

# UNIT Three

## Alterations in the Hematologic System

### CHAPTER

# 11

## Alterations in White Blood Cells

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The white blood cells and lymphoid tissues where these cells originate and mature function to protect the body against invasion by foreign agents. Disorders of the white blood cells include a deficiency of leukocytes (leukopenia) or increased numbers as occurs with proliferative disorders. The proliferative disorders may be reactive, such as occurs with infection, or neoplastic, such as occurs with leukemias and lymphomas.

### HEMATOPOIETIC AND LYMPHOID TISSUE

Blood consists of blood cells (*i.e.*, white blood cells, thrombocytes or platelets [see Chapter 12], and red blood cells [see Chapter 13]) and the plasma in which the cells are suspended. The generation of blood cells takes place in the *hematopoietic* (from the Greek *haima* for "blood" and *poiesis* for "making") system.<sup>1</sup> The hematopoietic system encompasses all of the blood cells and their precursors, the bone marrow where blood cells have their origin, and the lymphoid tissues where some blood cells circulate as they develop and mature.

## Leukocytes (White Blood Cells)

The leukocytes, or white blood cells, constitute only 1% of the total blood volume. They originate in the bone marrow and circulate throughout the lymphoid tissues of the body. There they function in the inflammatory and immune processes. They include the granulocytes, the lymphocytes, and the monocytes (Fig. 11-1).

### Granulocytes

The granulocytes are all phagocytic cells and are identifiable because of their cytoplasmic granules. These white blood cells are spherical and have distinctive multilobar nuclei. The granulocytes are divided into three types (neutrophils, eosinophils, and basophils) according to the staining properties of the granules.

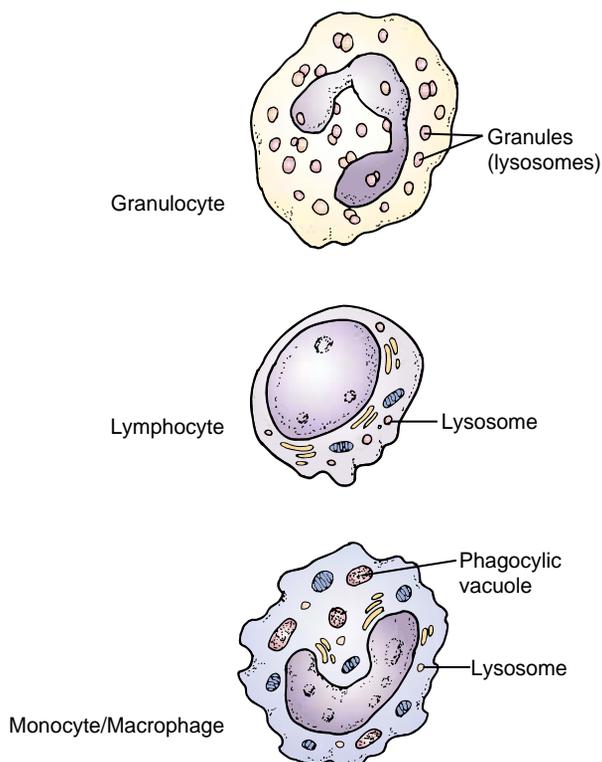
**Neutrophils.** The neutrophils, which constitute 55% to 65% of the total number of white blood cells, have granules that are neutral and thus do not stain with an acidic or a basic dye. Because their nuclei are divided into three to five lobes, they are often called polymorphonuclear leukocytes (PMNs).

The neutrophils are primarily responsible for maintaining normal host defenses against invading bacteria, fungi, products of cell destruction, and a variety of foreign substances. The cytoplasm of mature neutrophils contains fine granules. These granules contain degrading enzymes that are used in destroying foreign substances and correspond to lysosomes found in

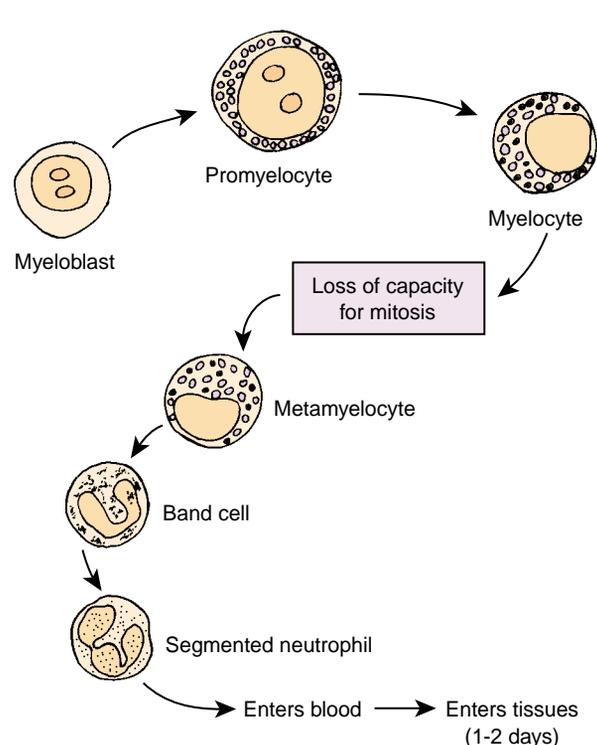
other cells. Enzymes and oxidizing agents associated with these granules are capable of degrading a variety of natural and synthetic substances, including complex polysaccharides, proteins, and lipids. The degradative functions of the neutrophil are important in maintaining normal host defenses and in mediating the inflammatory response (see Chapter 9).

The neutrophils have their origin in the myeloblasts that are found in the bone marrow (Fig. 11-2). The myeloblasts are the committed precursors of the granulocyte pathway and do not normally appear in the peripheral circulation. When they are present, it suggests a disorder of blood cell proliferation and differentiation. The myeloblasts differentiate into promyelocytes and then myelocytes. Generally, a cell is not called a myelocyte until it has at least 12 granules. The myelocytes mature to become metamyelocytes (Greek *meta* for "beyond"), at which point they lose their capacity for mitosis. Subsequent development of the neutrophil involves reduction in size, with transformation from an indented to an oval to a horseshoe-shaped nucleus (*i.e.*, band cell) and then to a mature cell with a segmented nucleus. Mature neutrophils are often referred to as *segs* because of their segmented nucleus. The development from stem cell to mature neutrophil takes about 2 weeks. It is at this point that the neutrophil enters the bloodstream.

After release from the marrow, the neutrophils spend only about 4 to 8 hours in the circulation before moving into the tissues.<sup>2</sup> Their survival in the tissues lasts about 4 to 5 days. They die in the tissues while discharging their phagocytic function or die of senescence. The pool of circulating neutrophils (*i.e.*, those that appear in the blood count) is in rapid equilibrium with a similar-sized pool of cells marginating along the



■ **FIGURE 11-1** ■ White blood cells—granulocyte, lymphocyte, and monocyte.



■ **FIGURE 11-2** ■ Development of neutrophils. (Adapted from Cormack D.H. [1993]. *Ham's histology* [9th ed.]. Philadelphia: J.B. Lippincott)

walls of small blood vessels. These are the neutrophils that respond to chemotactic factors and migrate into the tissues toward the offending agent during an inflammatory response. Epinephrine, exercise, stress, and corticosteroid drug therapy can cause rapid increases in the circulating neutrophil count by shifting cells from the marginating to the circulating pool. Endotoxins or microbes may have the opposite effect, by attracting neutrophils to move out of the circulation and into the tissues.

**Eosinophils.** The cytoplasmic granules of the eosinophils stain red with the acidic dye eosin. These leukocytes constitute 1% to 3% of the total number of white blood cells and increase in number during allergic reactions. They are thought to release enzymes or chemical mediators that detoxify agents associated with allergic reactions. Eosinophils are also involved in parasitic infections. Although most parasites are too large to be phagocytized by eosinophils, the eosinophils attach themselves to the parasite by special surface molecules and release hydrolytic enzymes and other substances from their granules that kill the parasite.

**Basophils.** The granules of the basophils stain blue with a basic dye. These cells constitute only about 0.3% to 0.5% of the white blood cells. The basophils in the circulating blood are similar to the large mast cells located immediately outside the capillaries in body tissues. Both the basophils and mast cells release heparin, an anticoagulant, into the blood. The mast cells and basophils also release histamine, a vasodilator, and other inflammatory mediators. The mast cells and basophils play an exceedingly important role in allergic reactions (see Chapter 10).

