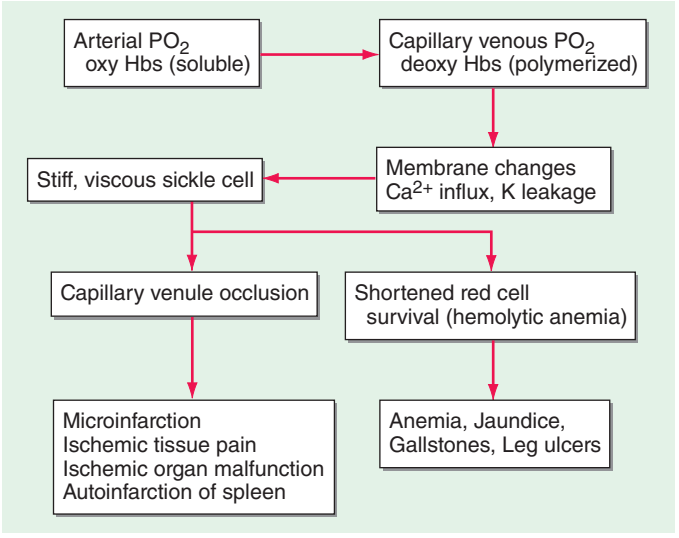

FIGURE 127-3 **Pathophysiology of sickle cell crisis.**

by quantitating the P_{50}, the partial pressure of oxygen at which the hemoglobin sample becomes 50% saturated with oxygen. Direct tests for the percent carboxyhemoglobin and methemoglobin, using spectrophotometric techniques, can readily be obtained from most clinical laboratories on an urgent basis.

Laboratory evaluation remains an adjunct, rather than the sole diagnostic aid. Diagnosis is best established by recognition of a characteristic history, physical findings, peripheral blood smear morphology, and abnormalities of the complete blood cell count (e.g., profound microcytosis with minimal anemia in thalassemia trait).

STRUCTURALLY ABNORMAL HEMOGLOBINS

SICKLE CELL SYNDROMES

The sickle cell syndromes are caused by a mutation in the β-globin gene that changes the sixth amino acid from glutamic acid to valine. HbS ($\alpha_2\beta_2^{6\ Glu\rightarrow Val}$) polymerizes reversibly when deoxygenated to form a gelatinous network of fibrous polymers that stiffen the RBC membrane, increase viscosity, and cause dehydration due to potassium leakage and calcium influx (Fig. 127-3). These changes also produce the sickle shape. Sickled cells lose the pliability needed to traverse small capillaries. They possess altered "sticky" membranes that are abnormally adherent to the endothelium of small venules. These abnormalities provoke unpredictable episodes of microvascular vasoocclusion and premature RBC destruction (hemolytic anemia). Hemolysis occurs because the spleen destroys the abnormal RBC. The rigid adherent cells clog small capillaries and venules, causing tissue ischemia, acute pain, and gradual end-organ damage. This venoocclusive component usually dominates the clinical course. Prominent manifestations include episodes of ischemic pain (i.e., painful crises) and ischemic malfunction or frank infarction in the spleen, central nervous system, bones, joints, liver, kidneys, and lungs (Fig. 127-3).

Several sickle syndromes occur as the result of inheritance of HbS from one parent and another hemoglobinopathy, such as β thalassemia or HbC ($\alpha_2\beta_2^{6\ Glu\rightarrow Lys}$), from the other parent. The prototype disease, sickle cell anemia, is the homozygous state for HbS (Table 127-2).

Clinical Manifestations of Sickle Cell Anemia Most patients with sickling syndromes suffer from hemolytic anemia, with hematocrits from 15 to 30%, and significant reticulocytosis. Anemia was once thought to exert protective effects against vasoocclusion by reducing blood viscosity. However, natural history and drug therapy trials suggest that an *increase* in the hematocrit and feedback inhibition of reticulocytosis might be beneficial, even at the expense of increased blood viscosity. The role of adhesive reticulocytes in vasoocclusion might account for these paradoxical effects.

