Late in the course, PCV often progresses to a **spent phase** characterized by extensive marrow fibrosis that displaces hematopoietic cells. This is accompanied by increased extramedullary hematopoiesis in the spleen and liver, often leading to prominent organomegaly (Fig. 13-35). Transformation to AML, with its typical features, occurs in about 1% of patients.

Clinical Features. PCV is uncommon, having an incidence of 1 to 3 per 100,000 per year. It appears insidiously, usually in adults of late middle age. Most symptoms are related to the increased red cell mass and hematocrit. Usually, there is also an increased total blood volume. Together, these factors cause abnormal blood flow, particularly on the low-pressure venous side of the circulation, which becomes greatly distended. Patients are plethoric and cyanotic due to stagnation and deoxygenation of blood in peripheral vessels. Headache, dizziness, hypertension, and gastrointestinal symptoms are common. Intense pruritus and peptic ulceration may occur, both possibly resulting from the release of histamine from basophils. High cell turnover gives rise to hyperuricemia; symptomatic gout is seen in 5% to 10% of cases.

More ominously, the abnormal blood flow and platelet function lead to an increased risk of both major bleeding and thrombotic episodes. About 25% of patients first come to attention due to deep venous thrombosis, myocardial infarction, or stroke. Thromboses sometimes also occur in the hepatic veins (producing Budd-Chiari syndrome) and the portal and mesenteric veins (leading to bowel infarction). It should be remembered that thrombotic complications sometimes precede the appearance of the typical hematologic findings. Minor hemorrhages (epistaxis, bleeding gums) are common, and life-threatening hemorrhages occur in 5% to 10% of cases.

The hemoglobin concentration ranges from 14 to 28 gm/dL, and the hematocrit is usually 60% or more. Sometimes chronic bleeding leads to iron deficiency, which can suppress erythropoiesis sufficiently to lower the hematocrit into the normal range, an example of two defects counteracting one another to "correct" a laboratory abnormality. The white cell count ranges from 12,000 to 50,000 cells/mm^3, and the platelet count is often greater than 500,000 platelets/mm^3. The platelets usually exhibit morphologic abnormalities such as giant forms and are often defective in functional aggregation studies.

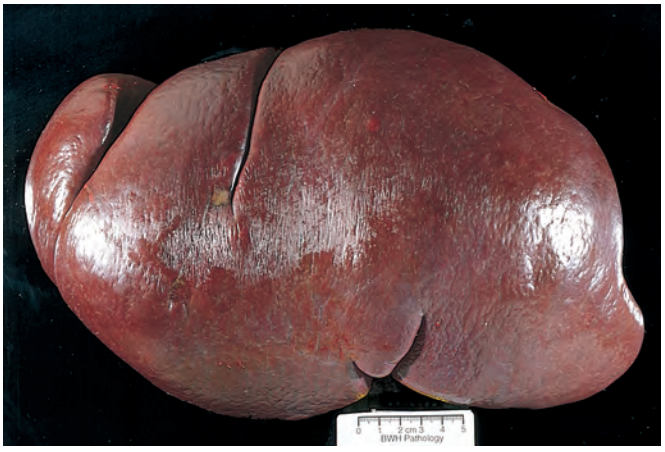

Figure 13-35 Polycythemia vera, spent phase. Massive splenomegaly (3020 gm; normal: 150 to 200 gm) largely due to extramedullary hematopoiesis occurring in the setting of advanced marrow myelofibrosis. (Courtesy Dr. Mark Fleming, Department of Pathology, Children's Hospital, Boston, Mass.)

Without treatment, death from bleeding or thrombosis occurs within months of diagnosis. However, simply maintaining the red cell mass at nearly normal levels by phlebotomy extends the median survival to about 10 years. JAK2 inhibitors are in preclinical development and represent a promising form of targeted therapy.

Extended survival with treatment has revealed that PCV tends to evolve to a "spent phase," during which clinical and anatomic features of primary myelofibrosis develop. The disease undergoes this transition in about 15% to 20% of patients after an average period of 10 years. It is marked by the appearance of obliterative fibrosis in the bone marrow (myelofibrosis) and extensive extramedullary hematopoiesis, principally in the spleen, which enlarges greatly. The mechanisms underlying the progression to the spent phase are not known.

In about 2% of patients, PCV transforms to AML. Surprisingly, the AML clone often lacks *JAK2* mutations, suggesting that the causative *JAK2* mutations occur in an abnormal stem cell that already harbors potentially oncogenic mutations, and therefore is "at risk" for giving rise to several different myeloid tumors. Unlike CML, transformation to ALL is rarely observed, consistent with the cell of origin being a progenitor committed to myeloid differentiation.

Essential Thrombocytosis

Essential thrombocytosis (ET) is often associated with activating point mutations in JAK2 (50% of cases) or MPL (5% to 10% of cases), a receptor tyrosine kinase that is normally activated by thrombopoietin. In addition, recent DNA sequencing studies have revealed that most of the remaining cases have mutations in calreticulin, a protein with several described functions in the endoplasmic reticulum and the cytoplasm. Since JAK2 and calreticulin mutations are mutually exclusive, it is hypothesized that the calreticulin mutations also increase JAK-STAT signaling through currently unknown mechanisms.

ET manifests clinically with elevated platelet counts and is separated from PCV and primary myelofibrosis based on the absence of polycythemia and marrow fibrosis, respectively. In those cases without tyrosine kinase mutations, causes of reactive thrombocytosis, such as inflammatory disorders and iron deficiency, must be excluded before the diagnosis can be established.

Constitutive JAK2 or MPL signaling renders the progenitors thrombopoietin-independent and leads to hyperproliferation. The *JAK2* mutation is the same as that found in almost all cases of PCV. Why some patients with *JAK2* mutations present with PCV and others with ET is not understood. Some cases of "ET" may in fact be PCV disguised by iron deficiency (which is more common in individuals diagnosed with ET), but this is probably true of only a small fraction of patients. As mentioned, most cases without JAK2 or MPL mutations have calreticulin mutations instead.

Bone marrow cellularity is usually only mildly increased, but megakaryocytes are often markedly increased in