

The laboratory features of HA are related to hemolysis per se and the erythropoietic response of the bone marrow. Hemolysis regularly produces an increase in unconjugated bilirubin and aspartate aminotransferase (AST) in the serum; urobilinogen will be increased in both urine and stool. If hemolysis is mainly intravascular, the telltale sign is hemoglobinuria (often associated with hemosiderinuria); in the serum, there is hemoglobin, lactate dehydrogenase (LDH) is increased, and haptoglobin is reduced. In contrast, the bilirubin level may be normal or only mildly elevated. The main sign of the erythropoietic response by the bone marrow is an increase in reticulocytes (a test all too often neglected in the initial workup of a patient with anemia). Usually the increase will be reflected in both the percentage of reticulocytes (the more commonly quoted figure) and the absolute reticulocyte count (the more definitive parameter). The increased number of reticulocytes is associated with an increased mean corpuscular volume (MCV) in the blood count. On the blood smear, this is reflected in the presence of macrocytes; there is also polychromasia, and sometimes one sees nucleated red cells. In most cases, a bone marrow aspirate is not necessary in the diagnostic workup; if it is done, it will show erythroid hyperplasia. In practice, once an HA is suspected, specific tests will usually be required for a definitive diagnosis of a specific type of HA.

GENERAL PATHOPHYSIOLOGY

The mature red cell is the product of a developmental pathway that brings the phenomenon of differentiation to an extreme. An orderly sequence of events produces synchronous changes, whereby the gradual accumulation of a huge amount of hemoglobin in the cytoplasm (to a final level of 340 g/L, i.e., about 5 mM) goes hand in hand with the gradual loss of cellular organelles and of biosynthetic abilities. In the end, the erythroid cell undergoes a process that has features of apoptosis, including nuclear pyknosis and actual loss of the nucleus. However, the final result is more altruistic than suicidal; the cytoplasmic body, instead of disintegrating, is now able to provide oxygen to all cells in the human organism for some remaining 120 days of the red cell life span.

As a result of this unique process of differentiation and maturation, intermediary metabolism is drastically curtailed in mature red cells (Fig. 129-1); for instance, cytochrome-mediated oxidative phosphorylation has been lost with the loss of mitochondria (through a process of physiologic autophagy); therefore, there is no backup to anaerobic glycolysis, which in the red cell is the only provider of adenosine triphosphate (ATP). Also the capacity of making protein has been lost with the loss of ribosomes. This places the cell's limited metabolic apparatus at risk, because if any protein component deteriorates, it cannot be replaced, as it would be in most other cells; and in fact the activity of most enzymes gradually decreases as red cells age. At the same time, during their long time in circulation, various red cell components inevitably accumulate damage; in senescent red cells, the membrane protein band 3 molecules (see below and Fig. 129-1), having bound hemichromes on their intracellular domains, tend to cluster. Now they bind anti-band 3 IgG antibodies (present in most people) and C3 complement fragments; thus they become opsonized and are eventually removed by phagocytosis in the reticuloendothelial system.

Another consequence of the relative simplicity of red cells is that they have a very limited range of ways to manifest distress under hardship; in essence, any sort of metabolic failure will eventually lead either to structural damage to the membrane or to failure of the cation pump. In either case, the life span of the red cell is reduced, which is the definition of a *hemolytic disorder*. If the rate of red cell destruction exceeds the capacity of the bone marrow to produce more red cells, the hemolytic disorder will manifest as HA.

Thus, the essential pathophysiologic process common to all HAs is an increased red cell turnover; and in many HAs, this is due at least in part to an acceleration of the senescence process described above. The gold standard for proving that the life span of red cells is reduced (compared to the normal value of about 120 days) is a *red cell survival study*, which can be carried out by labeling the red cells with ^{51}Cr and measuring residual radioactivity over several days or weeks; however, this classic test is now available in very few centers, and it is rarely necessary.

