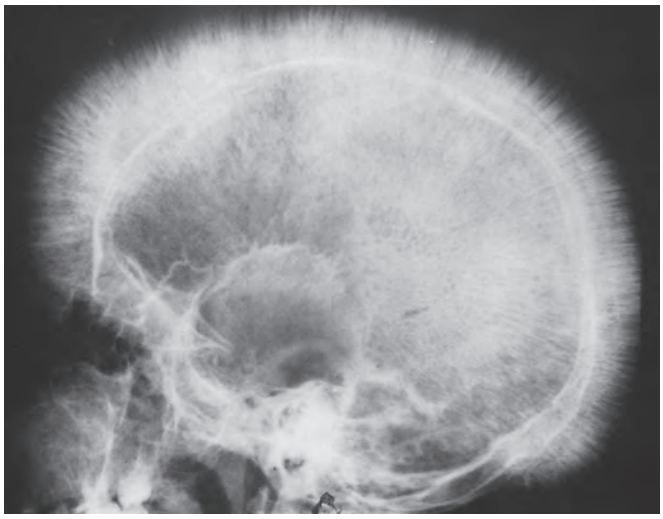

Figure 14-13 Thalassemia. X-ray film of the skull showing new bone formation on the outer table, producing perpendicular radiations resembling a crewcut. (Courtesy Dr. Jack Reynolds, Department of Radiology, University of Texas Southwestern Medical School, Dallas, Texas.)

The clinical course of β-thalassemia major is brief unless blood transfusions are given. Untreated children suffer from growth retardation and die at an early age from the effects of anemia. In those who survive long enough, the cheekbones and other bony prominences are enlarged and distorted. Hepatosplenomegaly due to extramedullary hematopoiesis is usually present. Although blood transfusions improve the anemia and suppress complications related to excessive erythropoiesis, they lead to complications of their own. Cardiac disease resulting from progressive iron overload and secondary hemochromatosis (Chapter 18) is an important cause of death, particularly in heavily transfused patients, who must be treated with iron chelators to prevent or reduce this complication. With transfusions and iron chelation, survival into the third decade is possible, but the overall outlook remains guarded. Hematopoietic stem cell transplantation is the only therapy offering a cure and is being used increasingly. Prenatal diagnosis is possible by molecular analysis of DNA.

β-Thalassemia Minor. β-Thalassemia minor is much more common than β-thalassemia major and understandably affects the same ethnic groups. Most patients are heterozygous carriers of a β^+ or β^0 allele. These patients are usually asymptomatic. Anemia, if present, is mild. The peripheral blood smear typically shows some red cell abnormalities, including hypochromia, microcytosis, basophilic stippling, and target cells. Mild erythroid hyperplasia is seen in the bone marrow. Hemoglobin electrophoresis usually reveals an increase in HbA_2 ($\alpha_2\delta_2$) to 4% to 8% of the total hemoglobin (normal, 2.5% ± 0.3%), which is a reflection of an elevated ratio of δ-chain to β-chain synthesis. HbF levels are generally normal or occasionally slightly increased.

Recognition of β-thalassemia trait is important for two reasons: (1) it superficially resembles the hypochromic microcytic anemia of iron deficiency, and (2) it has implications for genetic counseling. Iron deficiency can usually be excluded through measurement of serum iron, total iron-binding capacity, and serum ferritin (see Iron Deficiency Anemia). The increase in HbA_2 is diagnostically useful, particularly in individuals (such as women of childbearing age) who are at risk for both β-thalassemia trait and iron deficiency.

α-Thalassemias

The α-thalassemias are caused by inherited deletions that result in reduced or absent synthesis of α-globin chains. Normally, there are four α-globin genes, and the severity of α-thalassemia depends on how many α-globin genes are affected. As in β-thalassemias, the anemia stems both from a lack of adequate hemoglobin and the presence of excess unpaired globin chains (β, γ, and δ), which vary in type at different ages. In newborns with α-thalassemia, excess unpaired γ-globin chains form γ_4 tetramers known as *hemoglobin Barts,* whereas in older children and adults excess β-globin chains form β_4 tetramers known as *HbH*. Because free β and γ chains are more soluble than free α chains and form fairly stable homotetramers, hemolysis and ineffective erythropoiesis are less severe than in β-thalassemias. A variety of molecular lesions give rise to α-thalassemia, but gene deletion is the most common cause of reduced α-chain synthesis.

Clinical Syndromes. The clinical syndromes are determined and classified by the number of α-globin genes that are deleted. Each of the four α-globin genes normally contributes 25% of the total α-globin chains. α-Thalassemia syndromes stem from combinations of deletions that remove one to four α-globin genes. Not surprisingly, the severity of the clinical syndrome is proportional to the number of α-globin genes that are deleted. The different types of α-thalassemia and their salient clinical features are listed in Table 14-3.

Silent Carrier State. Silent carrier state is associated with the deletion of a single α-globin gene, which causes a barely detectable reduction in α-globin chain synthesis. These individuals are completely asymptomatic but have slight microcytosis.

α-Thalassemia Trait. α-Thalassemia trait is caused by the deletion of two α-globin genes from a single chromosome (α/α −/−) or the deletion of one α-globin gene from each of the two chromosomes (α/− α/−) (Table 14-3). The former genotype is more common in Asian populations, the latter in regions of Africa. Both genotypes produce similar quantitative deficiencies of α-globin and are clinically identical, but have different implications for the children of affected individuals, who are at risk of clinically significant α-thalassemia (HbH disease or hydrops fetalis) only when at least one parent has the −/− haplotype. As a result, symptomatic α-thalassemia is relatively common in Asian populations and rare in black African populations. The clinical picture in α-thalassemia trait is identical to that described for β-thalassemia minor, that is, small red cells (microcytosis), minimal or no anemia, and no abnormal physical signs. HbA_2 levels are normal or low.

Hemoglobin H Disease. HbH disease is caused by deletion of three α-globin genes. As discussed, HbH disease is most common in Asian populations. With only one normal