

ing acute splenic infarction, ascites demonstrating prominent megakaryocytosis, or focal, but severe bone pain, the use of radiation may produce gratifying effects.

Allogeneic marrow transplantation following ablative chemotherapy and radiotherapy has been attempted in a few patients and offers a rational means for curing myelofibrosis. However, it is controversial whether or not the application of this rigorous therapy to a chronic disease, generally limited to the elderly, is judicious. Disappearance of fibrosis and regeneration of normal medullary hematopoiesis has been achieved in responsive patients.

Another significant approach to the treatment of myelofibrosis is the utilization of antifibrotic agents such as penicillamine or colchicine. Biochemically, as myelofibrosis progresses, there is increasing conversion of soluble to insoluble collagen. Penicillamine interferes with the cross-linkage of collagen and, therefore, with its use, a decrease in fibrous tissue occurs. It is still unclear whether penicillamine has a significant effect on the natural course of this disease. Colchicine appears to cause its antifibrotic effect through two mechanisms: (1) it produces a decreased rate of procollagen, and (2) it increases the secretion of collagenases. New agents called lathyrogens, such as β -aminoproprionitrile, are being studied and show promise in blocking the cross-linking of collagen by inhibiting the copper-dependent enzyme important in collagen cross-linking.

Recently, interferon α has been used to prevent the progression of myelofibrosis to blastic transformation, allowing patients to maintain a remission status without allogeneic bone marrow transplantation. Lastly, allopurinol therapy is warranted in almost all patients to prevent the hyperuricemia from progressing to gout or urate nephropathy.

Prognosis

Patients with IMF comprise extremely heterogeneous populations, and survival varies considerably. Median survival is approximately 5 years from the time of diagnosis; however, at least two major subpopulations have been identified. The first (low-risk) group is characterized by a benign or slowly progressive disease with a median survival of 10 years or longer and young age (less than 45). The second, less fortunate (high-risk) group is distinguished by a short-lived survival of 2 years and older age group (more than 45). Many patients in this subgroup die following acute blastic transformation.

Besides age, a number of prognostic indicators have been identified; the most important in regard to long survival include the following:

1. Lack of symptoms
2. Effective erythropoiesis, as evidenced by hemoglobin level greater than 10 g/dL, reticulocyte count greater than 2%, and bone marrow showing normal erythropoiesis
3. Platelet counts above $100 \times 10^9/L$
4. Absence of significant hepatosplenomegaly

Conversely, patients with severe, ineffective hematopoiesis and marrow failure, marked splenomegaly with plasma volume expansion and portal hypertension, anemia, or excessive hemolysis fair poorly, with an average survival of only 1 to 2 years. The major causes of death are acute myocardial infarction, congestive heart failure, gastrointestinal and cerebral hemorrhage, pneumonia, and infection.

Between 5% and 15% of cases have a terminal transformation to leukemia, acute myelogenous leukemia in most instances, with a rapidly progressive, fatal course. Rare patients die of liver or renal failure, and development of acute lymphocytic leukemia and erythroleukemia has been reported. IMF is infrequently found in children, but when discovered has a rapidly fatal course. It is associated with trisomy 21 and appears to be a variant of acute megakaryoblastic leukemia.

Major scientific advances and application of new knowledge have taken place in recent years. Relevant discoveries in the areas of collagen biochemistry and histochemistry, bone marrow ultrastructure, cell culture studies, and cell growth regulation have allowed a more in-depth understanding of the pathologic processes involved in the disease of myelofibrosis. As new, innovative strategies are applied to the treatment of this complex disease, it is hoped that there will be a significant improvement in both the survival and quality of life of patients with IMF.

► ERYTHROCYTOSIS

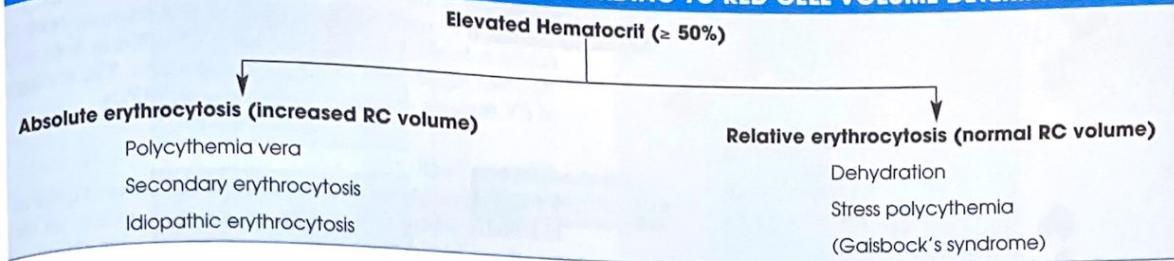
A number of diverse conditions may cause an elevation in the hematocrit (Hct). Initially, these disorders can be separated into two groups based on the determination of the red cell mass (Table 18–5). In the *absolute erythrocytosis* group, the red cell mass (or red cell volume) is elevated, implying a true increase in the number of circulating erythrocytes. By contrast, in *relative erythrocytosis*, there is an increased Hct in the absence of an elevation in red cell volume. This state is the result of an increase in the ratio of red cell mass to the plasma volume, as would occur with dehydration (in which the plasma volume was contracted or decreased).

Absolute erythrocytosis may be further divided into three distinct groups: (1) polycythemia vera, a chronic myeloproliferative disorder, arising as a clonal hematologic malignancy of the bone marrow; (2) secondary erythrocytosis, representing a physiologic response to abnormal stimulus (e.g., tissue hypoxia, increased erythropoietic activity); or (3) an idiopathic group for which neither a myeloproliferative nor secondary cause of sustained erythrocytosis can be implicated. An overall comparison of these three groups of polycythemia can be found in Table 18–6. Primary polycythemia vera is discussed in length first.

Polycythemia Vera: Description, History, and Pathogenesis

Polycythemia vera (PV) is a hematopoietic stem cell disorder predominantly characterized by accelerated erythropoiesis and, to varying degrees, excessive proliferation of myeloid and megakaryocytic elements of the bone marrow (Figs. 18–9 and 18–10, and Color Plates 208 and 209). As mentioned earlier, the absolute increase in red cell mass is an important finding for establishing the diagnosis of PV. A routine complete blood count (CBC) shows the following values: in women, the RBC count is increased to more than $5.9 \times 10^{12}/L$, and in men, to more than $6.6 \times 10^{12}/L$. In keeping with other myeloproliferative disorders, the manifestations of splenomegaly, myeloid metaplasia, and myelofibrosis are variably expressed at diagnosis and throughout the course of the disease. Most commonly at the time of initial presentation, the degree of extramedullary hematopoiesis is usually mild, and marrow fibrosis is most often minimal. However, 15% to 20% of

► Table 18-5
CLASSIFICATION OF THE POLYCYTHEMIAS ACCORDING TO RED CELL VOLUME DETERMINATIONS



patients transform to a spent phase with progressive anemia and increasing splenomegaly, this development being virtually indistinguishable from idiopathic myelofibrosis.

