have concurrent leukocytosis or thrombocytosis, erythrocytosis is the hallmark and the cause of the most serious clinical complications of this disease. Typically, patients complain of headache, visual problems, mental clouding, and pruritus after bathing. Occlusive vascular events such as stroke, transient ischemic attacks, myocardial ischemia, and digital pain, paresthesias, or gangrene are common. Pulmonary, deep vein, hepatic, and portal vein thromboses may occur. Paradoxically, patients are also predisposed to hemorrhagic events, which are presumably caused by abnormal platelet function, and they may exhibit gastrointestinal bleeding. Physical examination often shows retinal vein occlusion, ruddy cyanosis, and splenomegaly.

Diagnosis and Differential Diagnosis

When patients are first diagnosed with an elevated hemoglobin concentration per unit volume (i.e., erythrocytosis), the initial evaluation should focus on whether this increase reflects an enhanced red cell mass (i.e., absolute erythrocytosis or polycythemia) or a normal red cell mass in the setting of a decreased plasma volume (i.e., relative erythrocytosis caused by dehydration or other causes). The latter condition is not true polycythemia (Table 46-2). Polycythemia or absolute erythrocytosis is an absolute increase in red cell mass caused by increased red blood cell production.

Under normal conditions, the body's ability to increase red blood cell production in states of hypoxemia, anemia, hemolysis, and acute blood loss ensures continuous oxygen delivery to tissues. In response to physiologic stimuli, pluripotent stem cell precursors are activated by erythropoietin (EPO) to differentiate into erythroid progenitor cells and eventually into hemoglobin-carrying erythrocytes. When numbers of mature red blood cells are adequate, a negative feedback mechanism suppresses further EPO production, and the serum hemoglobin level remains normal.

TABLE 46-2 CAUSES OF ERYTHROCYTOSIS

I. Relative or spurious erythrocytosis (normal red cell mass)
   A. Hemoconcentration due to dehydration (e.g., diarrhea, diaphoresis, diuretics, water deprivation, emesis, ethanol, hypertension, preeclampsia, pheochromocytoma, carbon monoxide intoxication)
II. True or absolute erythrocytosis
   A. Polycythemia vera
   B. Primary congenital polycythemia
   C. Secondary erythrocytosis due to
      1. Congenital causes (e.g., activating mutation of erythropoietin receptor)
      2. Hypoxia caused by carbon monoxide poisoning, high oxygen affinity hemoglobin, high-altitude residence, chronic pulmonary disease, hypoventilation syndromes such as sleep apnea, right-to-left cardiac shunt, neurologic defects involving the respiratory center
      3. Nonhypoxic causes with pathologic erythropoietin production
         a. Renal disease (e.g., cysts, hydronephrosis, renal artery stenosis, focal glomerulonephritis, renal transplantation)
         b. Tumors (e.g., renal cell cancer, hepatocellular carcinoma, cerebellar hemangioblastoma, uterine fibromyoma, adrenal tumors, meningioma, pheochromocytoma)
      4. Drug-associated causes
         a. Androgen therapy
         b. Exogenous erythropoietin growth factor therapy

Modified from Hoffman R, Benz EJ, Shattil SJ, et al, editors: Hematology: basic principles and practice, ed 2, New York, 1995, Churchill Livingstone.

Diagnosis of PV was formerly one of exclusion based on an elevated red cell mass, splenomegaly, thrombocytosis, leukocytosis, lack of hypoxemia and other secondary causes of polycythemia, and elevated levels of leukocyte alkaline phosphatase and serum vitamin B_{12}–binding protein levels. More information about the disease pathophysiology led to new diagnostic criteria (Table 46-3) based on the discovery of *JAK2* gene mutations in 97% of patients with PV. A suspected diagnosis of PV can now be confirmed by testing for a *JAK2* mutation, and identification of low serum EPO levels and EPO-independent erythroid colony growth have become secondary diagnostic criteria.

Peripheral blood often appears microcytic, with or without iron deficiency. Bone marrow examination shows a hypercellular marrow with pronounced hyperplasia of erythroid lineage cells. Cytogenetic features at the time of diagnosis are usually normal. The development of clonal cytogenetic abnormalities heralds transformation in the later stages of disease.

Treatment and Prognosis

Early recognition and treatment of PV are important because untreated patients with PV suffer significant morbidity and mortality from thromboembolic complications involving the cerebral, coronary, and mesenteric circulations. Twenty percent of patients show symptoms of arterial and venous thrombosis, and thrombosis remains the most common cause of death. Without treatment, one half of patients with PV die of thrombotic complications within 18 months of diagnosis. With therapy, PV is a chronic, progressive disease. The risk of transformation to acute myeloid leukemia (AML) is 2.3% at 10 years and 5.5% at 15 years. Patients with advanced age (>60 years), prior history of thrombosis, leukocytosis, and high hematocrit values are at high risk for subsequent vascular events. The JAK2 V617F mutation and clinical cardiovascular factors are also associated with an increased risk of thrombosis.

Intermittent phlebotomy is the mainstay of treatment and usually results in iron deficiency anemia, which further reduces the rate of red blood cell production. Cytoreductive therapy is indicated for patients who cannot tolerate or fail phlebotomy, those with a history of or risk factors for thrombosis, and those with symptomatic splenomegaly. Cytoreductive therapies include hydroxyurea (i.e., low-dose cytotoxic agent that does not appear to increase leukemic risk), interferon-α (i.e., for young

TABLE 46-3 WORLD HEALTH ORGANIZATION 2008 DIAGNOSTIC CRITERIA FOR POLYCYTHEMIA VERA

Major criteria*
1. Hemoglobin (Hgb) >18.5 g/dL (men), >16.5 (women); *or* Hgb or hematocrit (Hct) >99% reference range for age, sex, or altitude of residence; *or* Hgb >17 g/dL (men), >15 g/dL (women) if associated with a sustained increase of ≥2g/dL from baseline that cannot be attributed to correction of iron deficiency; *or* elevated red cell mass (>25% above mean normal predicted value)
2. Presence of *JAK2* V617F or similar mutation

Minor criteria
1. Bone marrow trilineage myeloproliferation
2. Subnormal serum erythropoietin level
3. Endogenous erythroid colony formation in vitro

*Both major criteria and one minor criterion *or* the first major criterion and two minor criteria must be met for the diagnosis of polycythemia vera.