- *Mean cell hemoglobin concentration* (MCHC). Higher HbS concentrations increase the probability that aggregation and polymerization will occur during any given period of deoxygenation. Thus, intracellular dehydration, which increases the MCHC, facilitates sickling. Conversely, conditions that decrease the MCHC reduce the disease severity. This occurs when the individual is homozygous for HbS but also has coexistent α-thalassemia, which reduces Hb synthesis and leads to milder disease.
- *Intracellular pH.* A decrease in pH reduces the oxygen affinity of hemoglobin, thereby increasing the fraction of deoxygenated HbS at any given oxygen tension and augmenting the tendency for sickling.
- *Transit time of red cells through microvascular beds.* As will be discussed, much of the pathology of sickle cell disease is related to vascular occlusion caused by sickling within microvascular beds. Transit times in most normal microvascular beds are too short for significant aggregation of deoxygenated HbS to occur, and as a result sickling is confined to microvascular beds with slow transit times. Blood flow is sluggish in the normal spleen and bone marrow, which are prominently affected in sickle cell disease, and also in vascular beds that are inflamed. The movement of blood through inflamed tissues is slowed because of the adhesion of leukocytes to activated endothelial cells and the transudation of fluid through leaky vessels. As a result, inflamed vascular beds are prone to sickling and occlusion.

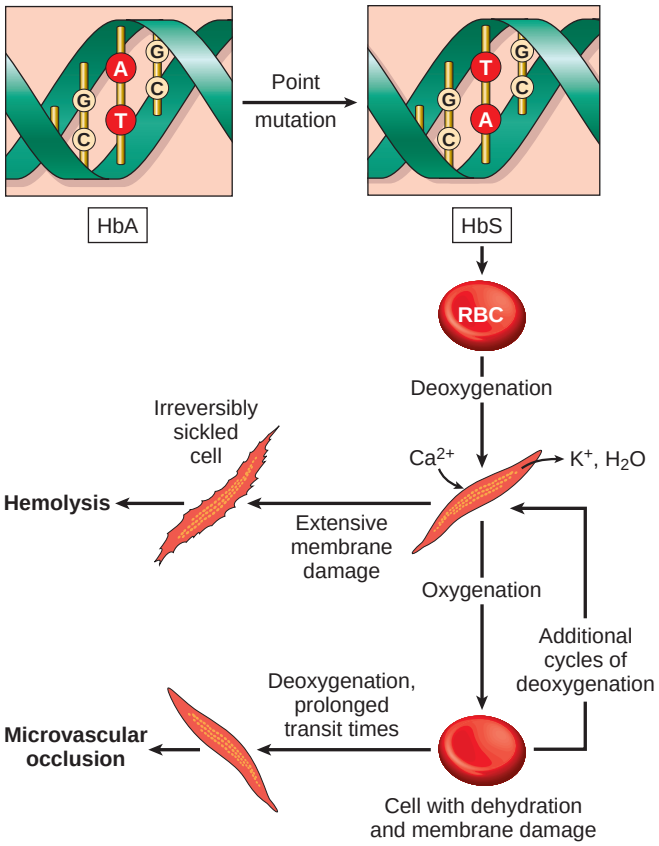

Figure 14-7 Pathophysiology of sickle cell disease.

Sickling causes cumulative damage to red cells through several mechanisms. As HbS polymers grow, they herniate through the membrane skeleton and project from the cell ensheathed by only the lipid bilayer. This severe derangement in membrane structure causes the influx of Ca^{2+} ions, which induce the cross-linking of membrane proteins and activate an ion channel that permits the efflux of K^+ and H_2O. With repeated episodes of sickling, red cells become increasingly dehydrated, dense, and rigid (Fig. 14-7). Eventually, the most severely damaged cells are converted to end-stage, nondeformable, irreversibly sickled cells, which retain a sickle shape even when fully oxygenated. The severity of the hemolysis correlates with the percentage of irreversibly sickled cells, which are rapidly sequestered and removed by mononuclear phagocytes (extravascular hemolysis). Sickled red cells are also mechanically fragile, leading to some intravascular hemolysis as well.

The pathogenesis of the *microvascular occlusions*, which are responsible for the most serious clinical features, is far less certain. Microvascular occlusions are not related to the number of irreversibly sickled cells in the blood, but instead may be dependent upon more subtle red cell membrane damage and local factors, such as inflammation or vasoconstriction, that tend to slow or arrest the movement of red cells through microvascular beds (Fig. 14-7). As mentioned above, sickle red cells express higher than normal levels of adhesion molecules and are sticky. Mediators released from granulocytes during inflammatory reactions up-regulate the expression of adhesion molecules on endothelial cells (Chapter 3) and further enhance the tendency for sickle red cells to get arrested during transit through the microvasculature. The stagnation of red cells within inflamed vascular beds results in extended exposure to low oxygen tension, sickling, and vascular obstruction. Once started, it is easy to envision how a vicious cycle of sickling, obstruction, hypoxia, and more sickling ensues. Depletion of nitric oxide (NO) may also play a part in the vascular occlusions. Free hemoglobin released from lysed sickle red cells can bind and inactivate NO, which is a potent vasodilator and inhibitor of platelet aggregation. The reduction in active NO leads to increased vascular tone (narrowing vessels) and enhances platelet aggregation, both of which may contribute to red cell stasis, sickling, and (in some instances) thrombosis.

MORPHOLOGY

In sickle cell anemia, the peripheral blood demonstrates variable numbers of **irreversibly sickled cells**, reticulocytosis, and target cells, which result from red cell dehydration (Fig. 14-8). **Howell-Jolly bodies** (small nuclear remnants) are also present in some red cells due to the asplenia (see later). The bone marrow is hyperplastic as a result of a compensatory erythroid hyperplasia. Expansion of the marrow leads to bone resorption and secondary new bone formation, resulting in prominent cheekbones and changes in the skull that resemble a "crewcut" on x-ray studies. Extramedullary hematopoiesis can also appear. The increased breakdown of hemoglobin can cause pigment gallstones and hyperbilirubinemia.

In early childhood, the spleen is enlarged up to 500 gm by red pulp congestion, which is caused by the trapping of sickled red cells in the cords and sinuses (Fig. 14-9). With time, however, the chronic erythrostasis leads to splenic infarction,