Neurologic events are a major cause of morbidity in patients with sickle cell disease. Acute large-vessel occlusions occur in children, with a recurrence rate of 70% if untreated; such strokes are an indication for long-term exchange transfusion, which has been shown to decrease the rate of repeated occlusions. For reasons that are poorly understood, such large-vessel occlusions rarely occur in adults. Adults may suffer hemorrhagic strokes as a result of aneurysmal dilation of proliferative vessels that form in response to repeated micro-occlusions in the cerebral vessels.

Any toxic or infectious insult that transiently suppresses bone marrow activity can cause an *aplastic crisis.* The shortened survival time of the RBC in sickle cell disease renders patients highly dependent on vigorous ongoing marrow activity, and short intervals of decreased reticulocyte formation can cause profound anemia. Most dramatic are infections associated with parvovirus B19, which directly infects erythroid precursors. Supportive care is usually all that is required. However, some patients go on to develop bone marrow necrosis, with a leukoerythroblastic picture; this development may be further complicated by bone marrow embolization to the lungs.

Certain vascular beds are especially prone to complications of sickle cell disease. The renal medulla is highly susceptible to damage by vaso-occlusion because its high tonicity and low oxygen tension both significantly increase the concentration of HbS. All patients with sickle cell disease develop defects in the ability to concentrate urine, and by adulthood, they are uniformly isosthenuric. Acute episodes of hematuria secondary to papillary necrosis are common.

The spleen is another site in which recurrent sickling uniformly occurs. By adulthood, all patients have become functionally asplenic from repeated infarctions of the microvasculature. This contributing factor increases the susceptibility of patients with sickle cell disease to infections with encapsulated organisms. Acute infection remains a significant cause of death. For unclear reasons, patients with sickle cell disease are particularly prone to osteomyelitis, and there is an unusually high incidence of *Salmonella* as the responsible organism.

Chronic Manifestations

Sickle cell disease used to be a disease of childhood. As more patients survive to adulthood, it has become clear that repeated episodes of vaso-occlusion lead to damage to almost every end organ (see Table 47-8). Renal failure and pulmonary failure are leading causes of death in adult patients with sickle cell disease. Other long-term complications include chronic skin ulcers, retinopathy, and liver dysfunction. In addition, most patients require cholecystectomy for pigment stones.

Treatment

Treatment of sickle cell disease remains largely supportive. Painful crises are treated with fluid, oxygen supplementation, and analgesics. Patients with any indication of infection should receive antibiotics. Patients with symptomatic anemia should be transfused. Exchange transfusion is indicated for chest syndrome, stroke, bone marrow necrosis, and priapism. More controversial indications for exchange transfusion include intractable pain and slow response to other supportive measures. The goal of exchange transfusion is to achieve a level of 30% to 40% HbS. As previously mentioned, patients who have sustained a thrombotic large-vessel stroke should undergo chronic exchange transfusion.

Treatment with hydroxyurea, an agent that increases the concentration of HbF in patients with sickle cell disease, reduces the incidence of vaso-occlusive crises. The efficacy of hydroxyurea in patients with recurrent crises has been demonstrated in a randomized study, and follow-up studies have revealed a survival advantage for patients treated with hydroxyurea.

Other Sickle Syndromes

Hemoglobin C

Hemoglobin C (HbC) is caused by another substitution, glutamic acid to lysine, in the sixth position of the β-globin chain. Homozygous HbC causes very mild symptoms of anemia and is usually clinically silent. Patients with hemoglobin S-C (HbSC) are compound heterozygotes for HbS and HbC. These patients are symptomatic, although the clinical manifestations are milder than in patients with homozygous HbS (HbSS). They have a higher hematocrit, and the higher viscosity increases the degree of retinopathy. They do not sustain splenic infarctions; unlike patients with HbSS, they usually have splenomegaly. Consequently, they occasionally have episodes of acute splenomegaly associated with profound decreases in hemoglobin concentration and hematocrit (splenic sequestration crisis). Although such crises also occur in children with HbSS, functional asplenia prevents this complication in adults with HbSS.

Sickle Cell β-Thalassemia

Patients who are double heterozygotes for HbS and β-thalassemia have a spectrum of disease dependent on the level of β-globin that they produce. Sickle cell β^+-thalassemia is a milder disease than HbSS, probably because of the decreased intracorpuscular concentration of HbS. Patients with sickle cell β^0-thalassemia (see discussion that follows) produce no normal β chains and have essentially the same phenotype as patients with HbSS.

Thalassemia

The thalassemic syndromes (Table 47-9) are a heterogeneous group of disorders associated with decreased or absent synthesis of either α- or β-globin chains. Severe thalassemic syndromes are associated with severe hemolytic anemia and are diagnosed in early childhood. However, mild forms of thalassemia minor frequently cause mild microcytic anemia with little or no evidence of hemolysis. These syndromes are often confused with iron deficiency because of the decreased MCV.

β-Thalassemia

Over 100 mutations have been described that lead to β-thalassemia, causing a decrease or absence of expression from the β-globin locus. The decreased expression of β-globin can be caused by structural mutations in the coding region of the gene, which result in nonsense mutations, truncated messenger RNA (mRNA), and no expression of intact globin from the affected allele (β^0-thalassemia). However, a large number of mutations that result in decreased transcription or translation or altered splicing of the β-globin mRNA result in reduction but not elimination of globin-chain expression from the affected allele (β^+-thalassemia).