IMMUNE DEFICIENCY DISEASES
Immune deficiency diseases may be caused by inherited defects affecting immune system development, or they may result from secondary effects of other diseases (e.g., infection, malnutrition, aging, immunosuppression, autoimmunity, or chemotherapy). Clinically, patients with immune deficiency present with increased susceptibility to infections as well as to certain forms of cancer. The type of infections in a given patient depends largely on the component of the immune system that is affected. Patients with defects in Ig, complement, or phagocytic cells typically suffer from recurrent infections with pyogenic bacteria, whereas those with defects in cell-mediated immunity are prone to infections caused by viruses, fungi, and intracellular bacteria.

Primary Immune Deficiencies:
Primary immune deficiency states are (fortunately) rare but have nevertheless contributed greatly to our understanding of the development and function of the immune system. Most primary immune deficiency diseases are genetically determined and affect either adaptive immunity (i.e., humoral or cellular) or innate host defense mechanisms.

*X-Linked Agammaglobulinemia (XLA, Bruton Disease):*
is one of the more common forms of primary immune deficiency. It is characterized by the failure of pre-B cells to differentiate into B cells; as a consequence, and as the name implies, there is a resultant absence of gamma globulin in the blood.

*Common Variable Immunodeficiency:*
This is a heterogeneous group of disorders characterized by hypogammaglobulinemia, impaired antibody responses to infection (or vaccination), and increased susceptibility to infections.

*Isolated IgA Deficiency:*
The most common of all the primary immune deficiency diseases, IgA deficiency affects about 1 in 700 white individuals. Recall that IgA is the major Ig in mucosal secretions and is thus involved in airway and gastrointestinal defense. Although most individuals with this condition are asymptomatic, weakened mucosal defenses predispose patients to recurrent sinopulmonary infections and diarrhea.
*Hyper-IgM Syndrome:

Patients with the hyper-IgM syndrome produce normal (or even supranormal) levels of IgM antibodies to antigens but lack the ability to produce the IgG, IgA, or IgE isotypes; the underlying defect is an inability of T cells to induce B-cell isotype switching. The most common genetic abnormality is mutation of the gene encoding CD40L. This gene is located on the X chromosome; consequently, in approximately 70% of the cases, hyper-IgM syndrome is X-linked. In the remaining patients, the mutations affect CD40 or other molecules involved in class switching, notably an enzyme called *activation-induced deaminase*.

*Thymic Hypoplasia: DiGeorge Syndrome:

DiGeorge syndrome results from a congenital defect in thymic development with deficient T-cell maturation. T cells are absent in the lymph nodes, spleen, and peripheral blood, and infants with this defect are extremely vulnerable to viral, fungal, and protozoal infections. Patients are also susceptible to infection with intracellular bacteria, because of defective T-cell-mediated immunity. B cells and serum immunoglobulins are generally unaffected.

*Severe Combined Immunodeficiency:

Severe combined immunodeficiency (SCID) represents a constellation of genetically distinct syndromes with the common feature of defects in both humoral and cell-mediated immune responses. Affected infants are susceptible to severe recurrent infections by a wide array of pathogens, including bacteria, viruses, fungi, and protozoans; opportunistic infections by *Candida*, *Pneumocystis*, CMV, and *Pseudomonas* also cause serious (and occasionally lethal) disease.

**Acquired Immunodeficiency Syndrome:**

AIDS is a retroviral disease caused by the human immunodeficiency virus (HIV). It is characterized by infection and depletion of CD4+ T lymphocytes, and by profound immunosuppression leading to opportunistic infections, secondary neoplasms, and neurologic manifestations. Although AIDS was first described in the United States, it has now been reported in virtually every country in the world.
Worldwide, more than 22 million people have died of AIDS since the epidemic was recognized in 1981; about 42 million people are living with the disease, and there are an estimated 5 million infections each year. Worldwide, 95% of HIV infections are in developing countries, with Africa alone carrying more than 50% of the HIV burden. Although the largest number of infections is in Africa, the most rapid increases in HIV infection in the past decade are in Southeast Asian countries, including Thailand, India, and Indonesia.

**Epidemiology**

1. Homosexual or bisexual males constitute the largest group of infected individuals, accounting for 48% of reported cases.
2. Heterosexual contacts of members of other high-risk groups constituted about 34% of infections.
3. Intravenous drug abusers with no history of homosexuality compose the next largest group, representing about 17% of all patients.
4. Recipients of blood and blood components (but not hemophiliacs) who received transfusions of HIV-infected whole blood or components (e.g., platelets, plasma) account for <1% of patients. Hemophiliacs, especially those who received large amounts of factor VIII or IX concentrates before 1985, make up less than <1% of all cases.
5. Mother-to-Infant Transmission.