The nature of this disease has been controversial over the years. Hippocrates recognized "plethora vera,"⁷ and Von Haller in 1730 associated thrombosis with the frequent occurrence of gangrene. Vasques,⁸ Cabot, and, in 1903, Osler,⁹ first characterized the disease as autonomous erythrocytosis, additionally noting the concurrent feature of splenomegaly. Turk¹⁰ in 1904 described the leukoerythroblastic blood picture as well as documenting the finding of increased granulocytic and megakaryocytic activity. The replacement of normal marrow by fibrotic and sclerotic tissue was reported by Hirsch¹¹ in 1935, and by 1938, Rosenthal and Sessen¹² had delineated the natural history and cause of the disease. The concept of the myeloproliferative diseases was originally

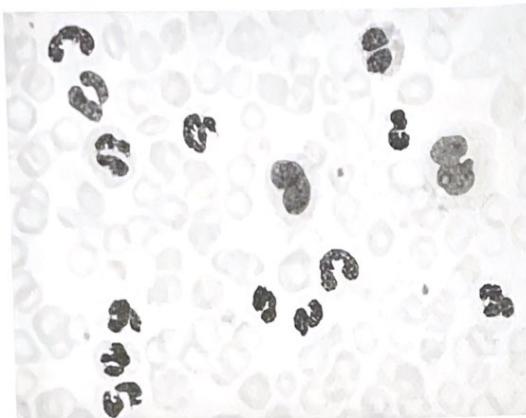
proposed in the 1950s by Dameshek,¹ and since that time the body of knowledge encompassing polycythemia has greatly expanded.

It has now been clearly established that the cell of origin in PV is an abnormal pluripotent stem cell. This has been demonstrated by studies of black women with PV who were heterozygous for the two different G6PD isoenzymes. In these women, only one of the isoenzymes was present in the progenitors and progeny of erythroid, granulocytic, monocytic, and megakaryocytic cell lines, whereas non-hematopoietic tissue displayed both isoenzymes A and B. In normal healthy women, equal amounts of both isoenzyme types were found in blood cells. These findings strongly suggested that abnormal hematopoietic cells arise from a single malignant clone. Furthermore, some patients eventually develop marrow fibrosis, and this occurrence is

► Table 18-6
FEATURES OF POLYCYTHEMIA VERA, SECONDARY (HYPOXIC) POLYCYTHEMIA, AND RELATIVE ERYTHROCYTOSIS

Manifestations	PV	Secondary Erythrocytosis	Relative Erythrocytosis
Clinical Features			
Cyanosis	Absent	Present	May be present
Heart or lung disease	Absent	Present	Absent
Splenomegaly	Present in 75%	Absent	Absent
Hepatomegaly	Present in 35%	Absent	Absent
Laboratory Features			
Red cell mass	Increased	Increased	Normal
Erythropoietin	Decreased (rarely normal)	Increased (rarely normal)	Normal
Arterial O ₂ saturation	Normal	Decreased	Normal
Leukocyte	Increased in 80%	Normal	Normal
Platelet count	Increased in 50%	Normal	Normal
NRBCs, poikilocytes	Often present	Absent	Absent
LAP	Increased in 70%	Normal	Normal
Bone marrow	Hypercellular; Increased erythropoiesis and myelopoesis; increased megakaryocytes; fibrosis	Increased erythropoiesis	Normal
Serum vitamin B ₁₂	Increased in 75%	Normal	Normal
Culture studies	Autonomous, erythroid proliferation	Epo-dependent colony formation	Not applicable

Abbreviations: NRBCs = nucleated red blood cells; EPO = erythropoietin



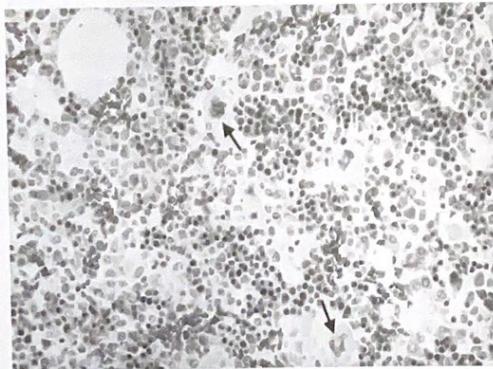
► FIGURE 18-9 Peripheral blood smear seen in polycythemia vera. Note hypochromia and increased cellularity (magnification $\times 400$).

a reactive process. Just as in myelofibrosis, the excessive fibroblastic proliferation is a result of the release of certain growth factors from abnormal megakaryocytes.

When blood and bone marrow cells from patients with PV are cultured on semisolid media, erythroid colonies (colony-forming unit–erythroid [CFU-E] and burst-forming unit–erythroid, [BFU-E]) are formed without the addition of exogenous erythropoietin. This led to the original presumption that erythroid colonies grow spontaneously in PV, because in normal individuals, formation of erythroid colonies is dependent on erythropoietin, which acts on the committed erythroid cell line, causing increased proliferation. Erythroid progenitors are extremely sensitive to low levels of erythropoietin supplied by the serum that is inherently present in the basic culture medium. Cultures of erythroid precursor cells are one of the tests currently advocated in the differential diagnosis of PV versus secondary polycythemia.

Epidemiology

Polycythemia vera is a relatively rare disease of older adults with an annual incidence of approximately 2 cases per 100,000 population. The median age at diagnosis is 60 years, but onset may occur from adolescence to old age. Only nine cases of childhood PV have been documented. The disease has a slightly higher incidence in men than in



► FIGURE 18-10 Bone marrow showing panhyperplasia in polycythemia vera. Note increased number of megakaryocytes (arrows). Hematoxylin and eosin stain (low power).

women; however, in younger patients PV reportedly shows less of a male preponderance. Familial occurrences, although rare, have been reported. A cluster of MPDs, including PV cases, has been reported in Ashkenazi Jews in northern Israel, where the incidence of MPDs in Jews was 10 times higher than in the Arab population. The etiology of PV remains unknown, as it is in other MPDs.

Clinical Features

PV has an insidious onset and is often discovered quite incidentally when, following a routine examination, an elevated red blood cell (RBC) count, hemoglobin (Hgb), or Hct is discovered following routine examination. Although some patients are asymptomatic, others develop characteristic symptoms related to increased red cell volume or hyperviscosity (Fig. 18-11). Common complaints caused by cerebral circulatory disturbances and transient ischemic attacks include headaches, dizziness, weakness, vertigo, visual phenomena (blurred vision, diplopia, scotomata), tinnitus, and rarely, mild dementia. Vascular complications are manifested equally in arteries and veins. Thrombotic episodes, such as phlebitis, myocardial infarction, erythromelalgia (painful red extremities), paresthesia, and burning sensation, particularly in the feet, reflect impairment of blood flow to the peripheral circulation. The coexistent thrombocytosis acts in conjunction with the hyperviscosity and high blood volume to increase the incidence of thrombosis, thromboembolism, and hemorrhage in these patients. Incidence of morbidity and mortality from vessel wall disease is already high in this age group, and the concomitant high Hct adversely influences the outcome of occlusive events.

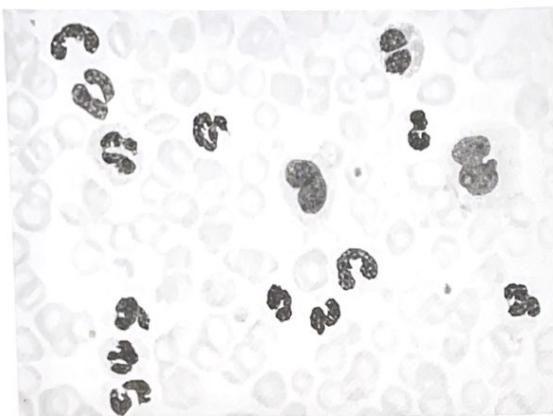
Hemorrhagic diathesis is often seen in patients with PV. Life-threatening hemorrhage may occur in association with trauma, surgery, or peptic ulcer. Spontaneous minor hemorrhages, in the form of epistaxis, gingival bleeding, and ecchymoses, are common events almost certainly caused by qualitative platelet abnormalities.

