mutation is common, family history of anemia may be absent. The peripheral blood smear often shows anisocytosis, abundant cells with punctate inclusions, and irregular shapes (i.e., poikilocytosis).

The two best tests for diagnosing unstable hemoglobins are the Heinz body preparation and the isopropanol or heat stability test. Many unstable Hb variants are electrophoretically silent. A normal electrophoresis does not rule out the diagnosis. Mass spectroscopy or direct gene analysis will provide a definitive diagnosis.

Severely affected patients may require transfusion support for the first 3 years of life, because splenectomy before age 3 is associated with a significantly higher immune deficit. Splenectomy is usually effective thereafter, but occasional patients may require lifelong transfusion support. After splenectomy, patients can develop cholelithiasis and leg ulcers, hypercoagulable states, and susceptibility to overwhelming sepsis. Splenectomy should thus be avoided or delayed unless it is the only alternative. Precipitation of unstable hemoglobins is aggravated by oxidative stress, e.g., infection and antimalarial drugs, which should be avoided where possible.

High-O_2 affinity hemoglobin variants should be suspected in patients with erythrocytosis. The best test for confirmation is measurement of the P_{50}. A high-O_2 affinity hemoglobin causes a significant left shift (i.e., lower numeric value of the P_{50}); confounding conditions, e.g., tobacco smoking or carbon monoxide exposure, can also lower the P_{50}.

High-affinity hemoglobins are often asymptomatic; rubor or plethora may be telltale signs. When the hematocrit approaches 60%, symptoms of high blood viscosity and sluggish flow (headache, lethargy, dizziness, etc.) may be present. These persons may benefit from judicious phlebotomy. Erythrocytosis represents an appropriate attempt to compensate for the impaired oxygen delivery by the abnormal variant. Overzealous phlebotomy may stimulate increased erythropoiesis or aggravate symptoms by thwarting this compensatory mechanism. The guiding principle of phlebotomy should be to improve oxygen delivery by reducing blood viscosity and increasing blood flow rather than restoration of a normal hematocrit. Phlebotomy-induced modest iron deficiency may aid in control.

Low-affinity hemoglobins should be considered in patients with cyanosis or a low hematocrit with no other reason apparent after thorough evaluation. The P_{50} test confirms the diagnosis. Counseling and reassurance are the interventions of choice.

Methemoglobin should be suspected in patients with hypoxic symptoms who appear cyanotic but have a $Pa{O_2}$ sufficiently high that hemoglobin should be fully saturated with oxygen. A history of nitrite or other oxidant ingestions may not always be available; some exposures may be inapparent to the patient, and others may result from suicide attempts. The characteristic muddy appearance of freshly drawn blood can be a critical clue. The best diagnostic test is methemoglobin assay, which is usually available on an emergency basis.

Methemoglobinemia often causes symptoms of cerebral ischemia at levels >15%; levels >60% are usually lethal. Intravenous injection of 1 mg/kg of methylene blue is effective emergency therapy. Milder cases and follow-up of severe cases can be treated orally with methylene blue (60 mg three to four times each day) or ascorbic acid (300–600 mg/d).

THALASSEMIA SYNDROMES

The thalassemia syndromes are inherited disorders of α- or β-globin biosynthesis. The reduced supply of globin diminishes production of hemoglobin tetramers, causing hypochromia and microcytosis. Unbalanced accumulation of α and β subunits occurs because the synthesis of the unaffected globins proceeds at a normal rate. Unbalanced chain accumulation dominates the clinical phenotype. Clinical severity varies widely, depending on the degree to which the synthesis of the affected globin is impaired, altered synthesis of other globin chains, and coinheritance of other abnormal globin alleles.

CLINICAL MANIFESTATIONS OF β THALASSEMIA SYNDROMES

Mutations causing thalassemia can affect any step in the pathway of globin gene expression: transcription, processing of the mRNA precursor, translation, and posttranslational metabolism of the β-globin polypeptide chain. The most common forms arise from mutations that derange splicing of the mRNA precursor or prematurely terminate translation of the mRNA.

