FUNCTION OF HEMOGLOBIN

To support oxygen transport, hemoglobin must bind O_2 efficiently at the partial pressure of oxygen (Po_2) of the alveolus, retain it in the circulation, and release it to tissues at the Po_2 of tissue capillary beds. Oxygen acquisition and delivery over a relatively narrow range of oxygen tensions depend on a property inherent in the tetrameric arrangement of heme and globin subunits within the hemoglobin molecule called *cooperativity* or *heme-heme interaction*.

At low oxygen tensions, the hemoglobin tetramer is fully deoxygenated (Fig. 127-2). Oxygen binding begins slowly as O_2 tension rises. However, as soon as some oxygen has been bound by the tetramer, an abrupt increase occurs in the slope of the curve. Thus, hemoglobin molecules that have bound some oxygen develop a higher oxygen affinity, greatly accelerating their ability to combine with more oxygen. This S-shaped oxygen equilibrium curve (Fig. 127-2), along which substantial amounts of oxygen loading *and unloading* can occur over a narrow range of oxygen tensions, is physiologically more useful than the high-affinity hyperbolic curve of individual monomers.

Oxygen affinity is modulated by several factors. The Bohr effect is the ability of hemoglobin to deliver more oxygen to tissues at low pH. It arises from the stabilizing action of protons on deoxyhemoglobin, which binds protons more readily than oxyhemoglobin because the latter is a weaker acid (Fig. 127-2). Thus, hemoglobin has a lower oxygen affinity at low pH. The major small molecule that alters oxygen affinity in humans is 2,3-bisphosphoglycerate (2,3-BPG; formerly 2,3-DPG), which lowers oxygen affinity when bound to hemoglobin. HbA has a reasonably high affinity for 2,3-BPG. HbF does not bind 2,3-BPG, so it tends to have a higher oxygen affinity in vivo. Hemoglobin also binds nitric oxide reversibly; this interaction influences vascular tone, but its clinical relevance remains incompletely understood.

Proper oxygen transport depends on the tetrameric structure of the proteins, the proper arrangement of hydrophilic and hydrophobic amino acids, and interaction with protons or 2,3-BPG.

DEVELOPMENTAL BIOLOGY OF HUMAN HEMOGLOBINS

Red cells first appearing at about 6 weeks after conception contain the embryonic hemoglobins Hb Portland ($\zeta_2\gamma_2$), Hb Gower I ($\zeta_2\varepsilon_2$), and Hb Gower II ($\alpha_2\varepsilon_2$). At 10–11 weeks, fetal hemoglobin (HbF; $\alpha_2\gamma_2$) becomes predominant. The switch to nearly exclusive synthesis of adult hemoglobin (HbA; $\alpha_2\beta_2$) occurs at about 38 weeks (Fig. 127-1). Fetuses and newborns therefore require α-globin but not β-globin for normal gestation. A major advance in understanding the HbF to HbA transition has been the demonstration that the transcription factor Bcl11a plays a pivotal role in its regulation. Small amounts of HbF are produced during postnatal life. A few red cell clones called *F cells* are progeny of a small pool of immature committed erythroid precursors (BFU-e) that retain the ability to produce HbF. Profound erythroid stresses, such as severe hemolytic anemias, bone marrow transplantation, or cancer chemotherapy, cause more of the F-potent BFU-e to be recruited. HbF levels thus tend to rise in some patients with sickle cell anemia or thalassemia. This phenomenon probably explains the ability of hydroxyurea to increase levels of HbF in adults. Agents such as butyrate and histone deacetylase inhibitors can also activate fetal globin genes partially after birth.

GENETICS AND BIOSYNTHESIS OF HUMAN HEMOGLOBIN

The human hemoglobins are encoded in two tightly linked gene clusters; the α-like globin genes are clustered on chromosome 16 and the β-like genes on chromosome 11 (Fig. 127-1). The α-like cluster consists of two α-globin genes and a single copy of the ζ gene. The non-α gene cluster consists of a single ε gene, the Gγ and Aγ fetal globin genes, and the adult δ and β genes.