The presence of splenomegaly in about 80% of patients is a finding of significant differential importance. The splenic enlargement is usually mild to moderate and results from extramedullary hematopoiesis and not from the expanded blood volume per se (the spleen size does not diminish as blood volume is reduced by phlebotomy). Patients having moderate splenomegaly appear more likely to evolve to IMF at an early stage. Modest hepatomegaly is observed in one-third of patients at the time of initial presentation (see Table 18-6).

Portal hypertension may occur because of the excessive flow of blood from the spleen into the portal system. Gastrointestinal disorders associated with PV include peptic ulcers and, possibly, massive hemorrhage from varices in the esophagus, stomach, or bowel.

A common physical finding is ruddy cyanosis (reddish-purple color) of the face, nose, ears, and lips. This facial plethora results from conjunctival and mucosal blood vessel congestion. Patients have stated that the appearance of their ruddy complexion has prompted friends to comment that they "look wonderful."

Aquagenic pruritus (itching), occurring in about 50% of patients, is especially troublesome after a hot shower. The pathogenesis of this persistent itching and urticaria is related to elevated levels of histamine produced by basophils and other granulocytes.



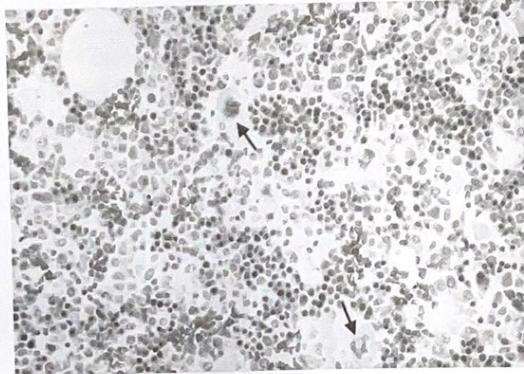
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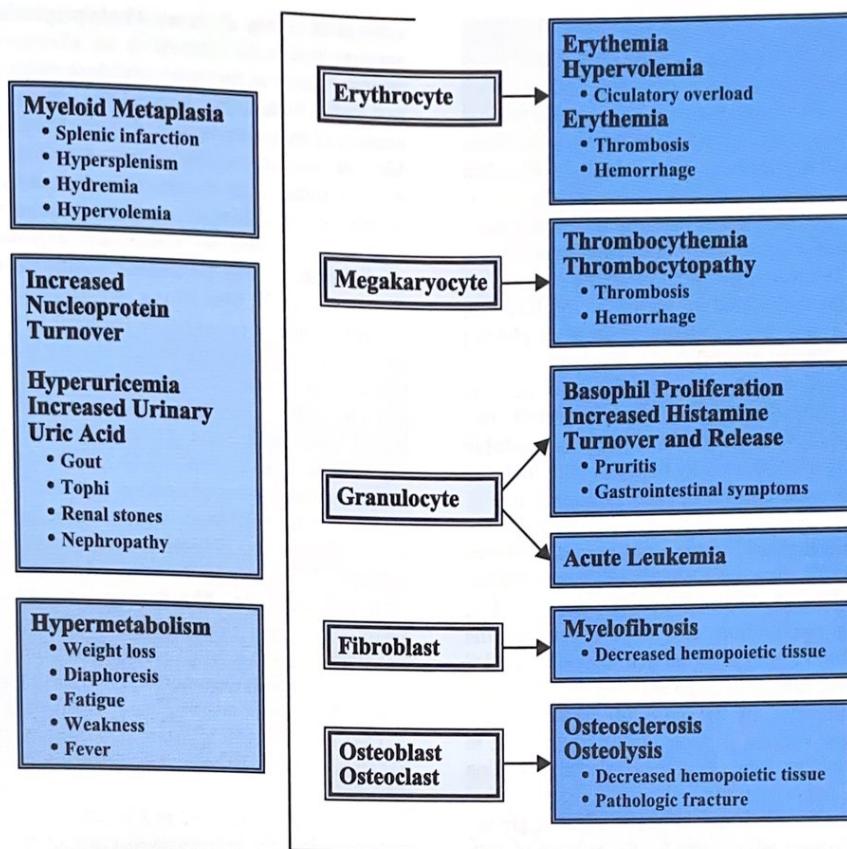
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► FIGURE 18-11 Physiologic complications of polycythemia vera. The clinical features of this disorder are attributable to the excessive proliferation of the three main hematopoietic cell lines and reactive proliferation of bone marrow fibroblasts. (Adapted from Gilbert, HS: The spectrum of myeloproliferative disorders. *Med Clin North Am* 57:355–359, with permission.)

Fever, night (and day) sweats, and weight loss may occur as a result of the hypermetabolic state. Gout ascribed to increased nucleoprotein turnover occurs in 5% to 10% of patients. Uric acid calculi or urate nephropathy may arise from the increased uric acid excretion.

Laboratory Features

Elevation of the RBC count, Hgb, and Hct are the most important findings in PV. The Hct concentration is usually more than 58% in men and more than 52% in women. Because of the variation in plasma volume, the Hct gives only an approximate indication of the size of the red cell mass. Therefore, the diagnosis of PV, particularly in borderline cases in which the Hct is in the upper normal range, may require the direct measurement of total red cell mass. This is most often determined using the well-established ^{51}Cr dilution technique. Absolute erythrocytosis is present in men with values of at least 36 mL/kg and in women with at least 32 mL/kg.

Determination of serum erythropoietin allows for a cost-effective diagnostic workup for evaluation of erythrocytosis. Most values in PV are decreased, indicating autonomous production of red cells by the bone marrow; however, sometimes the result may be in the normal range. There is no significant rise in the levels of erythropoietin following phlebotomy and normalization of the Hgb and Hct.

Characteristically, at presentation there is increased red cell

production in intramedullary sites. The erythrocytes are normochromic, normocytic, and have a normal life span. As the disease progresses, extramedullary ineffective hematopoiesis leads to an increasing anisocytosis and poikilocytosis, as well as shortened red cell life span secondary to splenic sequestration. Many patients demonstrate the microcytosis and hypochromia associated with iron deficiency, with low serum iron, decreased mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) occurring in about one-half of patients. This iron deficiency is attributed to consumption of iron resulting from the tremendous increase in erythropoiesis as well as possible occult gastrointestinal blood loss and defective platelet function. The reticulocyte count is usually normal, and only rarely are immature erythrocytes found in the peripheral blood.

Relative and absolute granulocytosis occurs in two-thirds of the patients. The elevation in the total WBC count is usually moderate, with counts in the range of 12 to $25 \times 10^9/\text{L}$. Occasionally, basophilia and eosinophilia are apparent, and few metamyelocytes, myelocytes, and even more immature cells may be seen on examination of the peripheral smear.

Thrombocytosis is present at the time of diagnosis in about one-half of the patients with PV. The platelet count is most often moderately elevated, with counts between 450 and $800 \times 10^9/\text{L}$, but in about 5% the platelet count exceeds $1000 \times 10^9/\text{L}$. Platelet life span may be shortened in

proportion to the extent of pooling in the spleen. Morphological alterations of platelets include the presence of giant platelets as well as deficient granulation. Studies show that most patients with PV form spontaneous megakaryocytic colonies analogous to the spontaneous erythroid colony formation seen in all myeloproliferative disorders. Platelets from most patients demonstrate some abnormality in aggregation studies, but the results of these laboratory tests correlate poorly with clinical thrombotic and hemorrhagic episodes. Also of interest is the fact that in the majority of patients, even those with bleeding diathesis, the bleeding time, which is the best measurement of *in vivo* platelet function, is nearly always normal.