### Lymphocytes

The lymphocytes have their origin in the lymphoid stem cells that are found in the bone marrow. The lymphocytes constitute 20% to 30% of the white blood cell count. They have no identifiable granules in the cytoplasm and are sometimes referred to as *agranulocytes*. They move between blood and lymphoid tissues, where they may be stored for hours or years. Their function in the lymph nodes or spleen is to defend against foreign microbes in the immune response (see Chapter 8). There are two types of lymphocytes: B lymphocytes and T lymphocytes. The lymphocytes play an important role in the immune response. The B lymphocytes differentiate to form antibody-producing plasma cells and are involved in humoral-mediated immunity. The T lymphocytes are responsible for orchestrating the immune response ( $CD4^+$  T cells) and effecting cell-mediated immunity ( $CD8^+$  T cells).

### Monocytes and Macrophages

Monocytes are the largest of the white blood cells and constitute about 3% to 8% of the total leukocyte count. They have abundant cytoplasm and a darkly stained nucleus, which has a distinctive U or kidney shape. The circulating life span of the monocyte is about 1 to 3 days, three to four times longer than that of the granulocytes. These cells survive for months to years in the tissues. The monocytes, which are phagocytic cells, are often referred to as *macrophages* when they enter the tissues. The monocytes engulf larger and greater quantities of foreign ma-

terial than do the neutrophils. These leukocytes play an important role in chronic inflammation and are also involved in the immune response by activating lymphocytes and by presenting antigen to T cells. When the monocyte leaves the vascular system and enters the tissues, it functions as a macrophage with specific activity. The macrophages are known as *histiocytes* in loose connective tissue, *microglial cells* in the brain, and *Kupffer's cells* in the liver.

## The Bone Marrow and Hematopoiesis

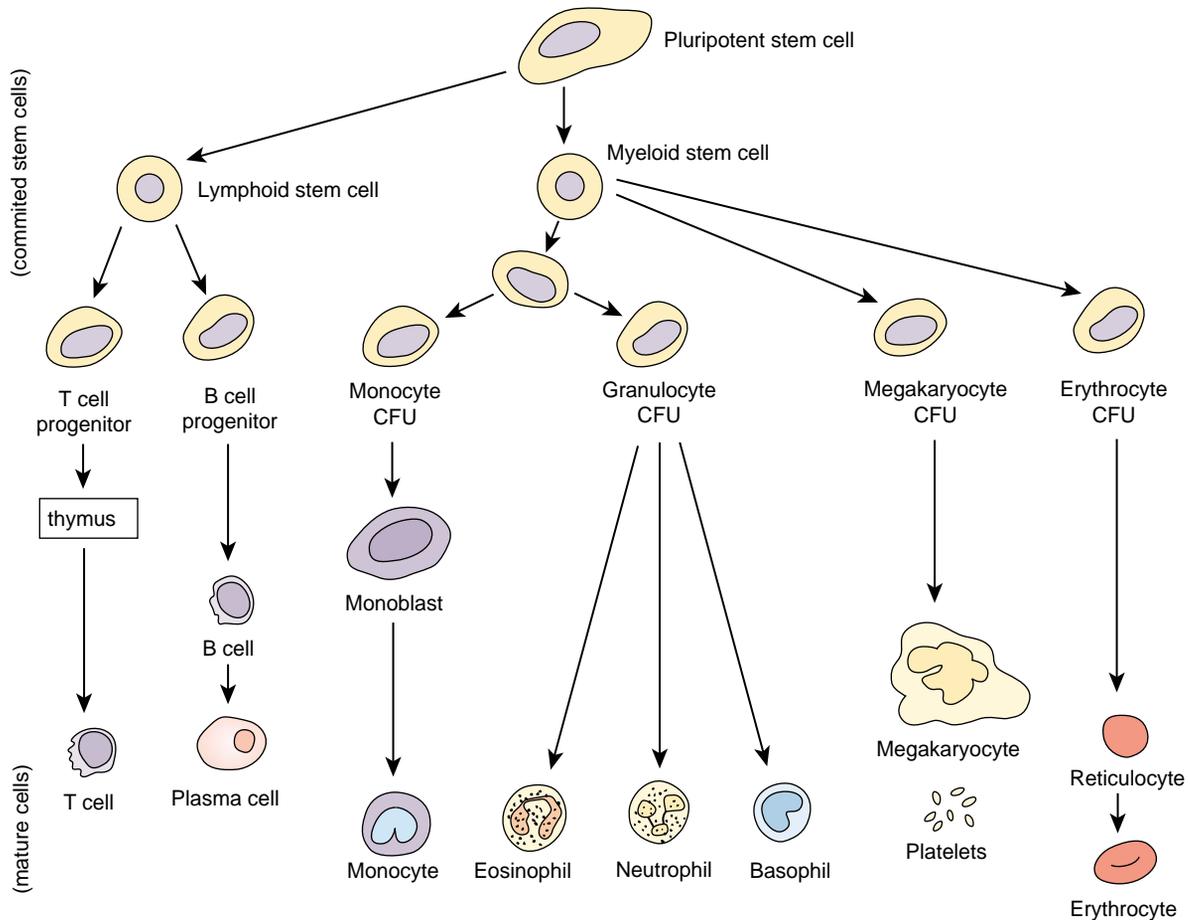
The blood-forming population of bone marrow is made up of three types of cells: self-renewing stem cells, differentiated progenitor (parent) cells, and functional mature blood cells. All of the blood cell precursors of the erythrocyte (*i.e.*, red cell), myelocyte (*i.e.*, granulocyte or monocyte), lymphocyte (*i.e.*, T lymphocyte and B lymphocyte), and megakaryocyte (*i.e.*, platelet) series are derived from a small population of primitive cells called the pluripotent stem cells (Fig. 11-3). Their lifelong potential for proliferation and self-renewal makes them an indispensable and lifesaving source of reserve cells for the entire hematopoietic system.

Several levels of differentiation lead to the development of committed stem cells, which are the progenitor for each of the blood cell types. A committed stem cell that forms a specific type of blood cell is called a *colony-forming unit* (CFU). Under normal conditions, the numbers and total mass for each type of circulating blood cell remain relatively constant. The blood cells are produced in different numbers according to needs and regulatory factors. This regulation of blood cells is controlled by a group of short-acting soluble mediators, called *cytokines*, that stimulate the proliferation, differentiation, and functional activation of the various blood cell precursors in bone marrow.<sup>3</sup> The cytokines that stimulate hematopoiesis are called *colony-stimulating factors* (CSFs), based on their ability to promote the growth of the hematopoietic cell colonies from bone marrow precursors. Lineage-specific CSFs that act on committed progenitor cells include: erythropoietin (EPO), granulocyte-monocyte colony-stimulating factor (GM-CSF), and thrombopoietin (TPO). The major sources of the CSFs are lymphocytes and stromal cells of the bone marrow. Other cytokines, such as the interleukins, support the development of lymphocytes and act synergistically to aid the functions of the CSFs (see Chapter 8).

## Lymphoid Tissues

The lymphoid tissues represent the structures where lymphocytes originate, mature, and interact with antigens. Lymphoid tissues can be classified into two groups: the central or generative organs and peripheral lymphoid organs (see Chapter 8). The central lymphoid structures consist of the bone marrow, where all lymphocytes arise, and the thymus, where T cells mature and reach a stage of functional competence. The thymus is also the site where self-reactive T cells are eliminated.

The peripheral lymphoid organs are the sites where mature lymphocytes respond to foreign antigens. They include the lymph nodes, the spleen, mucosa-associated lymphoid tissues, and the cutaneous immune system. In addition, poorly defined aggregates of lymphocytes are found in connective tissues and virtually all organs of the body.



■ **FIGURE 11-3** ■ Major maturational stages of blood cells. CFU, colony-forming units.

## KEY CONCEPTS

### HEMATOPOIESIS

- White blood cells are formed partially in the bone marrow (granulocytes, monocytes, and some lymphocytes) and partially in the lymph system (lymphocytes and plasma cells).
- They are formed from hematopoietic stem cells that differentiate into committed progenitor cells that in turn develop into the myelogenous and lymphocytic lineages needed for the formation of the different types of white blood cell.
- The growth and reproduction of the different stem cells is controlled by CSFs and other cytokines and chemical mediators.
- The life span of white blood cells is relatively short so that constant renewal is necessary to maintain normal blood levels. Any conditions that decrease the availability of stem cells or hematopoietic growth factors produce a decrease in white blood cells.

