good means for estimating marrow activity. In normal adults, the ratio of fat cells to hematopoietic elements is about 1:1. In hypoplastic states (e.g., aplastic anemia) the proportion of fat cells is greatly increased; conversely, fat cells often disappear when the marrow is involved by hematopoietic tumors and in diseases characterized by compensatory hyperplasias (e.g., hemolytic anemias), and neoplastic proliferations such as leukemias. Other disorders (e.g., metastatic cancers and granulomatous diseases) induce local marrow fibrosis. Such lesions are usually inaspirable and best seen in biopsies.

DISORDERS OF WHITE CELLS

Disorders of white blood cells can be classified into two broad categories: *proliferative disorders*, in which there is an expansion of leukocytes, and *leukopenias*, which are defined as a deficiency of leukocytes. Proliferations of white cells can be *reactive* or *neoplastic*. Reactive proliferations in the setting of infections or inflammatory processes, when leukocytes are needed for an effective host response, are fairly common. Neoplastic disorders, though less frequent, are much more important clinically. In the following discussion we will first describe the leukopenic states and summarize the common reactive disorders, and then consider in some detail the malignant proliferations of white cells.

Leukopenia

The number of circulating white cells may be markedly decreased in a variety of disorders. An abnormally low white cell count *(leukopenia)* usually results from reduced numbers of neutrophils *(neutropenia, granulocytopenia)*. *Lymphopenia* is less common; in addition to congenital immunodeficiency diseases (Chapter 6), it is most commonly observed in advanced human immunodeficiency virus (HIV) infection, following therapy with glucocorticoids or cytotoxic drugs, autoimmune disorders, malnutrition, and certain acute viral infections. In the latter setting lymphopenia actually stems from lymphocyte redistribution rather than a decrease in the number of lymphocytes in the body. Acute viral infections induce production of type I interferons, which activate T lymphocytes and change the expression of surface proteins that regulate T cell migration. These changes result in the sequestration of activated T cells in lymph nodes and increased adherence to endothelial cells, both of which contribute to lymphopenia. Granulocytopenia is more common and is often associated with diminished granulocyte function, and thus merits further discussion.

Neutropenia, Agranulocytosis

Neutropenia, a reduction in the number of neutrophils in the blood, occurs in a wide variety of circumstances. *Agranulocytosis*, a clinically significant reduction in neutrophils, has the serious consequence of making individuals susceptible to bacterial and fungal infections.

Pathogenesis. **Neutropenia can be caused by (1) inadequate or ineffective granulopoiesis, or (2) increased destruction or sequestration of neutrophils in the periphery.** Inadequate or ineffective granulopoiesis is observed in the setting of:

- *Suppression of hematopoietic stem cells*, as occurs in aplastic anemia (Chapter 14) and a variety of infiltrative marrow disorders (e.g., tumors, granulomatous disease); in these conditions granulocytopenia is accompanied by anemia and thrombocytopenia
- *Suppression of committed granulocytic precursors* by exposure to certain drugs (discussed later)
- Disease states associated with *ineffective hematopoiesis*, such as megaloblastic anemias (Chapter 14) and myelodysplastic syndromes, in which defective precursors die in the marrow
- Rare *congenital conditions* (e.g., Kostmann syndrome) in which inherited defects in specific genes impair granulocytic differentiation

Accelerated destruction or sequestration of neutrophils occurs with

- *Immunologically mediated injury* to neutrophils, which can be idiopathic, associated with a well-defined immunologic disorder (e.g., systemic lupus erythematosus), or caused by exposure to drugs
- *Splenomegaly*, in which splenic enlargement leads to sequestration of neutrophils and modest neutropenia, sometimes associated with anemia and often with thrombocytopenia
- *Increased peripheral utilization*, which can occur in overwhelming bacterial, fungal, or rickettsial infections

The most common cause of agranulocytosis is *drug toxicity*. Certain drugs, such as alkylating agents and antimetabolites used in cancer treatment, produce agranulocytosis in a predictable, dose-related fashion. Because such drugs cause a generalized suppression of hematopoiesis, production of red cells and platelets is also affected. Agranulocytosis can also occur as an idiosyncratic reaction to a large variety of agents. The roster of implicated drugs includes aminopyrine, chloramphenicol, sulfonamides, chlorpromazine, thiouracil, and phenylbutazone. The neutropenia induced by chlorpromazine and related phenothiazines results from a toxic effect on granulocytic precursors in the bone marrow. In contrast, agranulocytosis following administration of other drugs, such as sulfonamides, probably stems from antibody-mediated destruction of mature neutrophils through mechanisms similar to those involved in drug-induced immunohemolytic anemias (Chapter 14).

In some patients with acquired idiopathic neutropenia, autoantibodies directed against neutrophil-specific antigens are detected. Severe neutropenia can also occur in association with monoclonal proliferations of large granular lymphocytes (so-called *LGL leukemia*). The mechanism