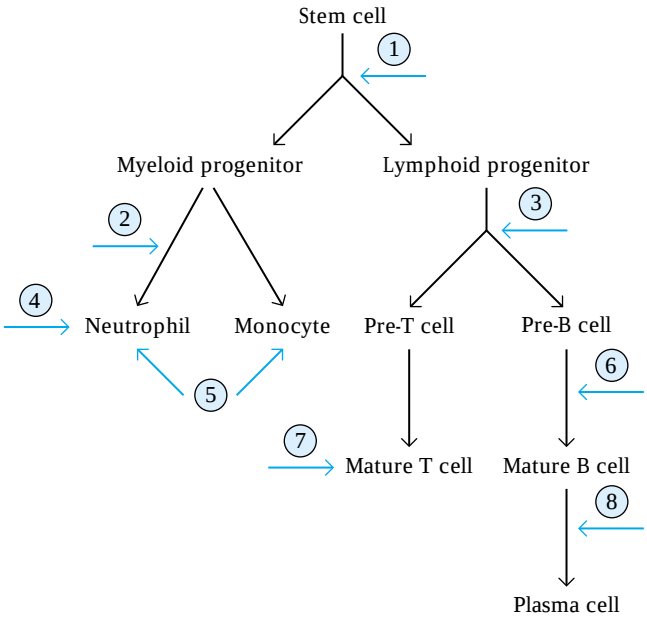
2. Granulocytes from patients with leukocyte-adhesion deficiency (LAD) express greatly reduced amounts of three integrin molecules designated CR3, CR4, and LFA-1.

a. What is the nature of the defect that results in decreased expression or in no expression of these receptors in LAD patients?
b. What is the normal function of the integrin molecule LFA-1? Give specific examples.

3. Immunologists have studied the defect in SCID mice in an effort to understand the molecular basis for severe combined immunodeficiency in humans. In both SCID mice and humans with this disorder, mature B and T cells fail to develop.

a. In what way do rearranged Ig heavy-chain genes in SCID mice differ from those in normal mice?
b. In SCID mice, rearrangement of κ light-chain DNA is not attempted. Explain why.
c. If you introduced a rearranged, functional μ heavy-chain gene into progenitor B cells of SCID mice, would the κ light-chain DNA undergo a normal rearrangement? Explain your answer.

4. The accompanying figure outlines some of the steps in the development of immune-system cells. The numbered arrows indicate the cell type whose function is defective or the developmental step that does not occur in particular immunodeficiency diseases. Identify the defective cell type or developmental step associated with each of the following diseases. Use each number only once.



a. Chronic granulomatous disease
b. Severe combined immunodeficiency disease (SCID)
c. Congenital agranulocytosis
d. Reticular dysgenesis
e. Common variable hypogammaglobulinemia
f. X-linked agammaglobulinemia
g. Leukocyte-adhesion deficiency (LAD)
h. Bare-lymphocyte syndrome

5. Indicate whether each of the following statements is true or false. If you think a statement is false, explain why.

a. HIV-1 and HIV-2 are more closely related to each other than to SIV.
b. HIV-1 causes immune suppression in both humans and chimpanzees.
c. SIV is endemic in the African green monkey.
d. The anti-HIV drugs zidovudine and indinavir both act on the same point in the viral replication cycle.
e. T-cell activation increases transcription of the HIV proviral genome.
f. Patients with advanced stages of AIDS always have detectable antibody to HIV.
g. The polymerase chain reaction is a sensitive test used to detect antibodies to HIV.
h. If HAART is successful, viral load will decrease.

6. Various mechanisms have been proposed to account for the decrease in the numbers of $CD4^+$ T cells in HIV-infected individuals. What seems to be the most likely reason for depletion of $CD4^+$ T cells?

7. Would you expect the viral load in the blood of HIV-infected individuals in the chronic phase of HIV-1 infection to vary?

8. If viral load begins to increase in the blood of an HIV-infected individual and the level of $CD4^+$ T cells decrease, what would this indicate about the infection?

9. Why do clinicians monitor the level of skin-test reactivity in HIV-infected individuals? What change might you expect to see in skin-test reactivity with progression into AIDS?

10. Certain chemokines have been shown to suppress infection of cells by HIV, and pro-inflammatory cytokines enhance cell infection. What is the explanation for this?

11. Treatments with combinations of anti-HIV drugs (HAART) have reduced virus levels significantly in some treated patients and delayed the onset of AIDS. If an AIDS patient becomes free of opportunistic infection and has no detectable virus in the circulation, can that person be considered cured?

12. Suppose you are a physician who has two HIV-infected patients. Patient B. W. has a fungal infection (candidiasis) in the mouth, and patient L. S. has a *Mycobacterium* infection. The $CD4^+$ T-cell counts of both patients are about 250 per mm^3. Would you diagnose either patient or both of them as having AIDS?