**In summary,** the hematopoietic system consists of a number of cells derived from the pluripotent stem cells originating in the bone marrow. These cells differentiate into committed cell lines that mature in red blood cells, platelets, and a variety of white blood cells. The development of the different types of blood cells is supported by chemical messengers called colony-stimulating factors. The lymphoid tissues are found in the central lymphoid structures (bone marrow and thymus) where lymphocytes arise, mature, and where self-reactive lymphocytes are eliminated and the peripheral lymphoid structures (lymph nodes, spleen, mucosal-associated lymphoid tissue, and the cutaneous immune system) where lymphocytes respond to foreign antigens.

### NON-NEOPLASTIC DISORDERS OF WHITE BLOOD CELLS

The number of leukocytes, or white blood cells, in the peripheral circulation normally ranges from 5000 to 10,000/ $\mu\text{L}$  of blood. The term *leukopenia* describes an absolute decrease in white blood cell numbers. The disorder may affect any of the

specific types of white blood cells, but most often it affects the neutrophils, which are the predominant type of granulocyte.

### Neutropenia (Agranulocytosis)

Neutropenia refers specifically to a decrease in neutrophils. It commonly is defined as a circulating neutrophil count of less than 1500 cells/ $\mu\text{L}$ . Agranulocytosis, which denotes a severe neutropenia, is characterized by a circulating neutrophil count of less than 200 cells/ $\mu\text{L}$ .<sup>4</sup>

The reduction in granulocytes can occur because there is reduced or ineffective production of neutrophils or because there is excessive removal of neutrophils from the blood. The causes of neutropenia are summarized in Table 11-1.

#### Acquired Neutropenia

Granulopoiesis may be impaired by a variety of bone marrow disorders, such as aplastic anemia or bone marrow depression caused by cancer chemotherapy and irradiation, that interfere with the formation of all blood cells. Overgrowth of neoplastic cells in cases of nonmyelogenous leukemia and lymphoma also may suppress the function of neutrophil precursors. Infections by viruses or bacteria may drain neutrophils from the blood faster than they can be replaced, thereby depleting the neutrophil storage pool in the bone marrow.<sup>4</sup> Because of the neutrophil's short life span of less than 1 day in the peripheral blood, neutropenia occurs rapidly when granulopoiesis is impaired. Under these conditions, neutropenia usually is accompanied by thrombocytopenia (*i.e.*, platelet deficiency).

In *aplastic anemia*, all of the myeloid stem cells are affected, resulting in anemia, thrombocytopenia, and agranulocytosis. Autoimmune disorders or idiosyncratic drug reactions may cause increased and premature destruction of neutrophils. In splenomegaly, neutrophils may be trapped in the spleen along with other blood cells. In Felty's syndrome, a variant of rheumatoid arthritis, there is increased destruction of neutrophils in the spleen.

Most cases of neutropenia are drug related. Chemotherapeutic drugs used in the treatment of cancer (*e.g.*, alkylating agents, antimetabolites) cause predictable dose-dependent

suppression of bone marrow function. The term *idiosyncratic* is used to describe drug reactions that are different from the effects obtained in most persons and that cannot be explained in terms of allergy. A number of drugs, such as chloramphenicol (an antibiotic), phenothiazine tranquilizers, sulfonamides, propylthiouracil (used in the treatment of hyperthyroidism), and phenylbutazone (used in the treatment of arthritis), may cause idiosyncratic depression of bone marrow function. Some drugs, such as hydantoin derivatives and primidone (used in the treatment of seizure disorders), can cause intramedullary destruction of granulocytes and thereby impair production. Many idiosyncratic cases of drug-induced neutropenia are thought to be caused by immunologic mechanisms, with the drug or its metabolites acting as antigens (*i.e.*, haptens) to incite the production of antibodies reactive against the neutrophils. Neutrophils possess human leukocyte antigens (HLA) and other antigens specific to a given leukocyte line. Antibodies to these specific antigens have been identified in some cases of drug-induced neutropenia.<sup>4</sup>



#### Congenital Neutropenia

A decreased production of granulocytes is a feature of a group of hereditary hematologic disorders, including cyclic neutropenia and Kostmann's syndrome. *Periodic* or *cyclic neutropenia* is an autosomal dominant disorder with variable expression that begins in infancy and persists for decades. It is characterized by periodic neutropenia that develops every 21 to 30 days and lasts approximately 3 to 6 days. Although the cause is undetermined, it is thought to result from impaired feedback regulation of granulocyte production and release. *Kostmann's syndrome*, which occurs sporadically or as an autosomal recessive disorder, causes severe neutropenia while preserving the erythroid and megakaryocyte cell lineages that result in red blood cell and platelet production. The total white blood cell count may be within normal limits, but the neutrophil count is less than 200/ $\mu\text{L}$ . Monocyte and eosinophil levels may be elevated.

A transient neutropenia may occur in neonates whose mothers have hypertension. It usually lasts from 1 to 60 hours

**TABLE 11-1** Causes of Neutropenia

Cause	Mechanism
Accelerated removal ( <i>e.g.</i> , inflammation and infection)	Removal of neutrophils from the circulation exceeds production
Drug-induced granulocytopenia	
Defective production	
Cytotoxic drugs used in cancer therapy	Predictable damage to precursor cells, usually dose dependent
Phenothiazine, thiouracil, chloramphenicol, phenylbutazone, and others	Idiosyncratic depression of bone marrow function
Hydantoinates, primidone, and others	Intramedullary destruction of granulocytes
Immune destruction	Immunologic mechanisms with cytolysis or leukoagglutination
Aminopyrine and others	
Periodic or cyclic neutropenia (occurs during infancy and later)	Unknown
Neoplasms involving bone marrow ( <i>e.g.</i> , leukemias and lymphomas)	Overgrowth of neoplastic cells, which crowd out granulopoietic precursors
Idiopathic neutropenia that occurs in the absence of other disease or provoking influence	Autoimmune reaction
Felty's syndrome	Intrasplenic destruction of neutrophils

but can persist for 3 to 30 days. This type of neutropenia, which is associated with increased risk of nosocomial infection, is thought to result from transiently reduced neutrophil production.<sup>4</sup>

### Clinical Course

The clinical features of neutropenia usually depend on the severity of neutropenia and the cause of the disorder. Because the neutrophil is essential to the cellular phase of inflammation, infections are common in persons with neutropenia, and extreme caution is needed to protect them from exposure to infectious organisms. Infections that may go unnoticed in a person with a normal neutrophil count could prove fatal in a person with neutropenia. These infections commonly are caused by organisms that normally colonize the skin, vagina, and the gastrointestinal tract.

The signs and symptoms of neutropenia initially are those of bacterial or fungal infections. They include malaise, chills, and fever, followed by extreme weakness and fatigue. The white blood cell count often is reduced to 1000/ $\mu\text{L}$  and, in certain cases, may fall to 200 to 300/ $\mu\text{L}$ . The most frequent site of serious infection is the respiratory tract, a result of bacteria, fungi, and protozoa that frequently colonize the airways. Ulcerative necrotizing lesions of the mouth are common in neutropenia. Ulcerations of the skin, vagina, and gastrointestinal tract also may occur.<sup>4</sup>

Antibiotics are used to treat infections in those situations in which neutrophil destruction can be controlled or the neutropoietic function of the bone marrow can be recovered. Hematopoietic growth factors such as GM-CSF are being used more commonly to stimulate the maturation and differentiation of the polymorphonuclear cell lineage. Treatment with these biologic response modifiers has reduced the period of neutropenia and the risk for development of potentially fatal septicemia.<sup>4,5</sup>

## Infectious Mononucleosis

Infectious mononucleosis is a self-limiting lymphoproliferative disorder caused by the Epstein-Barr virus (EBV), a member of the herpesvirus family.<sup>6,7</sup> EBV is commonly present in all human populations. Infectious mononucleosis is most prevalent in adolescents and young adults in the upper socioeconomic classes in developed countries. This is probably because the disease, which is relatively asymptomatic when it occurs during childhood, confers complete immunity to the virus. In families from upper socioeconomic classes, exposure to the virus may be delayed until late adolescence or early adulthood. In such persons, the mode of infection, size of the viral pool, and physiologic and immunologic condition of the host may determine whether the infection occurs.