Granulocytosis is common. The white count can fluctuate substantially and unpredictably during and between painful crises, infectious episodes, and other intercurrent illnesses.

Vasoocclusion causes protean manifestations. Intermittent episodes of vasoocclusion in connective and musculoskeletal structures produce ischemia manifested by acute pain and tenderness, fever, tachycardia, and anxiety. These recurrent episodes, called *painful crises*, are the most common clinical manifestation. Their frequency and severity vary greatly. Pain can develop almost anywhere in the body and may last from a few hours to 2 weeks. Repeated crises requiring hospitalization (>3 episodes per year) correlate with reduced survival in adult life, suggesting that these episodes are associated with accumulation of chronic end-organ damage. Provocative factors include infection, fever, excessive exercise, anxiety, abrupt changes in temperature, hypoxia, or hypertonic dyes.

Repeated microinfarction can destroy tissues having microvascular beds prone to sickling. Thus, splenic function is frequently lost within the first 18–36 months of life, causing susceptibility to infection, particularly by pneumococci. Acute venous obstruction of the spleen (*splenic sequestration crisis*), a rare occurrence in early childhood, may require emergency transfusion and/or splenectomy to prevent trapping of the entire arterial output in the obstructed spleen. Occlusion of retinal vessels can produce hemorrhage, neovascularization, and eventual detachments. Renal papillary necrosis invariably produces isosthenuria. More widespread renal necrosis leads to renal failure in adults, a common late cause of death. Bone and joint ischemia can lead to aseptic necrosis, especially of the femoral or humeral heads; chronic arthropathy; and unusual susceptibility to osteomyelitis, which may be caused by organisms, such as *Salmonella*, rarely encountered in other settings. The *hand-foot syndrome* is caused by painful infarcts of the digits and dactylitis. Stroke is especially common in children; a small subset tends to suffer repeated episodes. Stroke is less common in adults and is often hemorrhagic. A particularly painful complication in males is priapism, due to infarction of the penile venous outflow tracts; permanent impotence is a frequent consequence. Chronic lower leg ulcers probably arise from ischemia and superinfection in the distal circulation.

Acute chest syndrome is a distinctive manifestation characterized by chest pain, tachypnea, fever, cough, and arterial oxygen desaturation. It can mimic pneumonia, pulmonary emboli, bone marrow infarction and embolism, myocardial ischemia, or in situ lung infarction. Acute chest syndrome is thought to reflect in situ sickling within the lung, producing pain and temporary pulmonary dysfunction. Often it is difficult or impossible to distinguish among other possibilities. Pulmonary infarction and pneumonia are the most frequent underlying or concomitant conditions in patients with this syndrome. Repeated episodes of acute chest pain correlate with reduced survival. Acutely, reduction in arterial oxygen saturation is especially ominous because it promotes sickling on a massive

TABLE 127-2 CLINICAL FEATURES OF SICKLE HEMOGLOBINOPATHIES

Condition	Clinical Abnormalities	Hemoglobin Level, g/L (g/dL)	MCV, fL	Hemoglobin Electrophoresis
Sickle cell trait	None; rare painless hematuria	Normal	Normal	HbS/A: 40/60
Sickle cell anemia	Vasoocclusive crises with infarction of spleen, brain, marrow, kidney, lung; aseptic necrosis of bone; gallstones; priapism; ankle ulcers	70–100 (7–10)	80–100	HbS/A: 100/0 HbF: 2–25%
S/β° thalassemia	Vasoocclusive crises; aseptic necrosis of bone	70–100 (7–10)	60–80	HbS/A: 100/0 HbF: 1–10%
S/β+ thalassemia	Rare crises and aseptic necrosis	100–140 (10–14)	70–80	HbS/A: 60/40
Hemoglobin SC	Rare crises and aseptic necrosis; painless hematuria	100–140 (10–14)	80–100	HbS/A: 50/0 HbC: 50%