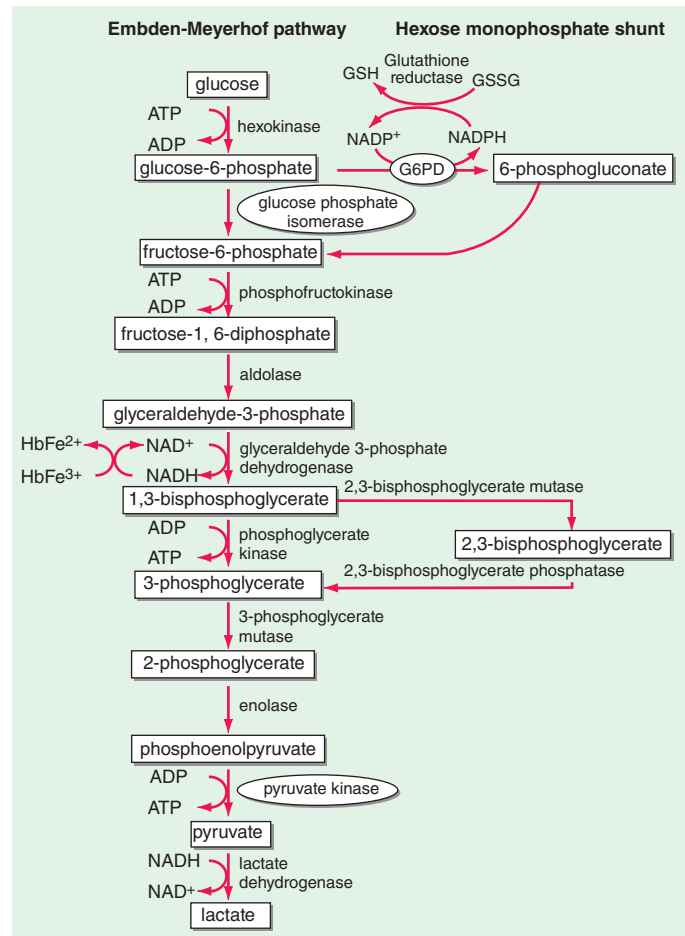


FIGURE 129-1 Red blood cell (RBC) metabolism. The Embden-Meyerhof pathway (glycolysis) generates ATP for energy and membrane maintenance. The generation of NADPH maintains hemoglobin in a reduced state. The hexose monophosphate shunt generates NADPH that is used to reduce glutathione, which protects the red cell against oxidant stress. Regulation of 2,3-bisphosphoglycerate levels is a critical determinant of oxygen affinity of hemoglobin. Enzyme deficiency states in order of prevalence: glucose 6-phosphate dehydrogenase (G6PD) > pyruvate kinase > glucose-6-phosphate isomerase > rare deficiencies of other enzymes in the pathway. The more common enzyme deficiencies are encircled.

If the hemolytic event is transient, it does not usually cause any long-term consequences, except for an increased requirement for erythropoietic factors, particularly folic acid. However, if hemolysis is recurrent or persistent, the increased bilirubin production favors the formation of gallstones. If a considerable proportion of hemolysis takes place in the spleen, as is often the case, splenomegaly may become increasingly a feature, and hypersplenism may develop, with consequent neutropenia and/or thrombocytopenia.

The increased red cell turnover also has metabolic consequences. In normal subjects, the iron from effete red cells is very efficiently recycled by the body; however, with chronic intravascular hemolysis, the persistent hemoglobinuria will cause considerable iron loss, needing replacement. With chronic extravascular hemolysis, the opposite problem, iron overload, is more common, especially if the patient needs frequent blood transfusions. Chronic iron overload will cause secondary hemochromatosis; this will cause damage particularly to the liver, eventually leading to cirrhosis, and to the heart muscle, eventually causing heart failure.

Compensated Hemolysis Versus Hemolytic Anemia Red cell destruction is a potent stimulus for erythropoiesis, which is mediated by erythropoietin (EPO) produced by the kidney. This mechanism is so effective that