The arterial oxygen saturation is normal in most patients with PV; however, infrequently the oxygen saturation may be slightly lowered (88% to 92%). This feature is helpful in excluding erythrocytosis secondary to pulmonary and cardiac abnormalities, wherein the oxygen saturation is routinely decreased.

The prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen levels are generally normal in patients with PV. When performing coagulation tests on PV patients, the anticoagulant-to-blood ratio must be maintained at the 1:9 ratio. Sodium citrate functions as an anticoagulant by binding calcium in plasma. In the case of erythrocytosis, wherein the plasma volume is decreased, citrate is left in excess in the vacutainer tube. This residual citrate is then available to bind calcium in the test system, thus causing falsely prolonged clotting times. When the Hct is greater than 55%, the following adjustment for the volume of anticoagulant should be applied:

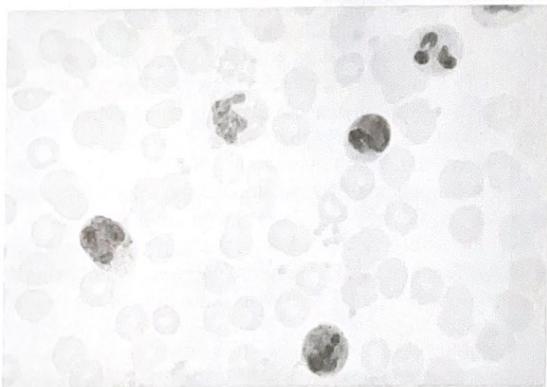
$$(0.00185)(V)(100 - \text{Hct}) = C$$

where V = volume of whole blood

C = anticoagulant, in mL

The LAP activity is increased in 70% of PV cases (Fig 18-12 and Color Plate 210). The determination of the LAP is not always the most helpful test in the differential diagnosis of erythrocytosis, because some patients with PV have a normal LAP score, as do the majority of patients with secondary erythrocytosis (in the absence of inflammation, infection, or hormonal therapy).

The bone marrow is hypercellular, with decreased fat



► FIGURE 18-12 Leukocyte alkaline phosphatase (LAP) stain of peripheral blood showing increased activity in polycythemia vera (red staining).

content in nearly all cases. Panhyperplasia is evident to a varying extent, in contrast to the exclusive erythroid hyperplasia seen in secondary erythrocytosis (see Fig. 18-10 and Color Plate 209). Besides the striking increase in the number of megakaryocytes, they are often increased in size. Marrow iron stores, demonstrated by Prussian blue staining, are reduced or absent. This decrease results from the increased utilization of iron in the process of excessive erythropoiesis and the subsequent expansion of red cell mass, in addition to the chronic occult blood loss. Early in the course of PV, fibrosis is a rare finding. If serial biopsies are performed, a progressive increase in reticulin deposits can often be demonstrated during the active phase of the disease and before the spent phase develops. As the disease runs its course, cellularity usually decreases, although megakaryocytosis may persist. The transition to frank myelofibrosis occurs in 15% to 20% of patients.

Autonomous or spontaneous erythroid colonies may be grown in culture medium without the addition of exogenous erythropoietin; this demonstrates that endogenous erythroid colony (EEC) formation can occur from culture of peripheral blood of PV patients. This finding is considered by many investigators to be of diagnostic value. The addition of both interleukin-3 (IL-3) or interferon α and subsequent increase in EEC has given an even better diagnostic discrimination between PV and secondary erythrocytosis patients.

Two of the three vitamin B₁₂-binding proteins, transcobalamin I and III, are frequently elevated in PV, as in other MPDs. Transcobalamin III is the binding protein most commonly elevated in PV, whereas transcobalamin I is predominantly increased in chronic myelogenous leukemia. These increased serum values are attributed to the excessive granulocyte turnover. Furthermore, the unsaturated B₁₂-binding capacity (UB₁₂BC) is increased in approximately 75% of patients.

Hyperuricemia and uricosuria are found in 40% of patients with PV at the time of presentation. This is a frequent finding in many hypoproliferative disorders in which increased synthesis and degradation of cellular nucleotides occur. Most patients remain asymptomatic, but uncommonly, clinical gout may develop.

Other relatively new parameters have been described in association with PV. The mean platelet distribution width (PDW, as measured by a Coulter counter analyzer) is a reflection of the average platelet size and is significantly increased in PV as compared with secondary erythrocytosis. The platelet nucleotide ratio (ATP:ADP as determined by a lumiaggregometer) may also be increased in PV as compared with values seen in secondary erythrocytosis.

A low-normal erythrocyte sedimentation rate (ESR) is commonly present in PV patients. The increased Hct, as well as the elevated ratio of red cell membrane to plasma fibrinogen and globulins, may account for this finding. Nonrandom chromosome abnormalities are seen in about 15% of patients, increasing to 50% with disease progression. The most common trisomies and deletions are trisomy 8, trisomy 9, and deletions of 20q, 5q, 6q, 7q, 11q, 13q, and 20q. These cytogenetic findings appear to correlate with disease stage and duration.

Differential Diagnosis

The diagnostic criteria for evaluating a patient with erythrocytosis should encompass procedures that systematically

exclude the various causes of secondary and relative polycythemia (Table 18-7). In 1968 the Polycythemia Vera Study Group (PVSG) developed a set of criteria that indicate with a high degree of probability the establishment of the diagnosis of PV (Table 18-8). Because of the sensitivity and specificity of these criteria, they have become the standard approach to this diagnostic problem worldwide. A recent revision to the PVSG's standard diagnostic criteria takes a more streamlined, cost-effective approach. The measurement of total red cell mass is now considered su-

**► Table 18-7
CLASSIFICATION OF THE DISORDERS
ASSOCIATED WITH ABSOLUTE
ERYTHROCYTOSIS**

Primary Polycythemia

Polycythemia vera

Secondary Erythrocytosis

Appropriate increase in erythropoietin (tissue hypoxia)

Chronic pulmonary disease

Cyanotic congenital heart disease

Cirrhosis

Alveolar hypoventilation (obesity/sleep apnea, Pickwickian syndrome, intrinsic lung disease)

High altitude

Inappropriate increase in erythropoietin

Renal ischemia

Renal tumors

Renal cysts

Renal transplantation rejection

Renal artery stenosis

Hydronephrosis

Neoplasms

Uterine fibroids

Hepatoma

Cerebellar hemangioblastoma

Endocrine disorders

Pheochromocytoma

Conn's syndrome

Ovarian tumors (androgen-secreting)

Cushing's syndrome

Defective oxygen transport

Smoking (carboxyhemoglobinemia)

Methemoglobinemia

High oxygen affinity hemoglobinopathies

Defective oxidative metabolism (cobalt therapy)

Relative Erythrocytosis

Dehydration

Stress erythrocytosis (Gaisböck's syndrome)

**► Table 18-8
PVSG CRITERIA FOR DIAGNOSIS OF
POLYCYTHEMIA VERA***

Category A (Major Criteria)

1. Elevated red cell mass
2. Normal arterial oxygen saturation
3. Splenomegaly

Category B (Minor Criteria)

1. Leukocytosis
2. Thrombocytosis
3. Elevated leukocyte alkaline phosphatase score
4. Increased serum vitamin B₁₂ or vitamin B₁₂-binding proteins

*To establish a diagnosis of polycythemia vera, either all three diagnostic criteria from category A or an elevated red cell mass and normal arterial oxygen saturation in addition to two criteria from category B must be present.