### Pathogenesis

Infectious mononucleosis is largely transmitted through oral contact with EBV-contaminated saliva. The virus initially penetrates the nasopharyngeal, oropharyngeal, and salivary epithelial cells. It then spreads to the underlying oropharyngeal lymphoid tissue, and more specifically, to B lymphocytes, all of which have receptors for EBV. Infection of the B cells may take one of two forms—it may kill the infected B cell or it may become incorporated into its genome. A small number of infected B cells are killed and in the process release the virions.

However, in most cells the virus associates with the B-cell genome. The B cells that harbor the EBV genome proliferate in the circulation and produce the well known *heterophil* antibodies that are used for the diagnosis of infectious mononucleosis.<sup>7</sup> A heterophil antibody is an immunoglobulin that reacts with antigens from another species—in this case, sheep red blood cells.

The normal immune response is important in controlling the proliferation of the EBV-infected B cells and cell-free virus. Most important in controlling the proliferation of EBV-infected B cells are the cytotoxic CD8<sup>+</sup> T cells and natural killer (NK) cells. The virus-specific T cells appear as large atypical lymphocytes that are characteristic of the infection.<sup>7</sup> In otherwise healthy persons, the humoral and cellular immune responses control viral shedding by limiting the number of infected B cells, rather than eliminating them.

Although infectious B cells and free virions disappear from the blood after recovery from the disease, the virus remains in a few transformed B cells in the oropharyngeal region and is shed in the saliva. Once infected with the virus, persons have asymptomatic infection for life, and a few intermittently shed EBV. Immunosuppressed persons shed the virus more frequently. Asymptomatic shedding of EBV by healthy persons accounts for most of the spread of infectious mononucleosis, despite the fact that it is not a highly contagious disease.

### Clinical Course

The onset of infectious mononucleosis usually is insidious. The incubation period lasts 4 to 8 weeks.<sup>8</sup> A prodromal period, which lasts for several days, follows and is characterized by malaise, anorexia, and chills. The prodromal period precedes the onset of fever, pharyngitis, and lymphadenopathy. Occasionally, the disorder comes on abruptly with a high fever. Most persons seek medical attention for severe pharyngitis, which usually is most severe on days 5 to 7 and persists for 7 to 14 days. Rarely severe toxic pharyngotonsillitis may cause airway obstruction.

The lymph nodes are typically enlarged throughout the body, particularly in the cervical, axillary, and groin areas. Hepatitis and splenomegaly are common manifestations of the disease and are thought to be immune mediated. Hepatitis is characterized by hepatomegaly, nausea, anorexia, and jaundice. Although discomforting, it usually is a benign condition that resolves without causing permanent liver damage. The spleen may be enlarged two to three times its normal size, and rupture of the spleen is an infrequent complication. A rash that resembles rubella develops in 10% to 15% of cases.<sup>7</sup> In less than 1% of cases, mostly in the adult age group, complications of the central nervous system (CNS) develop. These complications include cranial nerve palsies, encephalitis, meningitis, transverse myelitis, and Guillain-Barré syndrome.

The peripheral blood usually shows an increase in the number of leukocytes, with a white blood cell count between 12,000 and 18,000/ $\mu\text{L}$ , 95% of which are lymphocytes.<sup>7</sup> The rise in white blood cells begins during the first week and continues during the second week of the infection; the white blood cell count returns to normal around the fourth week. Although leukocytosis is common, leukopenia may be seen in some persons during the first 3 days of the illness. Atypical lymphocytes are common, constituting more than 20% of the total lymphocyte count. Heterophil antibodies usually appear during

the second or third week and decline after the acute illness has subsided. However, they may be detectable for as long as 9 months after onset of the disease.

Most persons with infectious mononucleosis recover without incident. The acute phase of the illness usually lasts 2 to 3 weeks, after which recovery occurs rapidly. Some degree of debility and lethargy may persist for 2 to 3 months. Treatment is primarily symptomatic and supportive. It includes bed rest and analgesics such as aspirin to relieve the fever, headache, and sore throat.<sup>8</sup>

**In summary,** neutropenia, a marked reduction in the number of circulating neutrophils, is one of the major disorders of the white blood cells. It can be acquired or congenital and can result from a combination of mechanisms. Severe neutropenia can occur as a complication of lymphoproliferative diseases, in which neoplastic cells crowd out neutrophil precursor cells, or of radiation therapy or treatment with cytotoxic drugs, which destroy neutrophil precursor cells. Neutropenia also may be encountered as an idiosyncratic reaction to various drugs. Because the neutrophil is essential to the cellular stage of inflammation, severe and often life-threatening infections are common in persons with neutropenia.

Infectious mononucleosis is a self-limited lymphoproliferative disorder caused by EBV, a member of the herpesvirus family. The highest incidence of infectious mononucleosis is found in adolescents and young adults, and it is seen more frequently in the upper socioeconomic classes of developed countries. The virus is usually transmitted in the saliva. The disease is characterized by fever, generalized lymphadenopathy, sore throat, and the appearance in the blood of atypical lymphocytes and several antibodies, including the well-known heterophil antibodies that are used in the diagnosis of infectious mononucleosis. Most persons with infectious mononucleosis recover without incident. Treatment is largely symptomatic and supportive.

## NEOPLASTIC DISORDERS OF HEMATOPOIETIC AND LYMPHOID ORIGIN

The neoplastic disorders of hematopoietic and lymphoid origin represent the most important of the white blood cell disorders. They include three somewhat overlapping categories: the lymphomas (Hodgkin's disease and non-Hodgkin's lymphoma), the leukemias, and plasma cell dyscrasias (multiple myeloma).

### Malignant Lymphomas

The lymphomas, Hodgkin's disease and non-Hodgkin's lymphoma, represent solid tumors derived from neoplastic lymphoid tissue cells (*i.e.*, lymphocytes or histiocytes) and their precursors or derivatives. The seventh most common cancer in the United States, the lymphomas are among the most studied human tumors and among the most curable.

## KEY CONCEPTS

### MALIGNANT LYMPHOMAS

- The lymphomas represent malignancies of cells derived from lymphoid cells and tissues.
- Hodgkin's disease is a group of cancers characterized by Reed-Sternberg cells that begins as a malignancy in a single lymph node and then spreads to contiguous lymph nodes.
- Non-Hodgkin's lymphomas represent a group of heterogeneous lymphocytic cancers that are multicentric in origin and spread to various tissues throughout the body, including the bone marrow.
- Both types of lymphomas are characterized by manifestations related to uncontrolled lymph node and lymphoid tissue growth, bone marrow involvement, and constitutional symptoms (fever, fatigue, weight loss) related to the rapid growth of abnormal lymphoid cells and tissues.

### Hodgkin's Disease

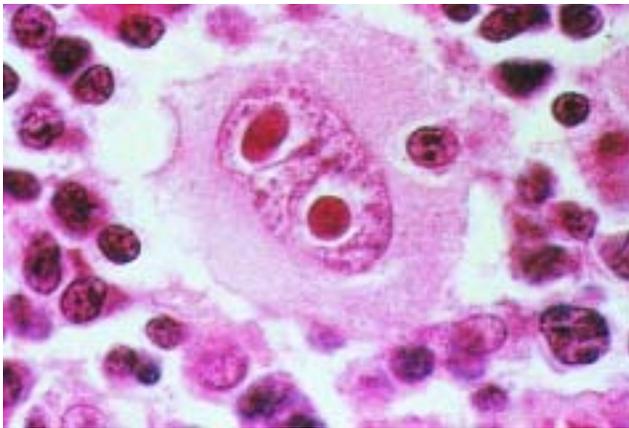
Hodgkin's disease is a specialized form of lymphoma that features the presence of an abnormal cell called a *Reed-Sternberg cell*.<sup>9</sup> It was estimated that approximately 7000 new cases of Hodgkin's disease would be diagnosed in 2002, with 1400 deaths.<sup>10</sup> Distribution of the disease is bimodal; the incidence rises sharply after 10 years of age, peaks in the early 20s, and then declines until 50 years of age. After 50 years of age, the incidence again increases steadily with age. The younger adult group consists equally of men and women, but after age 50 years, the incidence is higher among men.<sup>11</sup>

The cause of Hodgkin's disease is unknown. Although exposure to carcinogens or viruses as well as genetic and immune mechanisms have been proposed as causes, none have been proven to be involved in the pathogenesis of Hodgkin's disease.

