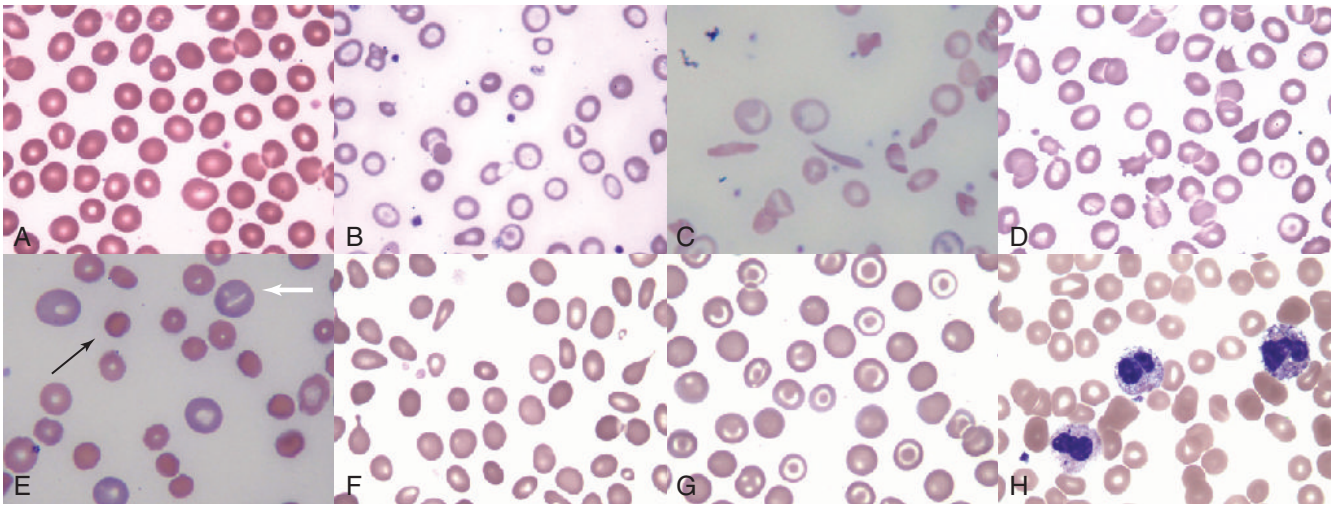


**FIGURE 47-2** Peripheral blood smears in patients with anemia. **A,** Normal red blood cells. **B,** Iron deficiency anemia. **C,** Sickle cell anemia. **D,** Microangiopathic hemolytic anemia. **E,** Spherocytosis *(black arrow)* and reticulocytosis *(white arrow)* in autoimmune hemolytic anemia. **F,** Teardrops in myelofibrosis. **G,** Target cells. **H,** Pseudo-Pelger-Huet anomaly in myelodysplasia.

microcytic (MCV <80), normocytic (MCV 80 to 100), or macrocytic (MCV >100).

## EVALUATION OF HYPOPROLIFERATIVE ANEMIAS

### Microcytic Anemias

The differential diagnosis of microcytic anemia is outlined in Table 47-2. Microcytosis and hypochromia are the hallmarks of anemias caused by defects in hemoglobin synthesis, which can reflect either failure of heme synthesis or abnormalities in globin production. The leading cause of microcytic anemia is iron deficiency, in which lack of heme synthesis results from the absence of iron to incorporate into the porphyrin ring (see later discussion). Up to 30% of patients with anemia of chronic inflammation have microcytosis. Lead poisoning blocks the incorporation of iron into heme, also resulting in a microcytic anemia.

Sideroblastic anemias arise from failure to synthesize the porphyrin ring, usually as a result of inhibition of the heme synthetic pathway enzymes. Congenital sideroblastic anemia may respond to pyridoxine, a cofactor for several of the heme synthetic pathway enzymes. A more common cause of acquired sideroblastic anemia is alcohol abuse; ethanol inhibits most of the enzymes in the heme synthetic pathway. Failure of globin synthesis occurs in thalassemic syndromes (see Hemolgobinopathies). All these disorders lead to decreased mean corpuscular hemoglobin concentration, resulting in hypochromia and a decrease in RBC size (i.e., low MCV).

#### Iron Deficiency Anemia

Iron deficiency is the leading cause of anemia worldwide. Although the presentation of classic iron deficiency anemia is linked with a microcytic anemia, early iron deficiency is associated with a normocytic anemia. Consequently, iron deficiency should be considered in all patients with anemia, and iron indices should be a part of the evaluation of any patient with hypoproductive anemia, regardless of the MCV.

Iron is acquired in the diet from heme sources (i.e., meat) and from nonheme sources (e.g., vegetables such as spinach). Iron from heme is better absorbed than nonheme iron. Iron absorption is increased in iron deficiency, hypoxia, ineffective erythropoiesis, and hereditary hemochromatosis (most commonly caused by mutations in the *HFE* gene). Iron is absorbed from the proximal small intestine; it is transported in the cell bound to ferroportin and through the plasma bound to transferrin. Its uptake into the RBC precursors is mediated through the transferrin receptor. Iron absorption from the intestine is further regulated by hepcidin (see Anemia of Chronic Inflammation). Iron outside hemoglobin-producing cells is stored in ferritin. Men and women have total-body iron concentrations of 50 mg/kg and 40 mg/kg, respectively. Between 60% and 75% of the iron is found in hemoglobin. A small amount (2 mg/kg) is found in heme and nonheme enzymes, and 5 mg/kg is found in myoglobin. The remainder is stored in ferritin, which resides primarily in liver, bone marrow, spleen, and muscle. The capacity for excreting iron is limited, and iron overload occurs in patients with excessive absorption from the gastrointestinal tract (as a result of ineffective erythropoiesis or congenital hemochromatosis) and in those with chronic transfusions. Iron overload leads to increased iron deposition in these tissues and secondary

**TABLE 47-2 DIFFERENTIAL DIAGNOSIS OF ANEMIA WITH LOW RETICULOCYTE COUNT**

| | |
|---|---|
| **MICROCYTIC ANEMIA (MCV <80 fL/cell)** | **Nonmegaloblastic Macrocytosis** |
| Iron deficiency | Liver disease |
| Thalassemia minor | Hypothyroidism |
| Anemia of chronic inflammation | Reticulocytosis |
| Sideroblastic anemia | **NORMOCYTIC ANEMIA (MCV 80-100 fL/cell)** |
| Lead poisoning | Early iron deficiency |
| **MACROCYTIC ANEMIA (MCV >100 fL/cell)** | Aplastic anemia |
| **Megaloblastic Anemias** | Myelophthisic disorders |
| Folate deficiency | Endocrinopathies |
| Vitamin $B_{12}$ deficiency | Anemia of chronic inflammation |
| Drug-induced megaloblastic anemia | Anemia of renal failure |
| Myelodysplasia | Mixed nutritional deficiency |

MCV, Mean corpuscular volume.