Source: From Beck, WS: Hematology, ed 3. MIT Press, Cambridge, 1982, p 297, with permission.

perfluous if the Hct is greater than 60%, erythropoietin is decreased, and splenomegaly is present.

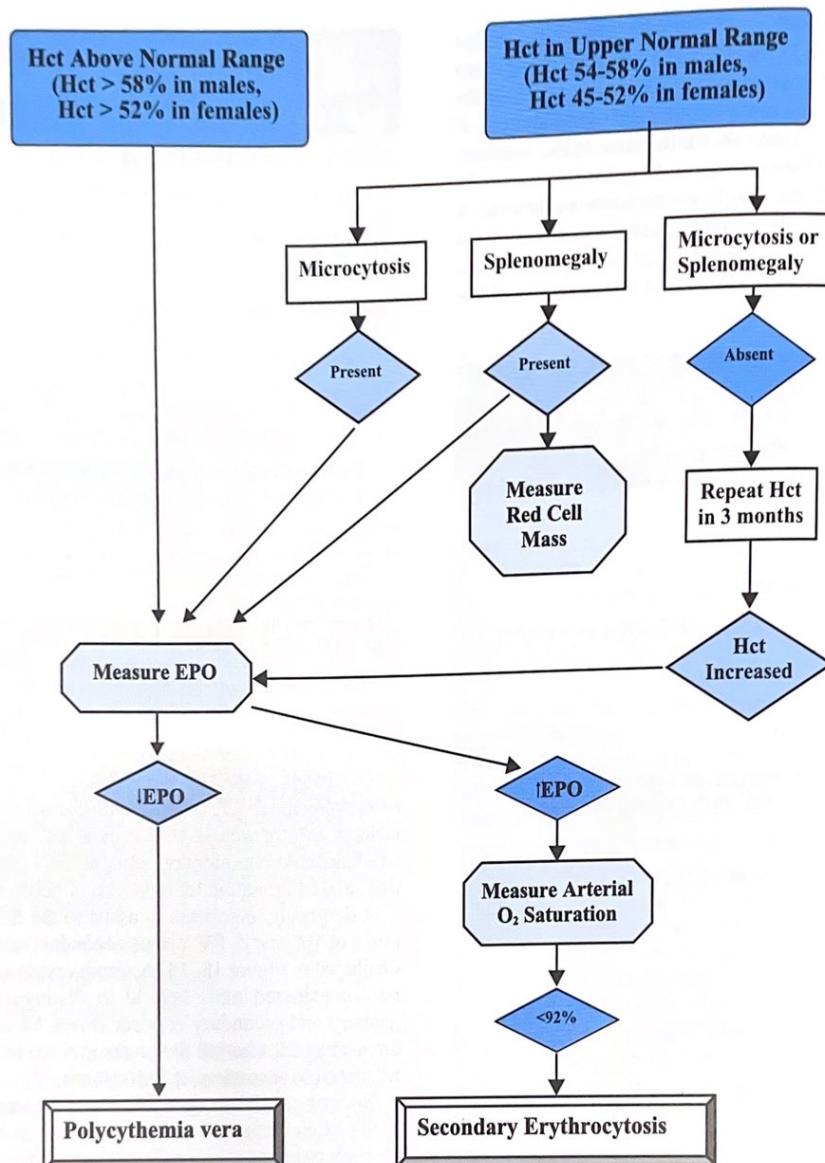
As always, a careful history and physical examination should preclude more extensive (and costly) diagnostic procedures. Of particular importance are such elements as smoking, cardiopulmonary status, alcohol intake, family history, and examination for evidence of hepatosplenomegaly.

A diagnostic algorithm to assist in the differential diagnosis of (primary) PV versus secondary erythrocytosis is displayed in Figure 18-13. A serum erythropoietin assay is now considered most helpful in distinguishing between primary and secondary erythrocytosis. Most values in PV are decreased, whereas the erythropoietin levels are always increased in secondary erythrocytosis.

Normal arterial oxygen and oxygen saturation (at least 92%), along with a normal chest x-ray, can help to rule out chronic pulmonary or cardiac disease; both are causes of secondary erythrocytosis. Additionally, these patients have symptoms and other complications as a consequence of their primary underlying disorder.

If evidence of tissue hypoxia is lacking, investigation for the presence of an occult erythropoietin-secreting tumor or other cause of inappropriate erythropoietin production should be undertaken. Common procedures at this level of evaluation include an intravenous pyelogram, renal ultrasound, CT scan of the abdomen or head, or both, and a liver scan. Carboxyhemoglobin levels should be measured in patients who smoke, because Hct levels above normal have been demonstrated in some of these patients.

Erythrocytosis in the absence of characteristic features of either PV or cardiopulmonary secondary erythrocytosis should prompt consideration of the possibility of inherited hemoglobin abnormality (high oxygen affinity hemoglobin). Hemoglobin electrophoresis is abnormal in the majority of these cases; however, the measurement of the oxygen affinity ($P_{50}O_2$) can help reveal the few cases in which the hemoglobin mutation is electrophoretically silent. Furthermore, family history can be very useful, as the inheritance mode of these disorders is autosomal dominant. In difficult



► FIGURE 18-13 Diagnostic evaluation of polycythemia vera. Epo = erythropoietin.

cases, culture studies of peripheral blood or bone marrow may identify autonomous producing erythroid colonies and, hence, verify a myeloproliferative disorder.

In summary, the most significant characteristic findings in PV are increased Hct, splenomegaly, pancytosis, and decreased erythropoietin. Occasionally a patient may present with a normal or near-normal Hgb, iron deficiency, splenomegaly, leukocytosis, and thrombocytosis; and the disease may, therefore, be difficult to distinguish from essential thrombocythemia. In this case, the presumed blood loss and iron deficiency is masking the erythrocytosis of the underlying PV, and a trial of iron administration is warranted to establish a definitive diagnosis. In PV, the Hgb and Hct can be expected to rise to polycythemic levels, thus clarifying the diagnosis. Conversely, the combination of heavy smoking and excessive alcohol consumption has led to false-positive diagnoses of PV. In this setting the smokers' erythrocytosis and alcoholic liver disease, manifested by

splenomegaly, elevated serum vitamin B₁₂ levels, leukocytosis, and, in some cases, elevated LAP, has erroneously prompted diagnosis of PV. Again, measurement of carboxyhemoglobin levels, bone marrow examination for the presence of panhyperplasia, and erythropoietin assay (expected decrease) can help to rule in PV.

Treatment

Early descriptions indicated that the life expectancy of untreated PV patients postdiagnosis averaged 6 to 36 months. Over the years, therapeutic modalities have been complex and controversial. Today, however, these patients can enjoy a relatively normal life span if their disease is adequately treated, controlled, and monitored by their physician. No treatment at present can completely eradicate this disease.

The major complications of PV are those of thrombotic events resulting from hyperviscosity and complications resulting from transition to an MPD (myelofibrosis, leukemia,

or both). The primary objective of therapy is the reduction of the total red cell mass, thereby eliminating the distressing plethora of symptoms. The use of phlebotomy or cytotoxic myelosuppressive agents, or both, to control the malignant proliferative process is advocated. Apparently no single therapy is optimal for patients of all ages and stages of this disease; therefore, decisions as to the most effective approach must be based primarily on individual patient characteristics. The treatment of the erythrocytic phase may be divided into induction and maintenance therapy.

