of heterozygotes under selective pressure from *Plasmodium falciparum*. The HbS gene became associated with five common β-globin gene haplotypes: Benin, Bantu, Senegal, Cameroon, and Arab-Indian. These haplotypes have a loose association with the severity of disease because each haplotype has a different average level of HbF. In some regions of Africa, India, and the Middle East, nearly half the population have sickle cell trait. Nigeria alone has ~150,000 newborns each year with sickle cell anemia, about one-third of the world's total newborns; most die before age 5. Coerced and free population movement have spread the HbS gene throughout the world. The HbS carrier, or sickle cell trait, prevalence is 2–15% in emigrant populations; ~100,000 patients in the United States have sickle cell disease; their death in childhood is rare, with the median age of death in the fifth or sixth decade.

■ PATHOPHYSIOLOGY

Pathophysiologic features of sickle cell disease are summarized in **Fig. 98-3**. HbS is physiologically similar to HbA in most respects except it polymerizes when deoxygenated. Contacts between one of the β^7 valine residues of deoxyHbS and specific amino acid residues of β- and α-globin culminate in fascicles of hemoglobin that injure the sickle erythrocyte. A delay occurs between the initiation of polymerization and the accumulation of sufficient polymer to damage the cell. It is unclear how much polymer is needed for cell injury, but it is clear that polymer leads directly and indirectly to the multiple abnormalities of the sickle erythrocyte that generate the pathophysiology of disease. Prominent among these abnormalities are HbS polymer penetration of the membrane causing vesiculation with membrane microparticle release; increased activity of the Gardos, K/CL cotransport, and P_{sickle} channels that dehydrate the cell, increasing mean corpuscular sickle hemoglobin concentration (MC[HbS]C), reducing cellular deformability, and increasing the polymerization potential of HbS; translocation of amino phospholipids such as phosphatidylserine to the outer leaflet of the membrane; and oxidation of erythrocyte contents. These and other abnormalities lead to the formation of irreversibly sickled cells