Hodgkin's disease is characterized by painless and progressive enlargement of a single node or group of nodes. It is believed to originate in one area of the lymphatic system, and if unchecked, it spreads throughout the lymphatic network. The initial lymph node involvement typically is above the level of the diaphragm. An exception is in elderly persons, in whom the subdiaphragmatic lymph nodes may be the first to be involved. Involvement of the retroperitoneal lymph nodes, liver, spleen, and bone marrow occurs after the disease becomes generalized.

A distinctive tumor cell (the Reed-Sternberg cell) is considered to be the true neoplastic element in Hodgkin's disease (Fig. 11-4).<sup>9,12</sup> These malignant proliferating cells may invade almost any area of the body and may produce a wide variety of signs and symptoms. The spleen is involved in one third of the cases at the time of diagnosis.<sup>12</sup>

**Manifestations.** A common finding in Hodgkin's disease is the presence of painless lymph node enlargement, involving a single lymph node or groups of lymph nodes. The cervical



■ **FIGURE 11-4** ■ Classic Reed-Sternberg cell. Mirror-image nuclei contain large eosinophilic nucleoli. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1144]. Philadelphia: Lippincott Williams & Wilkins)

and mediastinal nodes are involved most frequently. Less commonly, the axillary, inguinal and retroperitoneal nodes are initially involved.<sup>12</sup>

Persons with Hodgkin's disease are commonly designated as stage A if they lack constitutional symptoms and stage B if significant weight loss, fever, or night sweats are present. Approximately 40% of persons with Hodgkin's disease exhibit the "B" symptoms.<sup>12</sup> Other symptoms such as fatigue, pruritus, and anemia are indicative of disease spread. In the advanced stages of Hodgkin's disease, the liver, lungs, digestive tract, and, occasionally, the CNS may be involved. As the disease progresses, the rapid proliferation of abnormal lymphocytes leads to an immunologic defect, particularly in cell-mediated responses, rendering the person more susceptible to viral, fungal, and protozoal infections. Anergy, or the failure to develop a positive response to skin tests, such as the tuberculin test, is common early in the course of the disease. An increased neutrophil count and mild anemia are often noted.

**Diagnosis and Treatment.** A definitive diagnosis of Hodgkin's disease requires that the Reed-Sternberg cell be present in a biopsy specimen of lymph node tissue.<sup>12,13</sup> Computed tomographic (CT) scans of the abdomen commonly are used in screening for involvement of abdominal and pelvic lymph nodes. Radiologic visualization of the abdominal and pelvic lymph structures can be achieved through the use of bipedal lymphangiography. In this diagnostic test, radiopaque dye is injected into the lymphatic channels of the lower leg, enabling visualization of the iliac and para-aortic nodes. Nuclear studies, such as a gallium scan in which the tumor takes up the radionuclide, or a staging laparotomy to detect abdominal nodes and inspect the liver may be done.

The staging of Hodgkin's disease is of great clinical importance because the choice of treatment and the prognosis ultimately are related to the distribution of the disease. Staging is determined by the number of lymph nodes that are involved, whether the lymph nodes are on one or both sides of the diaphragm, and whether there is disseminated disease involving the bone marrow and liver.

Irradiation and chemotherapy are used in treating the disease. Most people with localized disease are treated with radiation therapy. As the accuracy of staging techniques, delivery of radiation, and curative efficacy of combination chemotherapy regimens have improved, the survival of people with Hodgkin's disease also has improved. With modern treatment methods an overall cure rate of 70% can be achieved.

### Non-Hodgkin's Lymphomas

The non-Hodgkin's lymphomas are a heterogeneous group of solid tumors composed of neoplastic lymphoid cells. The heterogeneity reflects the potential for malignant transformation at any stage of B- and T-lymphocyte differentiation. The non-Hodgkin's lymphomas occur three times more frequently than does Hodgkin's disease. In 2002, approximately 54,000 new cases were diagnosed in the United States, and approximately 24,400 deaths resulted from these disorders.<sup>10</sup> Non-Hodgkin's lymphomas are the fifth most common malignancy in men and the sixth in women,<sup>13</sup> and the disease's incidence and associated mortality rates have increased considerably during the last several decades.<sup>14</sup>

The etiology of most of the non-Hodgkin's lymphomas is unknown. A viral cause is suspected in at least some of the lymphomas. There is evidence of EBV infection in 95% of people with Burkitt's lymphoma, which is endemic to some parts of Africa.<sup>9,12</sup> By contrast, the virus is found in only a small percentage of Burkitt's lymphoma occurring in the United States and other nonendemic areas.<sup>12</sup> A second virus, the human T cell/lymphoma virus (HTLV-1), which is endemic in the southwestern islands of Japan, has been associated with adult T-cell leukemia/lymphoma. Evidence of infection has been demonstrated in 90% of adult T-cell leukemia/lymphoma cases in Japan.<sup>9,12</sup> Non-Hodgkin's lymphomas also are seen with increased frequency in persons with acquired immunodeficiency syndrome, in those who have received chronic immunosuppressive therapy after kidney or liver transplantation, and in individuals with acquired or congenital immunodeficiencies.

As neoplasms of the immune system, the non-Hodgkin's lymphomas can originate in either the T cells or B cells.<sup>9,12</sup> Most (80% to 85%) are of B-cell origin with the remainder being largely of T-cell origin. All of these variants have the potential to spread to various tissues throughout the body, especially the liver, spleen, and bone marrow. Non-Hodgkin's lymphomas commonly are divided into three groups, depending on the grade of the tumor: low-grade lymphomas, which are predominantly B-cell tumors; intermediate-grade lymphomas, which include B-cell and some T-cell lymphomas; and high-grade lymphomas, which are largely immunoblastic (B-cell), lymphoblastic (T-cell), Burkitt's, and non-Burkitt's lymphomas.<sup>12</sup>

**Clinical Course.** The clinical course of non-Hodgkin's lymphomas depends upon the lymphoma type and the stage of the disease. For example, the small lymphocyte tumors, which account for about 4% of all non-Hodgkin's lymphomas, are low-grade tumors associated with mild symptoms and prolonged survival. The diffuse large B-cell lymphomas, which account for about 20% of all non-Hodgkin's lymphomas, are particularly aggressive tumors that are rapidly fatal if not treated. However, with intensive combination chemotherapy, complete remission can be achieved in 60% to 80% of cases.

The most frequently occurring clinical manifestation in the non-Hodgkin's lymphomas is painless, superficial lymphadenopathy. There may be noncontiguous nodal spread of the disease with more frequent involvement of the gastrointestinal tract, liver, testes, and bone marrow. Frequently, there is increased susceptibility to bacterial, viral, and fungal infections associated with hypogammaglobulinemia and a poor humoral antibody response, rather than the impaired cellular immunity seen with Hodgkin's disease.

Leukemic transformation with high peripheral lymphocytic counts occurs in a small percentage of persons with non-Hodgkin's lymphoma.<sup>9</sup>

**Diagnosis and Treatment.** As with Hodgkin's disease, a lymph node biopsy is used to confirm the diagnosis of non-Hodgkin's lymphoma. Bone marrow biopsy, blood studies, abdominal computed tomographic scans, and nuclear medicine studies often are used to determine the stage of the disease.

For early-stage disease, radiation therapy is used as a single treatment. However, because most people present with late-stage disease, combination chemotherapy, combined adjuvant radiation therapy, or both are recommended. For rapidly progressive intermediate- or high-grade lymphomas, CNS prophylaxis is achieved with high doses of chemotherapeutic agents that can cross the blood-brain barrier or cranial irradiation. Bone marrow and peripheral stem cell transplantation are being investigated as potentially curative treatment modalities for people with highly resistant forms of the disease.

## Leukemias

The leukemias are malignant neoplasms of cells originally derived from hematopoietic stem cells. They are characterized by diffuse replacement of bone marrow with unregulated, proliferating, immature neoplastic cells. In most cases, the leukemic cells spill out into the blood, where they are seen in large numbers. The term *leukemia* (*i.e.*, "white blood") was first used by Virchow to describe a reversal of the usual ratio of red blood cells to white blood cells. The leukemic cells may also infiltrate the liver, spleen, lymph nodes, and other tissues throughout the body, causing enlargement of these organs.

