both protein and calorie deficient, the release of EPO is impaired in proportion to the reduction in metabolic rate; however, the degree of anemia may be masked by volume depletion and becomes apparent after refeeding. Deficiencies in other nutrients (iron, folate) may also complicate the clinical picture but may not be apparent at diagnosis. Changes in the erythrocyte indices on refeeding should prompt evaluation of iron, folate, and B_{12} status.

Anemia in Liver Disease A mild hypoproliferative anemia may develop in patients with chronic liver disease from nearly any cause. The peripheral blood smear may show spur cells and stomatocytes from the accumulation of excess cholesterol in the membrane from a deficiency of lecithin-cholesterol acyltransferase. Red cell survival is shortened, and the production of EPO is inadequate to compensate. In alcoholic liver disease, nutritional deficiencies are common and complicate the management. Folate deficiency from inadequate intake, as well as iron deficiency from blood loss and inadequate intake, can alter the red cell indices.

TREATMENT HYPOPROLIFERATIVE ANEMIAS

Many patients with hypoproliferative anemias experience recovery of normal hemoglobin levels when the underlying disease is appropriately treated. For those in whom such reversals are not possible—such as patients with end-stage kidney disease, cancer, and chronic inflammatory diseases—symptomatic anemia requires treatment. The two major forms of treatment are transfusions and EPO.

TRANSFUSIONS

Thresholds for transfusion should be determined based on the patient's symptoms. In general, patients without serious underlying cardiovascular or pulmonary disease can tolerate hemoglobin levels above 7–8 g/dL and do not require intervention until the hemoglobin falls below that level. Patients with more physiologic compromise may need to have their hemoglobin levels kept above 11 g/dL. Usually, a unit of packed red cells increases the hemoglobin level by 1 g/dL. Transfusions are associated with certain infectious risks (Chap. 138e), and chronic transfusions can produce iron overload. Importantly, the liberal use of blood has been associated with increased morbidity and mortality, particularly in the intensive care setting. Therefore, in the absence of documented tissue hypoxia, a conservative approach to the use of red cell transfusions is preferable.

ERYTHROPOIETIN (EPO)

EPO is particularly useful in anemias in which endogenous EPO levels are inappropriately low, such as CKD or AI. Iron status must be evaluated and iron replaced to obtain optimal effects from EPO. In patients with CKD, the usual dose of EPO is 50–150 U/kg three times a week intravenously. Hemoglobin levels of 10–12 g/dL are usually reached within 4–6 weeks if iron levels are adequate; 90% of these patients respond. Once a target hemoglobin level is achieved, the EPO dose can be decreased. A decrease in hemoglobin level occurring in the face of EPO therapy usually signifies the development of an infection or iron depletion. Aluminum toxicity and hyperparathyroidism can also compromise the response to EPO. When an infection intervenes, it is best to interrupt the EPO therapy and rely on transfusions to correct the anemia until the infection is adequately treated. The dose of EPO needed to correct chemotherapy-induced anemia in patients with cancer is higher, up to 300 U/kg three times a week, and only approximately 60% of patients respond. Because of evidence that there is an increased risk of thromboembolic complications and tumor progression with EPO administration, the risks and benefits of using EPO in such patients must be weighed carefully, and the target hemoglobin should be that necessary to avoid transfusions.

Longer-acting preparations of EPO can reduce the frequency of injections. Darbepoetin alfa, a molecularly modified EPO with additional carbohydrate, has a half-life in the circulation that is three to four times longer than recombinant human EPO, permitting weekly or every other week dosing.

127 Disorders of Hemoglobin

Edward J. Benz, Jr.

Hemoglobin is critical for normal oxygen delivery to tissues; it is also present in erythrocytes in such high concentrations that it can alter red cell shape, deformability, and viscosity. Hemoglobinopathies are disorders affecting the structure, function, or production of hemoglobin. These conditions are usually inherited and range in severity from asymptomatic laboratory abnormalities to death in utero. Different forms may present as hemolytic anemia, erythrocytosis, cyanosis, or vasoocclusive stigmata.

PROPERTIES OF THE HUMAN HEMOGLOBINS

HEMOGLOBIN STRUCTURE

Different hemoglobins are produced during embryonic, fetal, and adult life (Fig. 127-1). Each consists of a tetramer of globin polypeptide chains: a pair of α-like chains 141 amino acids long and a pair of β-like chains 146 amino acids long. The major adult hemoglobin, HbA, has the structure $\alpha_2\beta_2$. HbF ($\alpha_2\gamma_2$) predominates during most of gestation, and HbA_2 ($\alpha_2\delta_2$) is minor adult hemoglobin. Embryonic hemoglobins need not be considered here.

Each globin chain enfolds a single heme moiety, consisting of a protoporphyrin IX ring complexed with a single iron atom in the ferrous state (Fe^{2+}). Each heme moiety can bind a single oxygen molecule; a molecule of hemoglobin can transport up to four oxygen molecules.

The amino acid sequences of the various globins are highly homologous to one another. Each has a highly helical *secondary structure*. Their globular *tertiary structures* cause the exterior surfaces to be rich in polar (hydrophilic) amino acids that enhance solubility, and the interior to be lined with nonpolar groups, forming a hydrophobic pocket into which heme is inserted. The tetrameric *quaternary structure* of HbA contains two αβ dimers. Numerous tight interactions (i.e., $\alpha_1\beta_1$ contacts) hold the α and β chains together. The complete tetramer is held together by interfaces (i.e., $\alpha_1\beta_2$ contacts) between the α-like chain of one dimer and the non-α chain of the other dimer.

The hemoglobin tetramer is highly soluble, but individual globin chains are insoluble. Unpaired globin precipitates, forming inclusions that damage the cell and can trigger apoptosis. Normal globin chain synthesis is balanced so that each newly synthesized α or non-α globin chain will have an available partner with which to pair.

Solubility and reversible oxygen binding are the key properties deranged in hemoglobinopathies. Both depend most on the hydrophilic surface amino acids, the hydrophobic amino acids lining the heme pocket, a key histidine in the F helix, and the amino acids forming the $\alpha_1\beta_1$ and $\alpha_1\beta_2$ contact points. Mutations in these strategic regions tend to be the ones that alter oxygen affinity or solubility.

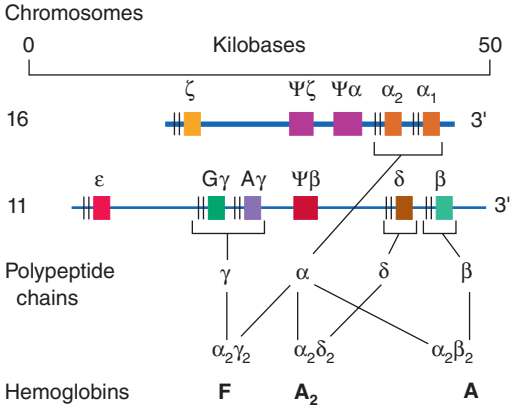

FIGURE 127-1 The globin genes. The α-like genes (α, ζ) are encoded on chromosome 16; the β-like genes (β, γ, δ, ε) are encoded on chromosome 11. The ζ and ε genes encode embryonic globins.