(Table 48-2). However, patients with a persistently elevated neutrophil count, especially associated with an elevated hematocrit or platelet count, should be evaluated to rule out a primary myeloproliferative disorder. Peripheral blood evaluation for the BCR/ABL fusion product can be performed to rule out CML, and assays for JAK2 and calreticulin mutations can help to rule out non-CML myeloproliferative neoplasms. A leukocyte alkaline phosphatase assay was formerly used to rule out CML because the result was 0 in chronic phase CML, but with the advent of BCR/ABL testing, it has become obsolete.

Neutrophilia related to acute infection, stress, or acute steroid administration primarily reflects demargination and is usually transient. Persistent neutrophilia usually reflects chronic bone marrow stimulation. Nevertheless, a bone marrow aspirate and biopsy are rarely indicated in the work-up of neutrophilia. The exception is for patients who demonstrate leukoerythroblastic changes, for which a bone marrow examination and culture may be indicated to rule out tuberculosis or fungal infection, marrow infiltration with tumor, or marrow fibrosis. Cytogenetic and molecular studies should be performed to help eliminate the diagnosis of marrow malignancies, and the marrow should be cultured for mycobacteria and fungi.

NEUTROPENIA

Differential Diagnosis

Neutropenia (i.e., leukopenia) may reflect decreased production, increased sequestration, or peripheral destruction of neutrophils (Table 48-3). Patients should first be evaluated for splenomegaly to rule out the possibility of sequestration.

For patients who are completely asymptomatic and for whom previous studies are unavailable, the possibility of constitutional or cyclic neutropenia should be entertained and can be evaluated by serial peripheral blood counts. The normal neutrophil count varies among ethnic groups and is lower in American blacks (i.e., constitutional neutropenia) than it is in whites. Cyclic neutropenia is a relatively benign disorder, in which cyclical changes occur in all hematopoietic cell lines but are most dramatic in the neutrophil lineage. At the nadir of the neutrophil counts, patients may have infections, but the disease is often clinically silent. In contrast, patients with congenital agranulocytosis or severe congenital neutropenia (SCN) exhibit profound neutropenia and infections in the perinatal period. Kostmann's syndrome is a subset of SCN that was described 50 years ago as an autosomal recessive disorder; later studies demonstrated that SCN might be autosomal dominant, autosomal recessive, X-linked, or sporadic and that the causes were also heterogeneous.

About 50% of autosomal dominant SCN and almost 100% of cyclic neutropenia cases are associated with inherited mutations in the neutrophil elastase gene. The mutations are thought to produce a misfolded neutrophil elastase protein, which accumulates in the endoplasmic reticulum and activates the unfolded protein response. This complex cellular stress response coordinates the degradation of misfolded protein in the endoplasmic reticulum and can trigger cellular apoptosis if the stress is severe. Later studies have established that autosomal recessive SCN (i.e. Kostmann's syndrome) is caused by mutations in the *HAX1* gene, which encodes a mitochondrial protein that is required for stabilization of the mitochondrial membrane. Absence of HAX1 results in loss of the mitochondrial membrane potential and induction of apoptosis.

Until G-CSF became available, most patients with SCN died in early childhood, but the availability of cytokine therapy has prolonged survival. However, SCN is also associated with a significantly increased incidence of acute leukemia, a complication that has become apparent as patients survive longer. Up to 30% of patients with SCN develop acute myelogenous leukemia over 10 years. Acute myelogenous leukemia in these patients is often associated with truncation mutations in the G-CSF receptor. These acquired somatic mutations may contribute to the pathogenesis of leukemia but do not contribute to the congenital neutropenia. The role of the G-CSF receptor mutations in the pathogenesis of leukemic transformation is controversial, as is the relationship between G-CSF therapy and the acquisition of these mutations.

Neutropenia may occur during or after viral, bacterial, or mycobacterial infections. Postviral neutropenia is especially common in children and probably reflects increased neutrophil consumption and a viral suppression of marrow neutrophil production. Neutropenia may be seen as a complication of overwhelming sepsis and is associated with a poor prognosis.

Drug-induced neutropenia may reflect dose-dependent marrow suppression or an idiosyncratic immune response. The former is one of the most common complications of chemotherapeutic drugs and is also common with antibiotics such as sulfamethoxazole-trimethoprim. Chloramphenicol causes

TABLE 48-2 DIFFERENTIAL DIAGNOSIS OF NEUTROPHILIA

PRIMARY HEMATOLOGIC DISEASE	Cytokine stimulation (e.g., granulocyte colony-simulating factor)
Congenital neutrophilia	Chronic inflammation
Leukocyte adhesion deficiency	Malignancy
Myeloproliferative disorders	Myelophthisis
DUE TO OTHER DISEASE PROCESSES	Marrow hyperstimulation
Infection (acute or chronic)	Chronic hemolysis, immune thrombocytopenia
Acute stress	Recovery from marrow suppression
Drugs (e.g., steroids, lithium)	After splenectomy
	Smoking

TABLE 48-3 DIFFERENTIAL DIAGNOSIS OF NEUTROPENIA

DECREASED PRODUCTION OF NEUTROPHILS	INCREASED PERIPHERAL DESTRUCTION
Congenital and/or constitutional cause	Overwhelming infection
Constitutional neutropenia	Immune destruction
Benign chronic neutropenia	Drug related
Kostmann's syndrome	Associated with collagen vascular disease
Benign cyclic neutropenia	Isoimmune (in newborns)
Postinfectious cause	Large granular lymphocyte leukemia
Nutritional deficiency (B_{12}, folate)	Hypersplenism and/or sequestration
Drug-induced cause	
Primary marrow failure	
Aplastic anemia	
Myelodysplasia	
Acute leukemia	