scale. Chronic acute or subacute pulmonary crises lead to pulmonary hypertension and cor pulmonale, an increasingly common cause of death as patients survive longer. Considerable controversy exists about the possible role played by free plasma HbS in scavenging nitrogen dioxide (NO_2), thus raising pulmonary vascular tone. Trials of sildenafil to restore NO_2 levels were terminated because of adverse effects.

Chronic subacute central nervous system damage in the absence of an overt stroke is a distressingly common phenomenon beginning in early childhood. Modern functional imaging techniques have pinpointed circulatory dysfunction due to a likely CNS sickle vasculopathy; these changes correlate with an array of cognitive and behavioral abnormalities in children and young adults. It is important to be aware of these often subtle changes because they can complicate clinical management or be misinterpreted as "difficult patient" behaviors.

Sickle cell syndromes are remarkable for their clinical heterogeneity. Some patients remain virtually asymptomatic into or even through adult life, while others suffer repeated crises requiring hospitalization from early childhood. Patients with sickle thalassemia and sickle-HbE tend to have similar, slightly milder symptoms, perhaps because of the ameliorating effects of production of other hemoglobins within the RBC. Hemoglobin SC disease, one of the more common variants of sickle cell anemia, is frequently marked by lesser degrees of hemolytic anemia and a greater propensity for the development of retinopathy and aseptic necrosis of bones. In most respects, however, the clinical manifestations resemble sickle cell anemia. Some rare hemoglobin variants actually aggravate the sickling phenomenon.

The clinical variability in different patients inheriting the same disease-causing mutation (sickle hemoglobin) has made sickle cell disease the focus of efforts to identify modifying genetic polymorphisms in other genes that might account for the heterogeneity. The complexity of the data obtained thus far has dampened the expectation that genome-wide analysis will yield individualized profiles that predict a patient's clinical course. Nevertheless, a number of interesting patterns have emerged from these modifying gene analyses. For example, genes affecting the inflammatory response or cytokine expression appear to be modifying candidates. Genes that affect transcriptional regulation of lymphocytes may also be involved.

Clinical Manifestations of Sickle Cell Trait Sickle cell trait is often asymptomatic. Anemia and painful crises are rare. An uncommon but highly distinctive symptom is painless hematuria often occurring in adolescent males, probably due to papillary necrosis. Isosthenuria is a more common manifestation of the same process. Sloughing of papillae with urethral obstruction has been reported, as have isolated cases of massive sickling or sudden death due to exposure to high altitudes or extremes of exercise and dehydration. Avoidance of dehydration or extreme physical stress should be advised.

Diagnosis Sickle cell syndromes are suspected on the basis of hemolytic anemia, RBC morphology (Fig. 127-4), and intermittent episodes of ischemic pain. Diagnosis is confirmed by hemoglobin electrophoresis, mass spectroscopy, and the sickling tests already discussed. Thorough characterization of the exact hemoglobin profile of the patient is important, because sickle thalassemia and hemoglobin SC disease have distinct prognoses or clinical features. Diagnosis is usually established in childhood, but occasional patients, often with compound heterozygous states, do not develop symptoms until the onset of puberty, pregnancy, or early adult life. Genotyping of family members and potential parental partners is critical for genetic counseling. Details of the childhood history establish prognosis and need for aggressive or experimental therapies. Factors associated with increased morbidity and reduced survival include more than three crises requiring hospitalization per year, chronic neutrophilia, a history of splenic sequestration or hand-foot syndrome, and second episodes of acute chest syndrome. Patients with a history of cerebrovascular accidents are at higher risk for repeated episodes and require partial exchange transfusion and especially close monitoring using Doppler carotid flow measurements. Patients with severe or repeated episodes of acute chest syndrome may need lifelong transfusion support, using partial exchange transfusion, if possible.

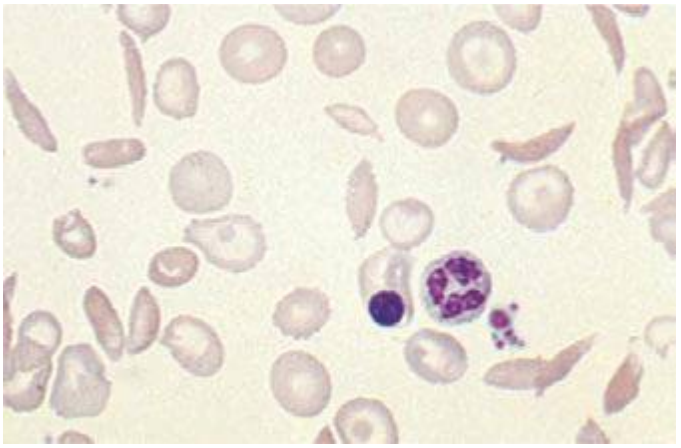

FIGURE 127-4 Sickle cell anemia. The elongated and crescent-shaped red blood cells seen on this smear represent circulating irreversibly sickled cells. Target cells and a nucleated red blood cell are also seen.

TREATMENT SICKLE CELL SYNDROMES

Patients with sickle cell syndromes require ongoing continuity of care. Familiarity with the pattern of symptoms provides the best safeguard against excessive use of the emergency room, hospitalization, and habituation to addictive narcotics. Additional preventive measures include regular slit-lamp examinations to monitor development of retinopathy; antibiotic prophylaxis appropriate for splenectomized patients during dental or other invasive procedures; and vigorous oral hydration during or in anticipation of periods of extreme exercise, exposure to heat or cold, emotional stress, or infection. Pneumococcal and *Haemophilus influenzae* vaccines are less effective in splenectomized individuals. Thus, patients with sickle cell anemia should be vaccinated early in life.

The management of an acute painful crisis includes vigorous hydration, thorough evaluation for underlying causes (such as infection), and aggressive analgesia administered by a standing order and/or patient-controlled analgesia (PCA) pump. Morphine (0.1–0.15 mg/kg every 3–4 h) should be used to control severe pain. Bone pain may respond as well to ketorolac (30–60 mg initial dose, then 15–30 mg every 6–8 h). Inhalation of nitrous oxide can provide short-term pain relief, but great care must be exercised to avoid hypoxia and respiratory depression. Nitrous oxide also elevates O_2 affinity, reducing O_2 delivery to tissues. Its use should be restricted to experts. Many crises can be managed at home with oral hydration and oral analgesia. Use of the emergency room should be reserved for especially severe symptoms or circumstances in which other processes, e.g., infection, are strongly suspected. Nasal oxygen should be used as appropriate to protect arterial saturation. Most crises resolve in 1–7 days. Use of blood transfusion should be reserved for extreme cases: transfusions do not shorten the duration of the crisis.

No tests are definitive to diagnose acute painful crisis. Critical to good management is an approach that recognizes that most patients reporting crisis symptoms do indeed have crisis or another significant medical problem. Diligent diagnostic evaluation for underlying causes is imperative, even though these are found infrequently. In adults, the possibility of aseptic necrosis or sickle arthropathy must be considered, especially if pain and immobility become repeated or chronic at a single site. Nonsteroidal anti-inflammatory agents are often effective for sickle cell arthropathy.

Acute chest syndrome is a medical emergency that may require management in an intensive care unit. Hydration should be monitored carefully to avoid the development of pulmonary edema, and oxygen therapy should be especially vigorous for protection of