simple infection) may cause blood flow to become sluggish and "spleenlike," leading to sickling and vaso-occlusion. This compromises pulmonary function, creating a potentially fatal cycle of worsening pulmonary and systemic hypoxemia, sickling, and vaso-occlusion. *Priapism* affects up to 45% of males after puberty and may lead to hypoxic damage and erectile dysfunction. Other disorders related to vascular obstruction, particularly *stroke* and retinopathy leading to *loss of visual acuity* and even blindness, can take a devastating toll. Factors proposed to contribute to stroke include the adhesion of sickle red cells to arterial vascular endothelium and vasoconstriction caused by the depletion of NO by free hemoglobin.

Although occlusive crises are the most common cause of patient morbidity and mortality, several other acute events complicate the course. *Sequestration crises* occur in children with intact spleens. Massive entrapment of sickle red cells leads to rapid splenic enlargement, hypovolemia, and sometimes shock. Both sequestration crises and the acute chest syndrome may be fatal and sometimes require prompt treatment with exchange transfusions. *Aplastic crises* stem from the infection of red cell progenitors by parvovirus B19, which causes a transient cessation of erythropoiesis and a sudden worsening of the anemia.

In addition to these dramatic crises, chronic tissue hypoxia takes a subtle but important toll. Chronic hypoxia is responsible for a generalized impairment of growth and development, as well as organ damage affecting the spleen, heart, kidneys, and lungs. Sickling provoked by hypertonicity in the renal medulla causes damage that eventually leads to hyposthenuria (the inability to concentrate urine), which increases the propensity for dehydration and its attendant risks.

Increased susceptibility to infection with encapsulated organisms is another threat. This is due in large part to altered splenic function, which is severely impaired in children by congestion and poor blood flow, and completely absent in adults because of splenic infarction. Defects of uncertain etiology in the alternative complement pathway also impair the opsonization of bacteria. *Pneumococcus pneumoniae* and *Haemophilus influenzae* septicemia and meningitis are common, particularly in children, but can be reduced by vaccination and prophylactic antibiotics.

It must be emphasized that there is great variation in the clinical manifestations of sickle cell disease. Some individuals are crippled by repeated vaso-occlusive crises, whereas others have only mild symptoms. The basis for this wide range in disease expression is not understood; both modifying genes and environmental factors are suspected.

The diagnosis is suggested by the clinical findings and the presence of irreversibly sickled red cells and is confirmed by various tests for sickle hemoglobin. In general, these involve mixing a blood sample with an oxygen-consuming reagent, such as metabisulfite, which induces sickling of red cells if HbS is present. Hemoglobin electrophoresis is also used to demonstrate the presence of HbS and exclude other sickle syndromes, such as HbSC disease. Prenatal diagnosis is possible by analysis of fetal DNA obtained by amniocentesis or chorionic biopsy.

The outlook for patients with sickle cell disease has improved considerably over the past 10 to 20 years. About 90% of patients survive to age 20, and close to 50% survive beyond the fifth decade. A mainstay of treatment is an inhibitor of DNA synthesis, hydroxyurea, which has several beneficial effects. These include (1) an increase in red cell HbF levels, which occurs by unknown mechanisms; and (2) an antiinflammatory effect, which stems from an inhibition of leukocyte production. These activities (and possibly others) are believed to act in concert to decrease crises related to vascular occlusions in both children and adults. Hematopoietic stem cell transplantation offers a chance at cure and is increasingly being explored as a therapeutic option.

Thalassemia Syndromes

The thalassemia syndromes are a heterogeneous group of disorders caused by inherited mutations that decrease the synthesis of either the α-globin or β-globin chains that compose adult hemoglobin, HbA ($\alpha_2\beta_2$), leading to anemia, tissue hypoxia, and red cell hemolysis related to the imbalance in globin chain synthesis. The two α chains in HbA are encoded by an identical pair of α-globin genes on chromosome 16, while the two β chains are encoded by a single β-globin gene on chromosome 11. β-thalassemia is caused by deficient synthesis of β chains, whereas α-thalassemia is caused by deficient synthesis of α chains. The hematologic consequences of diminished synthesis of one globin chain stem not only from hemoglobin deficiency but also from a relative excess of the other globin chain, particularly in β-thalassemia (described below).

Thalassemia syndromes are endemic in the Mediterranean basin (indeed, *thalassa* means "sea" in Greek), as well as the Middle East, tropical Africa, the Indian subcontinent, and Asia, and in aggregate are among the most common inherited disorders of humans. As with sickle cell disease and other common inherited red cell disorders, their prevalence seems to be explained by the protection they afford heterozygous carriers against malaria. Although we discuss the thalassemia syndromes with other inherited forms of anemia associated with hemolysis, it is important to recognize that the defects in globin synthesis that underlie these disorders cause anemia through two mechanisms: decreased red cell production, and decreased red cell lifespan.

β-Thalassemias

The β-thalassemias are caused by mutations that diminish the synthesis of β-globin chains. The clinical severity varies widely due to heterogeneity in the causative mutations. We will begin our discussion with the molecular lesions in β-thalassemia and then relate the clinical variants to specific underlying molecular defects.

Molecular Pathogenesis. The causative mutations fall into two categories: (1) β^0 *mutations*, associated with absent β-globin synthesis, and (2) β^+ *mutations*, characterized by reduced (but detectable) β-globin synthesis. Sequencing of β-thalassemia genes has revealed more than 100 different causative mutations, mostly consisting of point mutations. Details of these mutations and their effects are found in specialized texts. Figure 14-11 gives a few illustrative examples.

- *Splicing mutations.* These are the most common cause of β^+-thalassemia. Most of these mutations lie within