in the first months of life, vanishing from notice afterward; δ-globin gene mutations are innocuous and usually not detected; β-globin gene mutations can become clinically apparent after the synthesis of HbF dwindles to stable adult levels.

With rare exceptions, all disorders of hemoglobin are autosomal recessive or co-dominant disorders; a family history of anemia, a common feature of most symptomatic hemoglobinopathies and thalassemias, is often present. In addition to pallor and jaundice, splenomegaly is often present. In sickle cell disease, acute painful vasoocclusive episodes are a diagnostic feature. A small number of laboratory tests can confirm the diagnosis starting with a complete blood count that includes a reticulocyte count with a careful review of a peripheral blood film. A sustained increase in reticulocyte count indicates the presence of hemolytic anemia. Hemoglobin fractionation by high-performance liquid chromatography (HPLC) or capillary electrophoresis, especially when, in addition to the index case, family members are available for study, is often sufficient to confirm a diagnosis at the level of hemoglobin phenotype. DNA sequencing of the globin genes should allow definitive diagnosis. DNA-based diagnosis, which is readily available from excellent reference laboratories, is a prerequisite for most instances of genetic counseling.

Sickle cell disease and β thalassemia have some features in common. They are caused by mutations in the β-globin gene; both are chronic hemolytic anemias sharing complications associated with hemolysis such as venous thrombosis, leg ulcers, and pulmonary hypertension; and they can be cured by hematopoietic stem cell transplantation. Key differences are that only HbS polymerizes and that ineffective erythropoiesis is a prominent feature of β thalassemia and responsible for its severe anemia. Both diseases could be cured by inducing sufficiently high levels of HbF; in sickle cell disease, HbF prevents the polymerization of HbS; in β thalassemia, sufficient HbF compensates for the deficit of HbA.

SICKLE CELL DISEASE