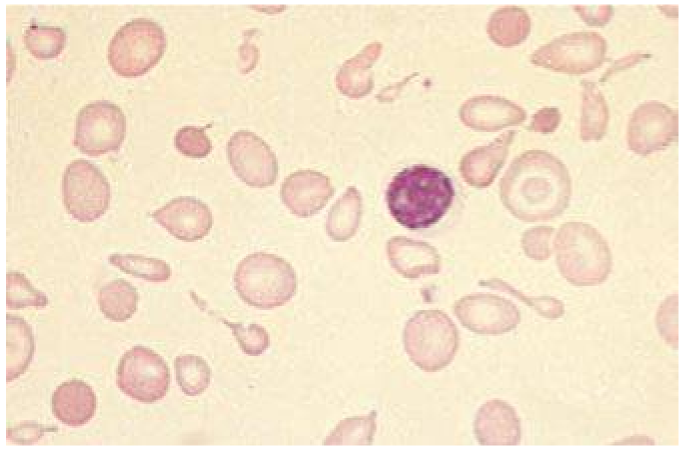

FIGURE 127-5 β Thalassemia intermedia. Microcytic and hypochromic red blood cells are seen that resemble the red blood cells of severe iron-deficiency anemia. Many elliptical and teardrop-shaped red blood cells are noted.

Hypochromia and microcytosis characterize all forms of β thalassemia because of the reduced amounts of hemoglobin tetramers (Fig. 127-5). In heterozygotes (β thalassemia trait), this is the only abnormality seen. Anemia is minimal. In more severe homozygous states, unbalanced α- and β-globin accumulation causes accumulation of highly insoluble unpaired α chains. They form toxic inclusion bodies that kill developing erythroblasts in the marrow. Few of the proerythroblasts beginning erythroid maturation survive. The surviving RBCs bear a burden of inclusion bodies that are detected in the spleen, shortening the RBC life span and producing severe hemolytic anemia. The resulting profound anemia stimulates erythropoietin release and compensatory erythroid hyperplasia, but the marrow response is sabotaged by the ineffective erythropoiesis. Anemia persists. Erythroid hyperplasia can become exuberant and produce masses of extramedullary erythropoietic tissue in the liver and spleen.

Massive bone marrow expansion deranges growth and development. Children develop characteristic "chipmunk" facies due to maxillary marrow hyperplasia and frontal bossing. Thinning and pathologic fracture of long bones and vertebrae may occur due to cortical invasion by erythroid elements and profound growth retardation. Hemolytic anemia causes hepatosplenomegaly, leg ulcers, gallstones, and high-output congestive heart failure. The conscription of caloric resources to support erythropoiesis leads to inanition, susceptibility to infection, endocrine dysfunction, and in the most severe cases, death during the first decade of life. Chronic transfusions with RBCs improve oxygen delivery, suppress the excessive ineffective erythropoiesis, and prolong life, but the inevitable side effects, notably iron overload, often prove fatal by age 30 years.

Severity is highly variable. Known modulating factors are those that ameliorate the burden of unpaired α-globin inclusions. Alleles associated with milder synthetic defects and coinheritance of α thalassemia trait reduce clinical severity by reducing accumulation of excess α globin. HbF persists to various degrees in β thalassemias. γ-Globin gene chains can substitute for β chains, generating more hemoglobin and reducing the burden of α-globin inclusions. The terms *β thalassemia major* and *β thalassemia intermedia* are used to reflect the clinical heterogeneity. Patients with β thalassemia major require intensive transfusion support to survive. Patients with β thalassemia intermedia have a somewhat milder phenotype and can survive without transfusion. The terms *β thalassemia minor* and *β thalassemia trait* describe asymptomatic heterozygotes for β thalassemia.

THALASSEMIA SYNDROMES

The four classic α thalassemias, most common in Asians, are α thalassemia-2 trait, in which one of the four α-globin loci is deleted;