Leukemia strikes approximately 31,000 persons in the United States each year. In 2002, approximately 30,800 new cases were diagnosed, and approximately 21,700 persons died of this disease.<sup>10</sup> More children are stricken with leukemia than with any other form of cancer, and it is the leading cause of death in children between the ages of 3 and 14 years. Although leukemia commonly is thought of as a childhood disease, it strikes more adults than children.

The causes of leukemia are unknown. The incidence of leukemia among persons who have been exposed to high levels of radiation is unusually high. The number of cases of leukemia reported in the most heavily exposed survivors of the atomic blasts at Hiroshima and Nagasaki during the 20-year period from 1950 to 1970 was nearly 30 times the expected rate.<sup>15</sup> An increased incidence of leukemia also is associated with exposure to benzene and the use of antitumor drugs (*i.e.*, mechlorethamine, procarbazine, cyclophosphamide, chloramphenicol, and the epipodophyllotoxins).<sup>16</sup> Leukemia may occur as a second cancer after aggressive chemotherapy for other cancers, such as Hodgkin's disease.<sup>17</sup> The existence of a

## KEY CONCEPTS

### LEUKEMIAS

- Leukemias are malignant neoplasms arising from the transformation of a single blood cell line derived from hematopoietic stem cells.
- The leukemias are classified as acute and chronic lymphocytic (lymphocytes) or myelogenous (granulocytes, monocytes) leukemias, according to their cell lineage.
- Because leukemic cells are immature and poorly differentiated, they proliferate rapidly and have a long life span; they do not function normally; they interfere with the maturation of normal blood cells; and they circulate in the bloodstream, cross the blood-brain barrier, and infiltrate many body organs.

genetic predisposition to acute leukemia is suggested by the increased leukemia incidence among a number of congenital disorders, including Down syndrome, von Recklinghausen's disease, and Fanconi's anemia. In individuals with Down syndrome, the incidence of acute leukemia is 10 times that of the general population.<sup>18</sup> In addition, there are numerous reports of multiple cases of acute leukemia occurring within the same family.

## Classification

The leukemias commonly are classified according to their predominant cell type (*i.e.*, lymphocytic or myelogenous) and whether the condition is acute or chronic. Biphenotypic leukemias demonstrate characteristics of both lymphoid and myeloid lineages. A rudimentary classification system divides leukemia into four types: acute lymphocytic (lymphoblastic) leukemia, chronic lymphocytic leukemia, acute myelogenous (myeloblastic) leukemia, and chronic myelogenous leukemia. The *lymphocytic leukemias* involve immature lymphocytes and their progenitors that originate in the bone marrow but infiltrate the spleen, lymph nodes, CNS, and other tissues. The *myelogenous leukemias*, which involve the pluripotent myeloid stem cells in bone marrow, interfere with the maturation of all blood cells, including the granulocytes, erythrocytes, and thrombocytes.

## Acute Leukemias

The acute leukemias usually have a sudden and stormy onset of signs and symptoms related to depressed bone marrow function (Table 11-2). Acute lymphocytic leukemia (ALL) is the most common leukemia in childhood, comprising 80% to 85% of leukemia cases.<sup>19</sup> The peak incidence occurs between 2 and 4 years of age. Acute myelogenous leukemia (AML) is chiefly an adult disease; although it is also seen in children and young adults. The incidence steadily increases after middle age. AML appears to be increasing among the elderly.<sup>12</sup>

ALL encompasses a group of neoplasms composed of immature precursor B or T lymphocytes (Fig. 11-5). Most cases (about 85%) of ALL are of pre-B-cell origin.<sup>9</sup> Approximately 90% of persons with ALL have nonrandom chromosome ab-

**TABLE 11-2** Clinical Manifestations of Acute Leukemia and Their Pathologic Basis\*

Clinical Manifestations	Pathologic Basis
Bone marrow depression	Anemia
Malaise, easy fatigability	Infection or increased metabolism by neoplastic cells
Fever	Decreased thrombocytes
Bleeding	
Petechiae	
Ecchymosis	
Gingival bleeding	
Epistaxis	
Bone pain and tenderness upon palpation	Subperiosteal bone infiltration, bone marrow expansion, and bone resorption
Headache, nausea, vomiting, papilledema, cranial nerve palsies, seizures, coma	Leukemic infiltration of central nervous system
Abdominal discomfort	Generalized lymphadenopathy, hepatomegaly, splenomegaly due to leukemic cell infiltration
Increased vulnerability to infections	Immaturity of the white cells and ineffective immune function
Hematologic abnormalities	Physical and metabolic encroachment of leukemia cells on red blood cell and thrombocyte precursors
Anemia	
Thrombocytopenia	
Hyperuricemia and other metabolic disorders	Abnormal proliferation and metabolism of leukemic cells

\*Manifestations vary with the type of leukemia.

normalities. The AMLs are an extremely heterogeneous group of disorders. Some arise from the pluripotent stem cells in which myeloblasts predominate, and others arise from the monocyte-granulocyte precursor, which is the cell of origin for myelomonocytic leukemia. Of all the leukemias, AML is most strongly linked with toxins and underlying congenital and hematologic disorders. It is the type of leukemia associated with Down syndrome.

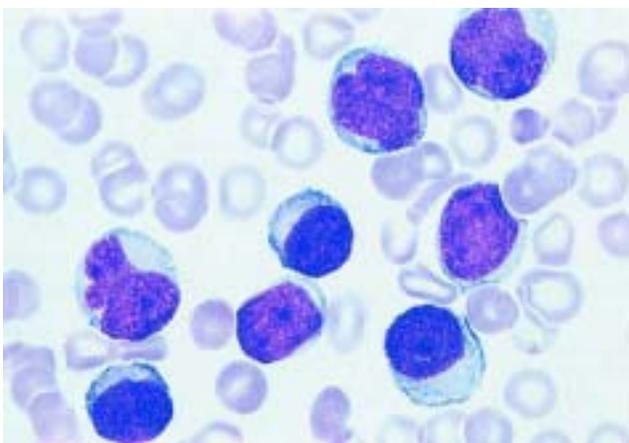
**Clinical Manifestations.** Although ALL and AML are distinct disorders, they typically present with similar clinical features. The warning signs and symptoms of acute leukemia are fatigue,

pallor, weight loss, repeated infections, easy bruising, nosebleeds, and other types of hemorrhage. These features often appear suddenly in children.

Persons with acute leukemia usually present for medical evaluation within 3 months of the onset of symptoms. Both ALL and AML are characterized by fatigue resulting from anemia; low-grade fever, night sweats, and weight loss caused by the rapid proliferation and hypermetabolism of the leukemic cells; bleeding caused by a decreased platelet count; and bone pain and tenderness caused by bone marrow expansion.<sup>19,20</sup> Infection results from neutropenia, with the risk of infection becoming high as the neutrophil count falls to less than 500 cells/ $\mu$ L. Generalized lymphadenopathy, splenomegaly, and hepatomegaly caused by infiltration of leukemic cells occur in all acute leukemias but are more common in ALL. In addition to the common manifestations of acute leukemia (e.g., fatigue, weight loss, fever, easy bruising), infiltration of malignant cells in the skin, gums, and other soft tissue is particularly common in the monocytic form of AML.

CNS involvement is more common in ALL than AML, and is more common in children than adults. Signs and symptoms of CNS involvement include cranial nerve palsies, headache, nausea, vomiting, papilledema, and occasionally seizures and coma.

Leukostasis is a condition in which the circulating blast count is markedly elevated (usually 100,000 cells/ $\mu$ L). The high number of circulating leukemic blasts increases blood viscosity and predisposes to the development of leukoblastic emboli with obstruction of small vessels in the pulmonary and cerebral circulations. Plugging of the pulmonary vessels leads to vessel rupture and infiltration of lung tissue, resulting in sudden shortness of breath and progressive dyspnea. Cerebral leukostasis leads to diffuse headache and lethargy, which can progress to confusion and coma. Once identified, leukostasis requires immediate and effective treatment to lower the blast count rapidly.



