attributed to gastrointestinal blood loss until proven otherwise. To prematurely ascribe iron deficiency in such individuals to any other cause is to run the risk of missing an occult gastrointestinal cancer or other bleeding lesion. An alert clinician investigating unexplained iron deficiency anemia occasionally discovers an occult bleeding source such as a cancer and thereby saves a life.

Pathogenesis. Whatever its basis, iron deficiency produces a *hypochromic microcytic anemia.* At the outset of chronic blood loss or other states of negative iron balance, reserves in the form of ferritin and hemosiderin may be adequate to maintain normal hemoglobin and hematocrit levels as well as normal serum iron and transferrin saturation. Progressive depletion of these reserves first lowers serum iron and transferrin saturation levels without producing anemia. In this early stage there is increased erythroid activity in the bone marrow. Anemia appears only when iron stores are completely depleted and is accompanied by lower than normal serum iron, ferritin, and transferrin saturation levels.

MORPHOLOGY

The bone marrow reveals a mild to moderate increase in erythroid progenitors. A diagnostically significant finding is the **disappearance of stainable iron from macrophages in the bone marrow**, which is best assessed by performing Prussian blue stains on smears of aspirated marrow. In peripheral blood smears, the red cells are small **(microcytic)** and pale **(hypochromic)**. Normal red cells with sufficient hemoglobin have a zone of central pallor measuring about one third of the cell diameter. In established iron deficiency the zone of pallor is enlarged; hemoglobin may be seen only in a narrow peripheral rim (Fig. 14-23). Poikilocytosis in the form of small, elongated red cells (pencil cells) is also characteristically seen.

Clinical Features

The clinical manifestations of the anemia are nonspecific and were detailed earlier. The dominating signs and symptoms frequently relate to the underlying cause of the anemia, for example, gastrointestinal or gynecologic disease, malnutrition, pregnancy, and malabsorption. In severe and long-standing iron deficiency, depletion of iron-containing enzymes in cells throughout the body also causes other changes, including koilonychia, alopecia, atrophic changes in the tongue and gastric mucosa, and intestinal malabsorption. Depletion of iron from the central nervous system may lead to the appearance of pica, in which affected individuals consume non-foodstuffs such as clay or food ingredients such as flour, and periodically move their limbs during sleep. Esophageal webs appear together with microcytic hypochromic anemia and atrophic glossitis to complete the triad of major findings in the rare *Plummer-Vinson syndrome* (Chapter 17).

The diagnosis of iron deficiency anemia ultimately rests on laboratory studies. Both the hemoglobin and hematocrit are depressed, usually to a moderate degree, in association with hypochromia, microcytosis, and modest poikilocytosis. The serum iron and ferritin are low, and the total plasma iron-binding capacity (reflecting elevated transferrin levels) is high. Low serum iron with increased iron-binding capacity results in a reduction of transferrin saturation to below 15%. Reduced iron stores inhibit hepcidin synthesis, and its serum levels fall. In uncomplicated iron deficiency, oral iron supplementation produces an increase in reticulocytes in about 5 to 7 days that is followed by a steady increase in blood counts and the normalization of red cell indices.

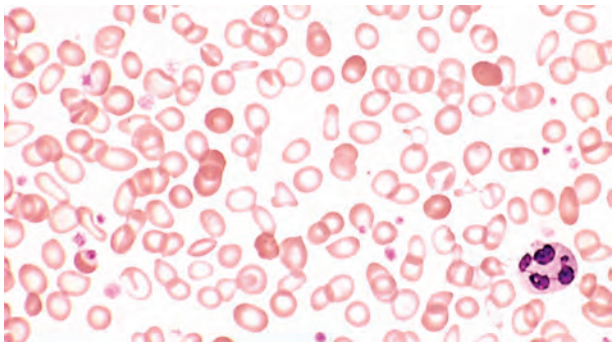

Figure 14-23 Hypochromic microcytic anemia of iron deficiency (peripheral blood smear). Note the small red cells containing a narrow rim of peripheral hemoglobin. Scattered fully hemoglobinized cells, present due to recent blood transfusion, stand in contrast. (Courtesy Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

Anemia of Chronic Disease

Impaired red cell production associated with chronic diseases that produce systemic inflammation is perhaps the most common cause of anemia among hospitalized patients in the United States. This form of anemia stems from a reduction in the proliferation of erythroid progenitors and impaired iron utilization. The chronic illnesses associated with this form of anemia can be grouped into three categories:

1. Chronic microbial infections, such as osteomyelitis, bacterial endocarditis, and lung abscess
2. Chronic immune disorders, such as rheumatoid arthritis and regional enteritis
3. Neoplasms, such as carcinomas of the lung and breast, and Hodgkin lymphoma

The anemia of chronic disease occurs in the setting of persistent systemic inflammation and is associated with low serum iron, reduced total iron-binding capacity, and abundant stored iron in tissue macrophages. Several effects of inflammation contribute to the observed abnormalities. Most notably, certain inflammatory mediators, particularly interleukin-6 (IL-6), stimulate an increase in the hepatic production of hepcidin. As was discussed under the anemia of iron deficiency, hepcidin inhibits ferroportin function in macrophages and reduces the transfer of iron from the storage pool to developing erythroid precursors in the bone marrow. As a result, the erythroid precursors are starved for iron in the midst of plenty. In addition, these progenitors do not proliferate adequately because erythropoietin levels are inappropriately low for the degree of anemia. The precise mechanism underlying this reduction in erythropoietin is uncertain, but transgenic mice expressing high levels of hepcidin develop a microcytic anemia associated with low erythropoietin levels, suggesting that hepcidin directly or indirectly suppresses erythropoietin production.