affected by the **partial pressure of O_2 (pO_2)** (through heme-heme interactions), the **pH** of the environment, the partial pressure of CO_2 (**pCO_2**), and the availability of **2,3-bisphosphoglycerate** (**2,3-BPG**). For example, the release of O_2 from Hb is enhanced when the pH is lowered or the pCO_2 is increased (the **Bohr effect**), such as in **exercising muscle**, and the oxygen-dissociation curve of Hb is shifted to the right. To cope long-term with the effects of **chronic hypoxia** or **anemia**, the concentration of **2,3-BPG** in **red blood cells** increases. **2,3-BPG** binds to the Hb and decreases its oxygen affinity. It therefore also shifts the oxygen-dissociation curve to the right. **Carbon monoxide** (**CO**) binds tightly (but reversibly) to the Hb iron, forming **carboxyhemoglobin**. **Hemoglobinopathies** are disorders caused either by production of a **structurally abnormal Hb** molecule; synthesis of **insufficient quantities** of normal Hb subunits, or, rarely, both (Figure 3.25). The sickling diseases **sickle cell anemia** (hemoglobin S disease) and **hemoglobin SC disease** as well as **hemoglobin C disease** and the **thalassemias** are representative hemoglobinopathies that can have severe clinical consequences.

Study Questions

Choose the ONE best answer.

3.1 Which one of the following statements concerning the hemoglobins is correct?

A. HbA is the most abundant hemoglobin in normal adults.
B. Fetal blood has a lower affinity for oxygen than does adult blood because HbF has an increased affinity for 2,3-bisphosphoglycerate.
C. The globin chain composition of HbF is $\alpha_2\delta_2$.
D. HbA_{1c} differs from HbA by a single, genetically determined amino acid substitution.
E. HbA_2 appears early in fetal life.

Correct answer = A. HbA accounts for over 90% of the hemoglobin in a normal adult. If HbA_{1c} is included, the percentage rises to approximately 97%. Because 2,3-bisphosphoglycerate (2,3-BPG) reduces the affinity of hemoglobin for oxygen, the weaker interaction between 2,3-BPG and HbF results in a higher oxygen affinity for HbF relative to HbA. HbF consists of $\alpha_2\gamma_2$. HbA_{1c} is a glycosylated form of HbA, formed nonenzymically in red cells. HbA_2 is a minor component of normal adult hemoglobin, first appearing shortly before birth and rising to adult levels (about 2% of the total hemoglobin) by age 6 months.

3.2 Which one of the following statements concerning the ability of acidosis to precipitate a crisis in sickle cell anemia is correct?

A. Acidosis decreases the solubility of HbS.
B. Acidosis increases the affinity of hemoglobin for O_2.
C. Acidosis favors the conversion of hemoglobin from the taut to the relaxed conformation.
D. Acidosis shifts the oxygen-dissociation curve to the left.
E. Acidosis decreases the ability of 2,3-bisphosphoglycerate to bind to hemoglobin.

Correct answer = A. HbS is significantly less soluble in the deoxygenated form, compared with oxyhemoglobin S. A decrease in pH (acidosis) causes the oxygen-dissociation curve to shift to the right, indicating a decreased affinity for oxygen. This favors the formation of the deoxy, or taut, form of hemoglobin, and can precipitate a sickle cell crisis. The binding of 2,3-bisphosphoglycerate is increased, because it binds only to the deoxy form of hemoglobins.

3.3 Which one of the following statements concerning the binding of oxygen by hemoglobin is correct?

A. The Bohr effect results in a lower affinity for oxygen at higher pH values.
B. Carbon dioxide increases the oxygen affinity of hemoglobin by binding to the C-terminal groups of the polypeptide chains.
C. The oxygen affinity of hemoglobin increases as the percentage saturation increases.
D. The hemoglobin tetramer binds four molecules of 2,3-bisphosphoglycerate.
E. Oxyhemoglobin and deoxyhemoglobin have the same affinity for protons.

Correct answer = C. The binding of oxygen at one heme group increases the oxygen affinity of the remaining heme groups in the same molecule. A rise in pH results in increased affinity for oxygen. Carbon dioxide decreases oxygen affinity because it lowers the pH; moreover, binding of carbon dioxide to the N-termini stabilizes the taut, deoxy form. Hemoglobin binds one molecule of 2,3-bisphosphoglycerate. Deoxyhemoglobin has a greater affinity for protons and, therefore, is a weaker acid.