■ **FIGURE 11-5** ■ Acute lymphoblastic anemia (L2 ALL). The lymphoblasts in the peripheral blood contain irregular and indented nuclei with prominent nucleoli and a moderate amount of cytoplasm. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1129]. Philadelphia: Lippincott-Raven)

Hyperuricemia occurs as the result of increased proliferation or increased breakdown of purine nucleotides (*e.g.*, one of the compounds of nucleic acid) secondary to leukemic cell death that results from chemotherapy. It may increase before and during treatment. Prophylactic therapy with allopurinol, a drug that inhibits uric acid synthesis, is routinely administered to prevent renal complications secondary to uric acid crystallization in the urine.

**Diagnosis and Treatment.** A definitive diagnosis of acute leukemia is based on blood and bone marrow studies; it requires the demonstration of leukemic cells in the peripheral blood, bone marrow, or extramedullary tissue. Laboratory findings reveal the presence of immature (blasts) white blood cells in the circulation and bone marrow, where they may constitute 60% to 100% of the cells. As these cells proliferate and begin to crowd the bone marrow, the development of other blood cell lines in the marrow is suppressed. Consequently, there is a loss of mature myeloid cells, such as erythrocytes, granulocytes, and platelets. Anemia is almost always present, and the platelet count is decreased.

Chemotherapy and selective irradiation (*e.g.*, CNS irradiation) are used in the treatment of acute leukemia. Remission is defined as eradication of leukemic cells as detectable by conventional technology. Chemotherapy includes induction therapy designed to elicit a remission, intensification therapy to produce a further reduction in leukemic cells after a remission is achieved, and maintenance therapy to maintain the remission. Because systemic chemotherapeutic agents cannot cross the blood-brain barrier and eradicate leukemic cells that have entered the CNS, CNS irradiation is administered concurrent with systemic chemotherapy.<sup>19,20</sup> The long-term effects of treatment on childhood cancer survivors is discussed in Chapter 5.

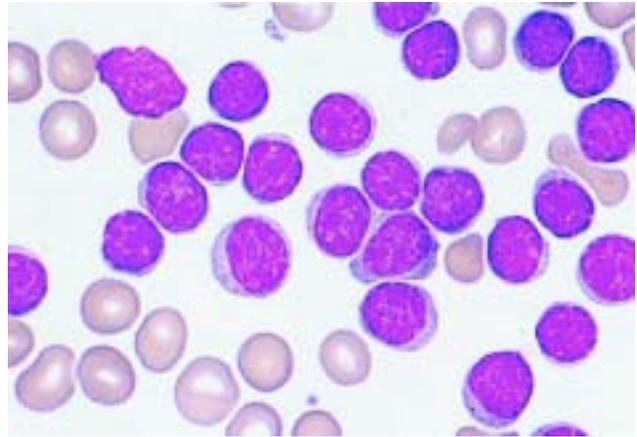
Massive destruction of malignant cells can occur during the initial phase of treatment. This phenomenon, known as *tumor lysis syndrome*, can lead to life-threatening metabolic disorders, including hyperkalemia, hyperphosphatemia, hyperuricemia, hypomagnesemia, hypocalcemia, and acidosis, with the potential for causing acute renal failure. Prophylactic aggressive hydration with alkaline solutions and administration of allopurinol to reduce uric acid levels is given to counteract these effects.

Bone marrow transplantation may be considered for persons with ALL and AML who experience no response to other forms of therapy. There has been recent interest in the use of stem cell transplantation in ALL<sup>21</sup> and AML.<sup>22</sup>

### Chronic Leukemias

Chronic leukemias have a more insidious onset than do acute leukemias and may be discovered during a routine medical examination by a blood count. Chronic lymphocytic leukemia (CLL) is mainly a disorder of older persons; fewer than 10% of those who have the disease are younger than 50 years. Men are affected twice as frequently as women. Chronic myelogenous leukemia (CML) accounts for 15% to 20% of all leukemias in adults. It is predominantly a disorder of adults between the ages of 30 and 50 years, but it can affect children as well. The incidence is slightly higher in men than women.

CLL is a disorder characterized by the proliferation and accumulation of relatively mature lymphocytes that are immunologically incompetent (Fig. 11-6). In the United States,



■ **FIGURE 11-6** ■ Chronic lymphocytic leukemia. A smear of peripheral blood shows numerous small-to-medium-sized lymphocytes. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1125]. Philadelphia: Lippincott Williams & Wilkins)

more than 95% of cases of CLL are of B-cell origin. The leukemic B cells fail to respond to antigenic stimulation; thus, persons with CLL have hypogammaglobulinemia. Infections remain a major cause of morbidity and mortality.

CML is a myeloproliferative disorder that involves expansion of all bone marrow elements. CML is associated in all cases with the presence of the Ph (Philadelphia) chromosome, representing a reciprocal translocation of the long arm of chromosome 22 to the long arm of chromosome 9.<sup>9,23</sup> In about 95% of persons with CML, the Ph chromosome can be identified in granulocytic, erythroid, and megakaryocytic precursors, as well as B cells, and in some cases, T cells.<sup>9</sup> Although CML originates in the pluripotent stem cells, granulocyte precursors remain the dominant cell type.

**Clinical Course.** Both CLL and CML have an insidious onset. However, the two types of chronic leukemias differ in their manifestations and clinical course.

CLL typically follows a slow, chronic course. The clinical signs and symptoms are largely related to the progressive infiltration of neoplastic lymphocytes in the bone marrow and extramedullary tissue and to secondary immunologic defects. Affected persons often have no symptoms at the time of diagnosis, and lymphocytosis is noted on a complete blood count obtained for another, unrelated disorder. Fatigue, reduced exercise tolerance, enlargement of superficial lymph nodes, or splenomegaly usually reflect a more advanced stage. As the disease progresses, lymph nodes gradually increase in size and new nodes are involved, sometimes in unusual areas such as the scalp, orbit, pharynx, pleura, gastrointestinal tract, liver, prostate, and gonads. Severe fatigue, recurrent or persistent infections, pallor, edema, thrombophlebitis, and pain are also experienced. As the malignant cell population increases, the proportion of normal marrow precursors is reduced until only lymphocytes remain in the marrow.<sup>20</sup>

Typically CML follows a triphasic course: a chronic phase of variable length, a short accelerated phase, and a terminal blast crisis phase. The onset of the chronic phase is usually slow with nonspecific symptoms such as weakness and weight loss. The most characteristic laboratory finding at the time of

presentation is leukocytosis with immature granulocyte cell types in the peripheral blood. Anemia and, eventually, thrombocytopenia develop. Anemia causes weakness, easy fatigability, and exertional dyspnea. Splenomegaly is often present at the time of diagnosis; hepatomegaly is less common; and lymphadenopathy is relatively uncommon. Although persons in the early chronic phase of CML generally have no symptoms, without effective treatment most will enter the accelerated phase within 3 to 5 years.

The accelerated phase is characterized by enlargement of the spleen and progressive symptoms. Splenomegaly often causes a feeling of abdominal fullness and discomfort. An increase in basophil count and more immature cells in the blood or bone marrow confirm transformation to the accelerated phase. During this phase, constitutional symptoms such as low-grade fever, night sweats, bone pain, and weight loss develop because of rapid proliferation and hypermetabolism of the leukemic cells. Bleeding and easy bruising may arise from dysfunctional platelets. Generally the accelerated phase is short (6 to 12 months).<sup>18</sup>

The terminal or blast crisis phase represents evolution to acute leukemia and is characterized by an increasing number of myeloid precursors, especially blast cells. Constitutional symptoms become more pronounced during this period, and splenomegaly may increase significantly. Isolated infiltrates of leukemic cells can involve the skin, lymph nodes, bones, and CNS. With very high blast counts (100,000/ $\mu$ L), symptoms of leukostasis may occur. The prognosis for patients who are in the blast crisis phase is poor, with survival rates averaging 2 to 4 months.

**Diagnosis and Treatment.** The diagnosis of chronic leukemia is based on blood and bone marrow studies. The treatment varies with the type of leukemic cell, the stage of the disease, other health problems, and the person's age. Most early cases of CLL require no specific treatment. Reassurance that persons with the disorder can live a normal life for many years is important. Indications for chemotherapy include progressive fatigue, troublesome lymphadenopathy, anemia, and thrombocytopenia. Complications such as autoimmune hemolytic anemia or thrombocytopenia may require treatment with corticosteroids or splenectomy. Unlike CML, transformation to acute leukemia with blast crisis is rare, and many persons live longer than 10 years and die of unrelated causes.

