rarer point mutations affect the production of α globin and the magnitude of imbalanced globin synthesis. Because of this mutational complexity, many different variations of the common α thalassemia syndromes are found.

■ PATHOPHYSIOLOGY

Reduced accumulation of α-globin leaves non-α-globins unpaired and unable to participate in the formation of functional hemoglobin tetramers. In the fetus, absent or reduced synthesis of α-globin allows unpaired γ-globin chains, which are usually part of the HbF tetramer, to form γ_4 or Hb Bart's; in adults, when γ-globin synthesis is mostly silenced, unpaired β-globin chains, lacking a suitable partner to form HbA, tetramerize as β_4 or HbH. Both Hb Bart's and HbH have very high O_2 affinity and do not unload O_2 in tissues; HbH is also unstable. Severe anemia in Hb Bart's hydrops fetalis is a result of absent normal hemoglobin and ineffective erythropoiesis; in HbH disease, unstable HbH leads to oxidative membrane damage with extravascular hemolysis in the spleen and ineffective erythropoiesis.

■ DIAGNOSIS

Microcytosis/hypochromia with nearly normal hemoglobin concentrations, in the absence of iron deficiency and the increased level of HbA_2 that is diagnostic of β thalassemia, is sufficient for a presumptive diagnosis of α thalassemia trait. When genetic counseling is needed and antenatal diagnosis contemplated, the molecular basis of the presumed α thalassemia is required. HbH disease, which is usually due to compound heterozygosity for one chromosome with both α-globin genes deleted and one chromosome with only a single α-globin gene, is defined by the hematologic findings shown in Table 98-6 along with varying levels of reticulocytosis. At birth, when hemoglobin is separated by HPLC, 20–30% Hb Bart's is present; in adults, traces to 40% HbH are present along with residual Hb Bart's in some cases. HbH inclusions can be induced in some red cells after incubation and staining with brilliant cresyl blue. Hemoglobin composition in Hb Bart's hydrops