Induction

Rapid reduction of the blood volume to normal can be accomplished by phlebotomy, thereby relieving the patient of the characteristic painful symptoms of hyperviscosity. This is a safe and relatively inexpensive method of controlling the erythrocytosis and is the cornerstone of treatment in PV. Removal of 250 to 500 mL of blood may be done every 2 to 3 days until the Hct is reduced to 40% to 45%. Studies have demonstrated that the cerebral blood flow is significantly improved and mental alertness heightened if the Hct can be maintained within this range. Phlebotomies can then be performed on a bimonthly basis. In elderly patients or those with a history of cardiovascular disease, it is undesirable to remove more than 200 to 300 mL of blood at a time. Surgery in an untreated patient is hazardous owing to the increased risk of thrombohemorrhagic complications. In such emergency situations, intensive phlebotomy accompanied by plasma infusion is advisable to maintain intravascular volume.

Because removal of every unit of blood will cause a loss of approximately 250 mg of elemental iron, nearly all patients regularly treated by phlebotomy will develop iron deficiency with microcytic, hypochromic red cell changes. Development of this iron deficiency and concomitant disruption of normal erythropoiesis allows maintenance of the Hct at an acceptable level and a decreased frequency of phlebotomies. Most patients do not show the classic symptoms of glossitis, dysphagia, cheilosis, weight loss, and so on generally associated with iron deficiency; however, some patients have unexplained tiredness. Iron therapy is not usually required, but if iron is administered, the Hct must be carefully monitored as it may rise quickly, necessitating more frequent phlebotomies. The microhematocrit method is preferable over the automated cell counter method, as the Hct may be overestimated by up to 10% at low mean corpuscular hemoglobin (MCH) and MCHC values.

Management by phlebotomy alone is recommended for patients younger than age 40, particularly for women in the childbearing years, unless specific thrombosis-associated risk factors are present (i.e., high platelet counts, preexisting vascular disease). The major limitation of phlebotomy is that it has no suppressive effect on the abnormal bone marrow proliferation, particularly that of thrombocytosis. Also, phlebotomy further excites hematopoiesis, therefore increasing the rate of production of red cells. Additionally, it does not alleviate pruritus or control any symptoms related to splenomegaly. Myelosuppression is often advocated to repress these manifestations.

Maintenance

Long-term control of the peripheral blood counts is essential to minimize the risk of thrombotic complications. Although phlebotomy relieves the burden of erythrocytosis,

the reduction is short term and all patients require close supervision by a physician to cope with the increased risk of thrombosis during the first years of treatment, especially those patients with elevated platelet counts.

Extensive data on the management of PV by use of phlebotomy alone or in combination with the various myelosuppressive modalities is now available thanks to the past 25 years of investigation by the PVSG. In a long-term study, 431 patients were randomized into three modes of treatment: phlebotomy alone, chlorambucil with phlebotomy as needed, and radioactive phosphorus ^{32}P and phlebotomy as needed.¹³ An additional study examined the results of long-term control of PV with a nonalkylating agent, hydroxyurea (HU). Patients treated with phlebotomy alone exhibited an increased incidence of thrombotic complications, whereas significantly greater percentages of patients who were regulated by either radioactive phosphorus or an alkylating agent subsequently developed acute leukemia and other neoplasms.¹⁴ The comparison studies also show that HU, supplemented by phlebotomy, is *not* accompanied by excessive thrombotic complications. As a result of these studies showing the leukemogenic potential of chlorambucil and ^{32}P , these agents are no longer used in treatment of PV, and HU has been advocated as the myelosuppressive drug of choice for PV. Other studies have demonstrated that patients treated with HU, which originally was not considered leukemogenic, have indeed shown an increased rate of development of acute leukemia. Because myelosuppressive treatment has not been shown to prolong survival in PV patients, the indications for the use of cytotoxic chemotherapy must outweigh the risk of inducing leukemia.

The following guidelines have been suggested to provide the best control of the disease:

1. In patients under age 40, the disease should be controlled with phlebotomy alone unless thrombosis-associated risk factors are demonstrated. Treatment with interferon α can also be considered, although it is still under investigation for use in young patients. If the requirement for phlebotomy is excessive or there is a history of a previous thrombotic episode, myelosuppression with HU may be cautiously used even in this young age group.
2. Because the role of myelosuppression is controversial in patients aged 40 to 70 years, phlebotomy alone can be used if no thrombosis-associated risks are present. If cardiovascular risk factors exist (coronary heart disease, hypertension, or history of smoking), HU may be used judiciously. Symptomatic hypersplenomegaly, resistant pruritus, bone pain, or poor veins may be other indications for the additive use of myelosuppression.

The average dose of 1 g/day of HU is sufficient to maintain a normal Hct and platelet count. Supplemental phlebotomies may be necessary. The initial response to HU treatment is positive, with between 80% and 90% of patients achieving good control of the disease and more than 60% retaining long-term control after 5 years. Weinfeld and co-workers¹⁵ report that most transformations to acute leukemia take place during the first 4 years of treatment. In a high percentage of patients, HU also seems to have a beneficial effect on pruritus and splenomegaly. Possible side effects include rashes, drug fever, and megaloblastoid changes.

Besides phlebotomy and HU therapy, several other alternative techniques and therapies have been successfully employed to control PV. Plateletpheresis may be considered to keep the platelet count between 100 and $400 \times 10^9/L$. If HU treatment fails, anagrelide, a platelet-lowering agent, can be used to treat thrombosis-associated PV. As with IMF, interferon α has been shown to be effective in treating MPDs and even inducing remission of the disease. Specifically, this agent has been shown to be helpful in eliminating the need for phlebotomy in PV patients. However, interferon α is associated with considerable side effects.

Adjuvant therapy is often necessary to control hyperuricemia and hyperuricosuria. In addition to standard colchicine therapy, allopurinol (300 mg/day), an agent that blocks the formation of uric acid from its precursors, is used to prevent or control acute attacks of gout. In patients receiving myelosuppressive therapy, the need for allopurinol is diminished because of the decreased nucleic acid turnover effected by suppression of cellular proliferation. Allopurinol may be continued indefinitely in patients treated by phlebotomy alone.

Severe pruritus is a most distressing symptom in many cases. It is best managed by controlling the erythrocytosis; however, it may persist in some patients despite a normal Hct and physical examination findings. The antihistamines cyproheptadine and cimetidine may be of benefit. Cholestyramine, an anion exchange resin that functions by binding bile acids, has been reported to provide some relief of pruritus.

Course and Prognosis

The course of patients with PV is determined by the natural history of the disease and the development of complications that may or may not be related to the mode of therapy employed.

As previously mentioned, this disease progresses through several stages, each of variable duration. In the active erythrocytic phase, the red cell mass can be maintained at satisfactory levels with administration of treatment that is dictated by age and the presence of certain risk factors. Many patients eventually enter a period characterized by increasing anemia, and this spent phase is associated with transformation to frank myelofibrosis in 15% to 20% of cases. The appearance of teardrop RBCs on peripheral blood smear heralds the transition of PV to IMF. The progressive splenomegaly appears to be a manifestation of the natural course of the disease, but splenectomy carries a high incidence of morbidity and mortality in this group of patients. The treatment of this phase is predominantly supportive and may be very difficult. The cause of the anemia may be multifactorial, being a result of one or more of the following factors: (1) iron, folic acid, or vitamin B₁₂ deficiency; (2) inefficient hematopoiesis; or (3) splenic sequestration and destruction of erythrocytes, leukocytes, and platelets. Treatment of the anemia may involve appropriate nutritional replacement or administration of steroids to help control the ineffective erythropoiesis. Ongoing transfusion of packed red cells is often required. Despite possible splenic sequestration, thrombocytosis and leukocytosis may persist. Myelosuppressive therapy may be indicated to control the myelofibrotic proliferation. Prognosis is poor for this phase of the disease and median survival is about 2 years.

