of this neutropenia is not clear; suppression of granulocytic progenitors by products of the neoplastic cell (usually a CD8+ cytotoxic T cell) is considered most likely.

MORPHOLOGY

The alterations in the **bone marrow** vary with cause. With excessive destruction of neutrophils in the periphery, the marrow is usually hypercellular due to a compensatory increase in granulocytic precursors. Hypercellularity is also the rule with neutropenias caused by ineffective granulopoiesis, as occurs in megaloblastic anemias and myelodysplastic syndromes. Agranulocytosis caused by agents that suppress or destroy granulocytic precursors is understandably associated with marrow hypocellularity.

Infections are a common consequence of agranulocytosis. Ulcerating necrotizing lesions of the gingiva, floor of the mouth, buccal mucosa, pharynx, or elsewhere in the oral cavity (agranulocytic angina) are quite characteristic. These are typically deep, undermined, and covered by gray to green-black necrotic membranes from which numerous bacteria or fungi can be isolated. Less frequently, similar ulcerative lesions occur in the skin, vagina, anus, or gastrointestinal tract. Severe life-threatening invasive bacterial or fungal infections may occur in the lungs, urinary tract, and kidneys. The neutropenic patient is at particularly high risk for deep fungal infections caused by *Candida* and *Aspergillus*. Sites of infection often show a massive growth of organisms with little leukocytic response. In the most dramatic instances, bacteria grow in colonies (botryomycosis) resembling those seen on agar plates.

Clinical Features. The symptoms and signs of neutropenia are related to infection, and include malaise, chills, and fever, often followed by marked weakness and fatigability. With agranulocytosis, infections are often overwhelming and may cause death within hours to days.

Serious infections are most likely when the neutrophil count falls below 500 per mm^3. Because infections are often fulminant, broad-spectrum antibiotics must be given expeditiously whenever signs or symptoms appear. In some instances, such as following myelosuppressive chemotherapy, neutropenia is treated with G-CSF, a growth factor that stimulates the production of granulocytes from marrow precursors.

Reactive Proliferations of White Cells and Lymph Nodes

Leukocytosis

Leukocytosis refers to an increase in the number of white cells in the blood. It is a common reaction to a variety of inflammatory states.

Pathogenesis. The peripheral blood leukocyte count is influenced by several factors, including:

- The size of the myeloid and lymphoid precursor and storage cell pools in the bone marrow, thymus, circulation, and peripheral tissues
- The rate of release of cells from the storage pools into the circulation
- The proportion of cells that are adherent to blood vessel walls at any time (the marginal pool)
- The rate of extravasation of cells from the blood into tissues

Table 13-2 Mechanisms and Causes of Leukocytosis

Increased Production in the Marrow
Chronic infection or inflammation (growth factor-dependent)
Paraneoplastic (e.g., Hodgkin lymphoma; growth factor-dependent)
Myeloproliferative disorders (e.g., chronic myeloid leukemia; growth factor-independent)
Increased Release from Marrow Stores
Endotoxemia
Infection
Hypoxia
Decreased Margination
Exercise
Catecholamines
Decreased Extravasation into Tissues
Glucocorticoids

As discussed in Chapter 3, leukocyte homeostasis is maintained by cytokines, growth factors, and adhesion molecules through their effects on the commitment, proliferation, differentiation, and extravasation of leukocytes and their progenitors. Table 13-2 summarizes the major mechanisms of neutrophilic leukocytosis and its causes, the most important of which is infection. In acute infection there is a rapid increase in the egress of mature granulocytes from the bone marrow pool, an alteration that may be mediated through the effects of tumor necrosis factor (TNF) and interleukin-1 (IL-1). If the infection or an inflammatory process is prolonged, IL-1, TNF, and other inflammatory mediators stimulate macrophages, bone marrow stromal cells and T cells to produce increased amounts of hematopoietic growth factors. These factors enhance the proliferation and differentiation of committed granulocytic progenitors and, over several days, cause a sustained increase in neutrophil production.

Some growth factors preferentially stimulate the production of a single type of leukocyte. For example, IL-5 mainly stimulates eosinophil production, while G-CSF induces neutrophilia. Such factors are differentially produced in response to various pathogenic stimuli and, as a result, the five principal types of leukocytosis (neutrophilia, eosinophilia, basophilia, monocytosis, and lymphocytosis) tend to be observed in different clinical settings (Table 13-3).

In sepsis or severe inflammatory disorders (e.g., Kawasaki disease), leukocytosis is often accompanied by morphologic changes in the neutrophils, such as toxic granulations, Döhle bodies, and cytoplasmic vacuoles (Fig. 13-2). *Toxic granules*, which are coarser and darker than the normal neutrophilic granules, represent abnormal azurophilic (primary) granules. *Döhle bodies* are patches of dilated endoplasmic reticulum that appear as sky-blue cytoplasmic "puddles."

In most instances it is not difficult to distinguish reactive and neoplastic leukocytoses, but uncertainties may arise in two settings. Acute viral infections, particularly in