**Etiology:**

AIDS is caused by HIV, a human retrovirus belonging to the lentivirus family. Like most retroviruses, the HIV-1 virion is spherical and contains an electron-dense, cone-shaped core surrounded by a lipid envelope derived from the host cell membrane. The virus core contains: (1) major capsid protein p24, (2) nucleocapsid protein p7/p9, (3) two copies of genomic RNA, and (4) three viral enzymes (protease, reverse transcriptase, and integrase). p24 is the most readily detected viral antigen and is therefore the target for the antibodies used to diagnose HIV infection in blood screening. The viral core is surrounded by a matrix protein called p17, lying beneath the virion envelope. The viral envelope itself is studded by two viral glycoproteins (gp120 and gp41).
Progression of HIV Infection:

HIV disease begins with acute infection, which is only partly controlled by the host immune response, and advances to chronic progressive infection of peripheral lymphoid tissues. The first cell types to be infected may be memory CD4+ T cells (which express CCR5) in mucosal lymphoid tissues. Because the mucosal tissues are the largest reservoir of T cells in the body and a major site of residence of memory T cells, the death of these cells results in considerable depletion of lymphocytes.

The transition from the acute phase to a chronic phase of infection is characterized by dissemination of the virus, viremia, and the development of host immune responses. Dendritic cells in epithelia at sites of virus entry capture the virus and then migrate into the lymph nodes. Once in lymphoid tissues, dendritic cells may pass HIV on to CD4+ T cells through direct cell-cell contact. Within days after the first exposure to HIV, viral replication can be detected in the lymph nodes. This replication leads to viremia, during which high numbers of HIV particles are present in the patient's blood, accompanied by an acute HIV syndrome that includes a variety of nonspecific signs and symptoms typical of many viral diseases. The virus disseminates throughout the body and infects helper T cells, macrophages, and dendritic cells in peripheral lymphoid tissues. As the infection spreads, the immune system mounts both humoral and cell-mediated immune responses directed at viral antigens. These immune responses partially control the infection and viral production, and such control is reflected by a drop in viremia to low but detectable levels by about 12 weeks after the primary exposure.

Chronic phase of the disease, lymph nodes and the spleen are sites of continuous HIV replication and cell destruction. During this period of the disease, the immune system remains competent at handling most infections with opportunistic microbes, and few or no clinical manifestations of the HIV infection are present. Therefore, this phase of HIV disease is called the clinical latency period. Although the majority of peripheral blood T cells do not harbor the virus, destruction of CD4+ T cells within lymphoid tissues steadily progresses during the latent period, and the number of circulating blood CD4+ T cells steadily declines. More than 90% of the body's approximately $10^{12}$ T cells are normally found in lymphoid tissues, and it is estimated that HIV destroys up to 1 to $2 \times 10^9$ CD4+ T cells every day. Early in the course of the disease, the body may continue to make new CD4+ T cells, and therefore CD4+ T cells can be replaced almost as quickly as they are destroyed. At this stage, up to 10%
of CD4+ T cells in lymphoid organs may be infected, but the number of circulating CD4+ T cells that are infected at any one time may be less than 0.1% of the total CD4+ T cells in an individual. Eventually, over a period of years, the continuous cycle of virus infection and T cell death leads to a steady decline in the number of CD4+ T cells in the lymphoid tissues and the circulation.

The loss of CD4+ cells leads to an inversion of the CD4:CD8 ratio in the peripheral blood. Thus, while the normal CD4:CD8 ratio is close to 2, patients with AIDS have a ratio of 0.5. Such inversion is a common finding in AIDS, but it may also occur in other viral infections and is therefore not diagnostic.

**Pathogenesis of CNS Involvement**:

The nervous system is a major target of HIV infection. Macrophages and cells belonging to the monocyte and macrophage lineage (microglia) are the predominant cell types in the brain that are infected with HIV. The virus is most likely carried into the brain by infected monocytes. The mechanism of HIV-induced damage of the brain, however, remains obscure. Because neurons are not infected by HIV, and the extent of neuropathologic changes is often less than might be expected from the severity of neurologic symptoms, most experts believe that the neurologic deficit is caused indirectly by viral products and soluble factors (e.g., cytokines such as TNF) produced by macrophages/microglia. In addition, nitric oxide induced in neuronal cells by gp41 and direct damage of neurons by soluble HIV gp120 have been postulated.

**Neoplasms**:

Patients with AIDS have a high incidence of certain tumors, particularly Kaposi sarcoma (KS), non-Hodgkin lymphomas, and cervical cancer in women. The basis of the increased risk of malignancy is multifactorial. KS, a vascular tumor that is otherwise rare in the United States, is the most common neoplasm in AIDS patients (although its incidence has decreased significantly with anti-retroviral therapy). The tumor is far more common among homosexual or bisexual males than in intravenous drug abusers or patients belonging to other risk groups. The lesions can arise early, before the immune system is compromised, or in advanced stages of HIV infection. Unlike the lesions in sporadic cases of KS, those that occur in AIDS patients are multicentric and tend to be more aggressive; they can affect the skin, mucous membranes, gastrointestinal tract, lymph nodes, and lungs.