Malignant transformation to acute leukemia, usually acute myeloblastic leukemia (AML), occurs in 10% to 15% of

cases. This complication is almost universally fatal. As discussed earlier, the therapeutic modality affects the rate of leukemic transformation. In patients treated by phlebotomy alone, the incidence of transition to leukemia is only 1% to 2%, whereas those treated by chemotherapy have a risk approaching 15%. A few cases each have been documented of PV transforming into a myelodysplastic syndrome, myeloma, and also chronic lymphocytic leukemia.

Reported survival rates in PV range from 8 to 15 years. Thrombohemorrhagic incidents account for 40% of deaths, and acute leukemia and myeloid metaplasia each account for 15%. As the mean age of diagnosis is 60 years, many other patients die of additional unrelated reasons.

Continued research of the pathophysiologic abnormalities associated with this disease as well as the effects of various treatment modalities will undoubtedly lengthen the future life expectancy of patients with PV.

Secondary Erythrocytosis

Absolute erythrocytosis may have a wide variety of causes (see Table 18-7). Secondary erythrocytosis differs from PV in that autonomous bone marrow proliferation occurs in PV. Increased secretion of erythropoietin has been implicated as the responsible stimulus for all cases of secondary erythrocytosis (see Fig 18-13). The causes of secondary erythrocytosis can be separated into three groups: (1) those in which there is an appropriate, compensatory increase in erythropoietin in response to tissue hypoxia; (2) those resulting from an inappropriate or pathologic secretion of erythropoietin; and (3) those resulting from defective oxygen transport.

Appropriate Increase in Erythropoietin

In this group of disorders, the underlying mechanism is release of erythropoietin as part of a compensatory effect to minimize impending tissue hypoxia. The most common causes of secondary polycythemia are cardiac or respiratory diseases that lead to significant arterial oxygen desaturation. Of the lung diseases causing hypoxia and erythrocytosis, chronic obstructive pulmonary disease (COPD) is the most frequent offender. In COPD, the release of erythropoietin appears to be appropriately responsive to the level of hypoxia, with the degree of increase in the Hct being inversely proportional to the arterial oxygen saturation. Other intrinsic lung diseases that may involve significant hypoxia are pulmonary fibrosis, pulmonary aneurysms, and hereditary hemorrhagic telangiectasia with pathologic lung changes.

Right-to-left shunting in congenital heart disease is caused by a number of different anatomic defects and leads to profound arterial hypoxia and extreme erythrocytosis. Indeed, some of the highest Hct levels (75% to 80%) have been reported in these patients. The serum erythropoietin level is most often normal in congenital heart disease patients because the erythrocytosis usually compensates for the decreased arterial oxygen saturation. The erythrocytosis in these cardiac anomalies results from the shunting of poorly oxygenated venous blood into systemic circulations and necessitates surgical intervention. It is recommended that patients with particularly high Hct levels undergo phlebotomy to reduce the Hct to less than 65%.

Ascent to high altitudes causes tissue hypoxia because of the low atmospheric pressure. This leads to the release of erythropoietin, with subsequent increase in red cell pro-

duction. Although tolerance to high altitude varies, most normal individuals experience no symptoms at altitudes of up to 7000 feet (2130 m). For the indigenous mountain inhabitants living higher than 16,440 feet (5000 m), hematuricots in the range of 60% to 70% are regularly seen. The physiologic adaptation of erythrocytosis allows most individuals to function normally, having life spans equivalent to their counterparts at sea level. The clinical and laboratory features of humans living at high altitudes include a ruddy cyanosis; venous and capillary engorgement of the conjunctiva, mucous membranes, and skin; emphysema; normocytic, normochromic erythrocytosis; increased reticulocyte count; and increased iron turnover. The syndrome of acute mountain sickness occurs in nonacclimatized persons who rapidly ascend to high altitudes. The manifestations of cerebral hypoxia are headaches, dizziness, insomnia, weakness, nausea, and vomiting.

The alveolar hypoventilation syndromes are characterized by impaired or inadequate ventilation. Intermittent alveolar hypoventilation has frequently been reported in normal men during sleep and, if severe, can cause hypoxia, cyanosis, apnea, and secondary polycythemia. This condition may also be seen in neuromuscular disorders, in the mechanical impairment of the chest wall, and in the colorful pickwickian syndrome (extreme obesity, somnolence, and associated erythrocytosis).

Methemoglobinemia can result from a hereditary deficiency of the enzyme NADH-methemoglobin reductase, from ingestion of various drugs or toxic substance exposure, or from hemoglobin M disease. Methemoglobin is formed when heme iron is oxidized to the ferric state. In this oxidized form, the heme moiety is incapable of carrying oxygen and cyanosis is clinically observed. Interestingly enough, even alarming degrees of cyanosis may be seen with arterial oxygen saturation still being normal (92% or higher). Mild, associated erythrocytosis is rare, but when it does occur, it is the result mostly of a shift to the left of the oxygen-dissociation curve (increased oxygen affinity).

Cases of familial secondary erythrocytosis have been demonstrated wherein the hemoglobin molecule itself is abnormal. Amino acid substitutions in these variants may interfere with release of oxygen to the tissues by preventing normal conformational changes required for deoxygenation. This extraordinarily avid oxygen affinity leads to tissue hypoxia and increased erythropoietin production. A left-shifted oxygen-dissociation curve is characteristic, and a compensatory erythrocytosis ensues. Approximately 30 different high-affinity hemoglobin variants have been described, including hemoglobins Chesapeake, Rainer, Yakima, Hiroshima, Little Rock, and San Diego. In many cases the aberrant hemoglobin is apparent on hemoglobin electrophoresis; however, in some patients the hemoglobin migrates along with hemoglobin A and is, therefore, undetectable. Determination of reduced oxygen affinity ($P_{50}O_2$) in patients with erythrocytosis of questionable origin is necessary to disclose these electrophoretically silent hemoglobins.

Inappropriate Increase in Erythropoietin

A wide range of disorders is associated with inappropriately increased erythropoietin production and resultant erythrocytosis, in spite of the absence of generalized tissue hypoxia. This secondary erythrocytosis confers no physiologic advantage, and the underlying disease accounts for most of the

clinical features observed in the patient. The Hct and red cell mass are increased, but classically there is no accompanying increase in WBC or platelet counts. Because the kidneys predominantly produce erythropoietin, renal disease can cause anemia as a result of decreased production or erythrocytosis as a result of increased production. Benign and malignant tumors may promote excessive secretion of erythropoietin. Renal tumors account for about 50% of these patients. When these disorders are associated with thrombocytosis or granulocytosis, it may be difficult to establish a clear diagnosis. In this case, documentation of increased erythropoietin and the absence of splenomegaly can assist in ruling out primary PV.

Defective Oxygen Transport

Heavy cigarette smoking (20 to 30 cigarettes per day) can result in chronic carbon monoxide intoxication, with levels of up to 10%. When hemoglobin is bound to carbon monoxide, the resulting carboxyhemoglobin loses its capacity to carry oxygen. Tissue hypoxia results, the oxygen-dissociation curve is shifted to the left, and, because of the reduced oxygen delivery, the erythropoietin level increases, causing a mild erythrocytosis. The incidence of erythrocytosis secondary to smoking has been estimated to be approximately 600 to 1000 per 100,000 population, which contrasts with the prevalence of about 10 per 100,000 population of PV. It is of interest to note that the reduction in plasma volume that occurs in individuals who smoke heavily can be reversed by abstaining from smoking for 4 to 5 days, and this smoking cessation should decrease the Hct. Smokers with a concomitant lung disease or nocturnal hypoventilation most often have increased Hct levels.