The treatment of CML is often palliative. The median survival is 5 to 7 years, with fewer than 50% of persons alive at 5 years.<sup>18</sup> Standard treatment includes the use of single-agent chemotherapy to control the disease in persons in the chronic phase of the disease. Interferon- $\alpha$  induces clinical remission in 70% to 80% of persons treated during the early chronic phase of the disease. During the blast crisis phase, combination therapy is administered, although response rates are low (20% to 30%) and remissions vary from 2 to 12 months. Allogeneic bone marrow or stem cell transplantation provides the only cure for CML.

## Multiple Myeloma

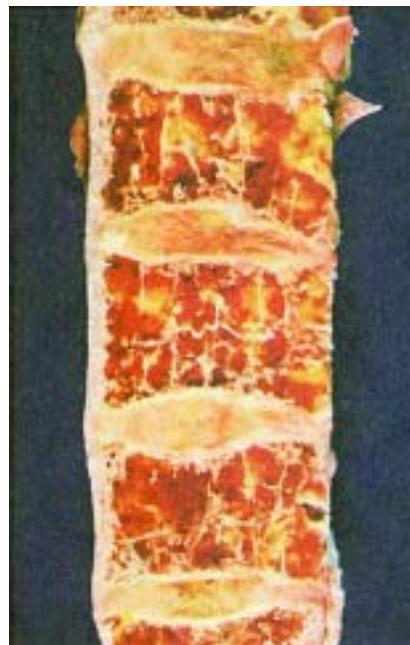
Multiple myeloma is a plasma cell cancer of the osseous tissue and accounts for 10% to 15% of all hematologic malignancies.<sup>24</sup> In the course of its dissemination, it also may involve

nonosseous sites. It is characterized by the uncontrolled proliferation of an abnormal clone of plasma cells, which secrete primarily IgG or IgA. Fewer than 3% of cases occur before the age of 40 years, with the median age of patients with multiple myeloma being 65 years.

The cause of multiple myeloma is unknown. It does not appear to be caused by previous exposure to toxic agents (*e.g.*, solvents such as benzene, paints, pesticides). Interestingly, an association with human herpesvirus 8 has been described, but the role of this virus in the pathogenesis of the disease remains to be established.<sup>24</sup>

In multiple myeloma, there is an atypical proliferation of one of the immunoglobulins, called the M protein, a monoclonal antibody.<sup>25</sup> Although multiple myeloma is characterized by excessive production of monoclonal immunoglobulin, levels of normal immunoglobulins are usually depressed. This contributes a general susceptibility to bacterial infections. Cytokines are important in the pathogenesis of the disorder. The multiple myeloma plasma cell has a surface-membrane receptor for interleukin-6, which is known to be a growth factor for the disorder. Another important growth factor for the myeloma cell is interleukin-1, which has important osteoclast activity.<sup>26</sup>

The main sites involved in multiple myeloma are the bones and bone marrow. In addition to the abnormal proliferation of marrow plasma cells, there is proliferation and activation of osteoclasts that leads to bone resorption and destruction (Fig. 11-7). This increased bone resorption predisposes the individual to pathologic fractures and hypercalcemia. Paraproteins secreted by the plasma cells may cause a hyperviscosity of body fluids and may break down into amyloid, a proteinaceous substance deposited between cells, causing heart failure and neuropathy.



■ **FIGURE 11-7** ■ **Multiple myeloma.** Multiple lytic lesions of the vertebrae are present. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1148]. Philadelphia: Lippincott Williams & Wilkins)

In some forms of multiple myeloma, the plasma cells produce only Bence Jones proteins, abnormal proteins that consist of the light chains of the immunoglobulin molecule. Because of their low molecular weight, Bence Jones proteins are partially excreted in the urine. Many of these abnormal proteins are directly toxic to renal tubular structures, which may lead to tubular destruction and, eventually, to renal failure.

The malignant plasma cells also can form plasmacytomas (plasma cell tumors) in bone and soft tissue sites. The most common site of soft tissue plasmacytomas is the gastrointestinal tract. The development of plasmacytomas in bone tissue is associated with bone destruction and localized pain. Occasionally, the lesions may affect the spinal column, causing vertebral collapse and spinal cord compression.<sup>24</sup>

**Manifestations.** Bone pain is one of the first symptoms to occur and one of the most common, occurring in approximately 80% of all individuals with diagnoses of multiple myeloma. Bone destruction also impairs the production of erythrocytes and leukocytes and predisposes the patient to anemia and recurrent infections. Many patients experience weight loss and weakness. Renal insufficiency occurs in 50% of patients. Neurologic manifestations caused by neuropathy or spinal cord compression also may be present.

**Diagnosis and Treatment.** Diagnosis is based on clinical manifestations, blood tests, and bone marrow examination. The hallmark of myeloma is the finding of paraproteins on serum protein electrophoresis. Bone radiographs are important in establishing the presence of bone lesions.

Although numerous treatments for multiple myeloma have been attempted since the early 1970s, the results have been disappointing. With standard chemotherapy, the median survival may reach 2 to 3 years. Multiple myeloma is a radiosensitive disease, but most radiation therapy is used primarily for palliation, specifically to treat lytic bone lesions and compression fractures and to decrease pain. Recently, thalidomide has been shown to induce responses in persons whose myeloma was refractory to conventional therapies.<sup>24</sup>

**In summary,** the lymphomas (Hodgkin's disease and non-Hodgkin's lymphoma) represent malignant neoplasms of cells native to lymphoid tissue (*i.e.*, lymphocytes and histiocytes) and their precursors or derivatives. Hodgkin's disease is characterized by painless and progressive enlargement of a single node or group of nodes. It is believed to originate in one area of the lymphatic system and, if unchecked, spreads throughout the lymphatic network. Non-Hodgkin's lymphomas are multicentric in origin and spread early to various tissues throughout the body, especially the liver, spleen, and bone marrow.

Leukemias are malignant neoplasms of the hematopoietic stem cells with diffuse replacement of bone marrow. Leukemias are classified according to cell type (*i.e.*, lymphocytic or myelogenous) and whether the disease is acute or chronic. The lymphocytic leukemias involve immature lymphocytes and their progenitors that originate in the bone marrow but infiltrate the spleen, lymph nodes, CNS, and other tissues. The myelogenous leukemias involve the pluripotent myeloid stem cells in bone marrow and interfere with the maturation

of all blood cells, including the granulocytes, erythrocytes, and thrombocytes. The acute leukemias (*i.e.*, ALL, which primarily affects children, and AML, which primarily affects adults) have a sudden and stormy onset, with symptoms of depressed bone marrow function (anemia, fatigue, bleeding, and infections); bone pain; and generalized lymphadenopathy, splenomegaly, and hepatomegaly. The chronic leukemias, which largely affect adults, have a more insidious onset. CLL often has the most favorable clinical course, with many persons living long enough to die of unrelated causes. The course of CML is slow and progressive, with transformation to a course resembling that of AML.

Multiple myeloma results in the uncontrolled proliferation of immunoglobulin-secreting plasma cells, usually a single clone of IgG- or IgA-producing cells, that results in increased bone resorption, leading to pathologic bone lesions.

## REVIEW QUESTIONS

- Trace the development of the different blood cells from their origin in the pluripotent bone marrow stem cell to their circulation in the bloodstream.
- Explain the signs and symptoms of neutropenia in terms of the function of the neutrophil.
- Explain the manifestations of infectious mononucleosis in terms of the immune systems response to infection by the Epstein-Barr virus.
- Contrast the signs and symptoms of Hodgkin's and non-Hodgkin's lymphoma based on the differences in involvement of lymphoid tissues and immune cells.
- One of the manifestations of Hodgkin's disease is the inability of persons with tuberculosis to display a positive response to the tuberculin skin test. Explain.
- Relate the constitutional symptoms of lymphomas (*e.g.*, fever, general malaise, and fatigue) to the pathophysiology of Hodgkin's disease and non-Hodgkin's lymphoma.
- Explain the manifestations of leukemia in terms of altered cell differentiation.
- Describe the pathophysiologic basis for the following complications of leukemia: leukostasis, tumor lysis syndrome, hyperuricemia, and blast crisis.
- Relate abnormal proliferation of an abnormal plasma cell clone to the manifestations of multiple myeloma.



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