Important regulatory sequences flank each gene. Immediately upstream are typical promoter elements needed for the assembly of the transcription initiation complex. Sequences in the 5′ flanking region of the γ and the β genes appear to be crucial for the correct developmental regulation of these genes, whereas elements that function like classic enhancers and silencers are in the 3′ flanking regions. The locus control region (LCR) elements located far upstream appear to control the overall level of expression of each cluster. These elements achieve their regulatory effects by interacting with *trans*-acting transcription factors. Some of these factors are ubiquitous (e.g., Sp1 and YY1), while others are more or less limited to erythroid cells or hematopoietic cells (e.g., GATA-1, NFE-2, and EKLF). The LCR controlling the α-globin gene cluster is modulated by a SWI/SNF-like protein called *ATRX*; this protein appears to influence chromatin remodeling and DNA methylation. The association of α thalassemia with mental retardation and myelodysplasia in some families appears to be related to mutations in the ATRX pathway. This pathway also modulates genes specifically expressed during erythropoiesis, such

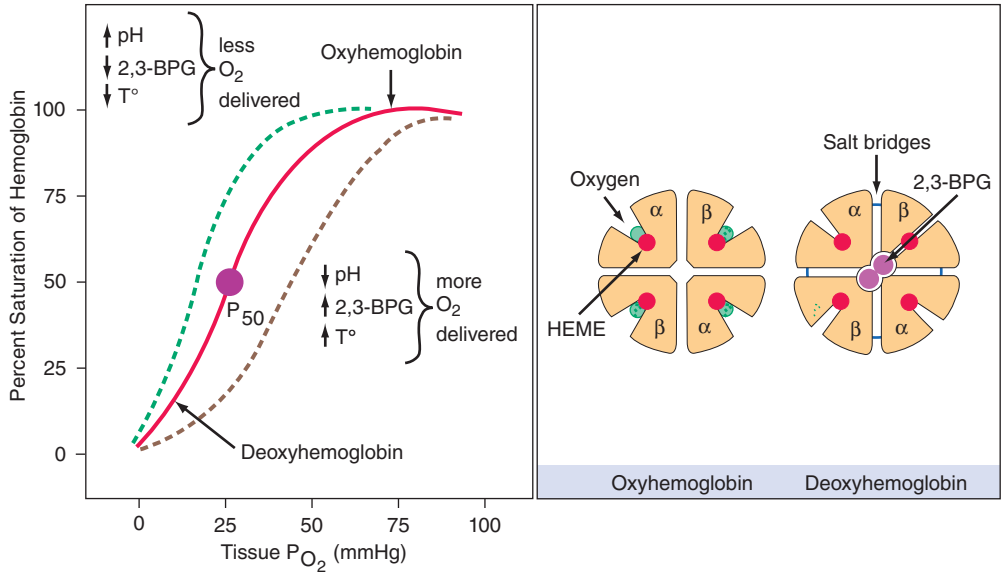

FIGURE 127-2 Hemoglobin-oxygen dissociation curve. The hemoglobin tetramer can bind up to four molecules of oxygen in the iron-containing sites of the heme molecules. As oxygen is bound, 2,3-bisphosphoglycerate (2,3-BPG) and carbon dioxide (CO_2) are expelled. Salt bridges are broken, and each of the globin molecules changes its conformation to facilitate oxygen binding. Oxygen release to the tissues is the reverse process, with salt bridges being formed and 2,3-BPG and CO_2 bound. Deoxyhemoglobin does not bind oxygen efficiently until the cell returns to conditions of higher pH, the most important modulator of O_2 affinity (Bohr effect). When acid is produced in the tissues, the dissociation curve shifts to the right, facilitating oxygen release and CO_2 binding. Alkalosis has the opposite effect, reducing oxygen delivery.