incidence of tumors, and immunodeficiency. The immunologic defects are of variable severity and may affect both B and T cells. The most prominent humoral immune abnormalities are defective production of isotype switched antibodies, mainly IgA and IgG2. The T cell defects, which are usually less pronounced, are associated with thymic hypoplasia. Patients experience upper and lower respiratory tract bacterial infections, multiple autoimmune phenomena, and increasingly frequent cancers with advancing age. The gene responsible for this disorder is located on chromosome 11 and encodes a protein called *ATM* (ataxia telangiectasia mutated) that is related structurally to phosphatidylinositol-3 (PI-3) kinase, but is a protein kinase. The ATM protein is a sensor of DNA damage (double-strand breaks) and it activates p53 by phosphorylation, which in turn can activate cell cycle checkpoints and apoptosis in cells with damaged DNA. ATM has also been shown to contribute to the stability of DNA double-strand break complexes during V(D)J recombination. Because of these abnormalities in DNA repair, the generation of antigen receptors may be abnormal. In addition, defective DNA repair may lead to abnormalities in the DNA recombination events that are involved in antibody isotype switching.

KEY CONCEPTS

Primary (Inherited) Immune Deficiency Diseases

- These diseases are caused by inherited mutations in genes involved in lymphocyte maturation or function, or in innate immunity.
- Deficiencies in innate immunity include defects of phagocyte function, complement, and innate immune receptors.
- Some of the common disorders affecting lymphocytes and the adaptive immune response are:
  - X-SCID: failure of T-cell and B-cell maturation; mutation in the common γ chain of a cytokine receptor, leading to failure of IL-7 signaling and defective lymphopoiesis
  - Autosomal recessive SCID: failure of T-cell development, secondary defect in antibody responses; approximately 50% of cases caused by mutation in the gene encoding ADA, leading to accumulation of toxic metabolites during lymphocyte maturation and proliferation
  - X-linked agammaglubulinemia (XLA): failure of B-cell maturation, absence of antibodies; caused by mutations in the *BTK* gene, which encodes B-cell tyrosine kinase, required for maturation signals from the pre-B cell and B-cell receptors
  - Common variable immunodeficiency: defects in antibody production; cause unknown in most cases
  - Selective IgA deficiency: failure of IgA production; cause unknown
  - X-linked hyper-IgM syndrome: failure to produce isotype-switched high-affinity antibodies (IgG, IgA, IgE); mutation in gene encoding CD40L
  - X-linked lymphoproliferative disease (XLP): defect in a signaling molecule causing defective responses against Epstein-Barr virus and lymphoproliferation
- These diseases present clinically with increased susceptibility to infections in early life.

Table 6-13 Causes of Secondary (Acquired) Immunodeficiencies

Cause	Mechanism
Human immunodeficiency virus infection	Depletion of CD4+ helper T cells
Irradiation and chemotherapy treatments for cancer	Decreased bone marrow precursors for all leukocytes
Involvement of bone marrow by cancers (metastases, leukemias)	Reduced site of leukocyte development
Protein-calorie malnutrition	Metabolic derangements inhibit lymphocyte maturation and function
Removal of spleen	Decreased phagocytosis of microbes

Secondary Immunodeficiencies

Secondary (acquired) immune deficiencies may be encountered in individuals with cancer, diabetes and other metabolic diseases, malnutrition, chronic infection, and in persons receiving chemotherapy or radiation therapy for cancer, or immunosuppressive drugs to prevent graft rejection or to treat autoimmune diseases (Table 6-13). As a group, the secondary immune deficiencies are more common than the disorders of primary genetic origin. Some of these secondary immunodeficiency states can be caused by defective lymphocyte maturation (when the bone marrow is damaged by radiation or chemotherapy or involved by tumors, such as leukemias and metastatic cancers), inadequate Ig synthesis (as in malnutrition), or lymphocyte depletion (from drugs or severe infections). The most common secondary immunodeficiency is AIDS, which is described in the next section.

Acquired Immunodeficiency Syndrome (AIDS)

AIDS is a disease caused by the retrovirus human immunodeficiency virus (HIV) and characterized by profound immunosuppression that leads to opportunistic infections, secondary neoplasms, and neurologic manifestations. The magnitude of this modern plague is truly staggering. By the end of 2009 (the last year for which complete US statistics are available), more than a million cases of AIDS had been reported in the United States, where AIDS is the second leading cause of death in men between ages 25 and 44, and the third leading cause of death in women in this age group. Although initially recognized in the United States, AIDS is a global problem. It has now been reported from more than 190 countries around the world, and the pool of HIV-infected persons in Africa and Asia is large and expanding. By the year 2011, HIV had infected 60 million people worldwide, and nearly 30 million adults and children have died of the disease. There are about 34 million people living with HIV, of whom 70% are in Africa and more than 20% in Asia; the prevalence rate of infection in adults in sub-Saharan Africa is more than 8%. It is estimated that 2.5 million people were newly infected with HIV in 2011 and 1.7 million deaths were caused by AIDS. In this dismal scenario, there may be some good news. Because of public health measures, the infection rate seems to be decreasing, and some authorities believe it may have peaked in the late 1990s. Furthermore, improved antiviral therapies have resulted in fewer people dying of the disease. However, these newer treatments are