Environmental pollution from industrial sources and vehicle exhaust emissions have also been associated with increased levels of carboxyhemoglobin and mild erythrocytosis. Although the increase in Hct is usually on the order of 2% to 4%, the Hct may still fall within normal limits.

Relative Erythrocytosis

Relative erythrocytosis may be seen in patients with an elevated Hct, normal red cell mass, and decreased plasma volume. Two groups can be clearly distinguished among patients with relative erythrocytosis: (1) those individuals suffering from dehydration, and (2) those with stress erythrocytosis. Relative erythrocytosis is most often clinically seen in the group of patients with depletion in circulating plasma volume caused by acute or subacute dehydration resulting from a number of conditions (such as burns). The second group of patients is characterized predominantly by asymptomatic middle-aged white men who are hypertensive, obese, and have a long history of heavy smoking. In 1905, Gaisböck¹⁶ first described a condition of "polycythemia hypertonica" in several hypertensive patients who had increased red cell counts and plethora, but no accompanying splenomegaly. Today, this condition is variously termed *Gaisböck's syndrome, stress or benign erythrocytosis, or pseudopolycythemia*. It is well documented that excessive smoking causes mild to moderate erythrocytosis and a decreased plasma volume, hence the term *smokers' polycythemia*, as previously mentioned. Undoubtedly some patients with erythrocytosis merely represent the extreme physiologic range of Hct. The combined effect of a high-normal red cell mass and a low-normal plasma volume, resulting in a so-called spurious erythrocytosis, is not

considered pathologic. Physical stress, extreme alcohol consumption, and diuretic therapy have also been documented as possible causes of plasma volume reduction.

This condition usually follows a benign course; however, a few patients may progress to an absolute erythrocytosis with an obvious underlying cause becoming apparent. There may be a few nonspecific symptoms reported in these patients such as headache, nausea, and dyspepsia. Hypertension, with possible increased risk of thromboembolic complications, is seen in approximately one-third of the patients. The Hct value is generally between 50% and 60%. Therapy indicated is in the form of encouragement of the cessation of smoking or alcohol intake, or both; reduction of obesity; treatment of hypertension; stress counseling; and discontinuation of diuretic therapy, where appropriate. Additionally, the Hct should be maintained below 50% by phlebotomy to decrease the risk of vascular occlusive episodes.

► ESSENTIAL THROMBOCYTHEMIA

Essential thrombocythemia (ET) is a rare, chronic myeloproliferative disorder characterized by marked thrombocytosis associated with abnormal platelet function. ET was the last of the MPDs to be identified as a distinct entity, owing to the fact that extreme thrombocytosis is also frequently observed in CML, IMF, and PV. Sex-linked G6PD cell marker studies established ET as a clonal disorder involving the multipotential stem cell, which supported the placement of ET within the MPD classification.

Diagnostic criteria that define ET were proposed by the PVSG in the mid-1970s. These guidelines include: (1) platelet count in excess of $600 \times 10^9/L$ (and generally greater than $1000 \times 10^9/L$); (2) megakaryocytic hyperplasia in the marrow; (3) absence of identifiable causes of reactive thrombocytosis; (4) the absence of the Ph; (5) hemoglobin no higher than 13 g/dL or normal red cell mass; (6) absence of significant marrow fibrosis; and (7) presence of stainable iron in marrow or failure of iron trial.¹⁷

Synonyms for this condition include idiopathic thrombocythemia, primary thrombocythemia, and primary hemorrhagic thrombocythemia.

Epidemiology

The mean age at time of diagnosis is approximately 60 years, the majority of patients being older than 50. This disease has occasionally been described as a benign form devoid of hemorrhagic or thrombotic symptoms in the 20- to 40-year-old age group, and very rarely in patients younger than age 20. Most studies do not demonstrate a statistical difference between frequency of males and females affected. The incidence of the disease has been estimated at 7 per million population per year. The etiology of thrombocythemia remains unknown.

Clinical Features

With the introduction of automated instruments that routinely perform whole blood platelet counts, asymptomatic patients with coincidental high platelet counts are being discovered more frequently, especially in young patients. Approximately two-thirds of patients are asymptomatic at diagnosis, with the remaining one-third presenting with hemorrhagic or vaso-occlusive symptoms, or both. In most instances bleeding is mild and manifestations are primarily

mucocutaneous (epistaxis and ecchymoses); however, life-threatening hemorrhage may occur following accidental trauma or, rarely, following surgery. Bleeding of the gastrointestinal tract as well as esophageal varices bleeding has also been reported. Hemorrhage has been attributed to several mechanisms: (1) platelet functional abnormalities; (2) thrombosis with infarction, ulceration of the infarction, and subsequent bleeding; (3) consumption of coagulation factors; and (4) increased numbers of circulating platelets, causing excessive production of prostacyclin (PGI_2) by endothelial cells (increased PGI_2 suppresses platelet granule release and aggregation).

Thrombosis is the other major manifestation of ET and is caused by intravascular clumping of sludged, hyperaggregable platelets. Vascular occlusive symptoms are usually related to small vessel obstruction (microvascular occlusion), although larger vessel occlusive events such as myocardial infarction and stroke may occur. Erythromelalgia of the toes, feet, and occasionally fingers (localized painful redness, burning, and "pins-and-needles" tingling sensation) is a characteristic vaso-occlusive symptom and may progress to cyanosis or necrosis of the extremities, or both. The involvement of the hands and feet may simulate a diabetic neuropathy. The erythromelalgia, just as in PV, is a source of continual torment and frustration for ET patients. The toxic effect of the metabolites of platelet arachidonic acid appears to be responsible for the erythromelalgia, and this may be relieved by decreasing the platelet count or by use of anti-inflammatory agents such as aspirin. Thrombotic complications are more common when the platelet count is greater than $2000 \times 10^9/L$.

Neurologic manifestations are usually of a transient ischemic nature and include visual disturbances, headaches, paresthesia, dizziness, transient ischemic attacks, and, rarely, seizures. Complete stroke is an uncommon occurrence. In older patients, underlying degenerative vascular disease in combination with thrombocytosis and platelet functional defects all contribute to the thrombohemorrhagic complications.

Other signs and symptoms that have been observed in this disease are recurrent abortions and fetal growth retardation, pruritus, gout, and priapism. Modest splenomegaly is present in approximately 40% of patients with ET. Splenic atrophy resulting from splenic vascular thrombosis and silent infarctions occur in up to 20% of patients.

Laboratory Features

The platelet count is always elevated, in the range 600 to $2500 \times 10^9/L$. Platelets are usually morphologically normal, although some degree of platelet anisocytosis may be apparent. When present, this correlates with an elevation of the platelet distribution width (PDW), as determined by automated Coulter instruments. Abnormal morphological findings may include giant platelets (megathrombocytes) as well as microthrombocytes, platelet aggregates, abnormally granulated platelets, and megakaryocytic cytoplasmic fragments (Fig. 18-14 and Color Plate 211).

A mild normocytic, normochromic anemia may be present in up to 50% of patients although the hemoglobin value is not usually less than 10 g/dL. Recurrent mucosal or gastrointestinal bleeding leads to iron-deficiency anemia, and MCV and MCHC are decreased, with a microcytic, hypochromic blood picture becoming apparent on examination of