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Disorders of Red Blood Cells

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NORMAL RED BLOOD CELL STRUCTURE AND FUNCTION

The red blood cells (RBCs), or erythrocytes, deliver oxygen to all the tissues in the body and carry carbon dioxide back to the lungs for excretion. The erythrocyte is uniquely adapted to these functions. It has a biconcave disk shape that maximizes the membrane surface area for gas exchange, and it has a cytoskeleton and membrane structure that allow it to deform sufficiently to pass through the microvasculature. Passage through capillaries whose diameter may be one fourth the resting diameter of the erythrocyte is made possible by interactions between proteins in the membrane (band 3 and glycophorin) and underlying cytoplasmic proteins that make up the erythrocyte cytoskeleton (spectrin, ankyrin, and protein 4.1).

The mature RBC contains no nucleus and is dependent throughout its life span on proteins synthesized before extrusion of the nucleus and release of the cell from the bone marrow into the peripheral circulation. About 98% of the cytoplasmic protein of the mature erythrocyte is hemoglobin. The remainder is mainly enzymatic proteins, such as those required for anaerobic metabolism and the hexose monophosphate shunt.

Defects in any of the intrinsic structural features of the erythrocyte can result in hemolytic anemia. Abnormalities of the membrane or cytoskeletal proteins are the causes of alterations in erythrocyte shape and flexibility. Inborn defects in the enzymatic pathways for glucose metabolism decrease the resistance to oxidant stress, and inherited abnormalities of hemoglobin structure and synthesis lead to polymerization of abnormal hemoglobin (sickle cell disease) or to the precipitation of unbalanced hemoglobin chains (thalassemia). All of these changes result in decreased erythrocyte survival.

Oxygen is transported by hemoglobin, a tetramer composed of two α chains, two β-like (β, γ, or δ) chains, and four heme molecules, each of which is composed of a protoporphyrin molecule complexed with iron. In fetal life, the main hemoglobin is fetal hemoglobin (HbF: α_2, γ_2); the switch from HbF to adult hemoglobin (HbA: $\alpha_2\beta_2$) occurs in the perinatal period. By 4 to 6 months of age, the level of HbF has fallen to about 1% of total hemoglobin. HbA_2 ($\alpha_2\delta_2$) is a minor adult hemoglobin, representing about 1% of adult hemoglobin (Table 47-1).

CLINICAL PRESENTATION

Anemia, defined as a reduction in RBC mass, is an important sign of disease. It may reflect decreased production of erythrocytes that reflects nutritional deficiencies, primary hematologic disease, or a response to systemic illness. Alternatively, anemia may reflect increased blood loss or cellular destruction from hemolysis. Hemolysis may occur as a result of intrinsic abnormalities of the RBC, immune-mediated RBC destruction, or a systemic vascular process. The investigation of anemia is a critical component of the evaluation of the patient and commonly provides valuable insight into systemic illness. Figure 47-1 provides an overview of the differential diagnosis of anemia.

The symptoms of anemia reflect both the severity and the rapidity with which the reduction in erythrocyte mass has occurred. Patients with acute hemorrhage or massive hemolysis may exhibit symptoms of hypovolemic shock. However, most patients develop anemia more slowly and have few symptoms. Usual complaints are fatigue, decreased exercise tolerance, dyspnea, and palpitations. In patients with coronary artery disease, anemia may precipitate angina. On physical examination, the major sign of anemia is pallor. Patients may be tachycardic and often have audible flow murmurs. Patients with hemolysis often exhibit jaundice and splenomegaly.

LABORATORY EVALUATION

The key components of the laboratory evaluation of anemia are the reticulocyte count, the peripheral blood smear, erythrocyte indices, nutritional studies, and the bone marrow aspirate and biopsy.

The *reticulocyte count* allows the critical distinction between anemia arising from a primary failure of RBC production and anemia resulting from increased RBC destruction or bleeding. Erythrocytes newly released from the marrow still contain small amounts of RNA; these cells, termed *reticulocytes,* can be detected with the use of automated counters and fluorescent nucleic acid–binding dyes or manually by staining of the peripheral blood smear with methylene blue or other supravital stains. In response to the stress of anemia, erythropoietin (EPO) production increases, promoting the production and release of increased numbers of reticulocytes. The number of reticulocytes in the

TABLE 47-1 STRUCTURE AND DISTRIBUTION OF HUMAN HEMOGLOBINS

NAME OF HEMOGLOBIN (Hb)	DISTRIBUTION	STRUCTURE
A	95-98% of adult Hb	$\alpha_2\beta_2$
A_2	1.5-3.5% of adult Hb	$\alpha_2\delta_2$
F	Fetal, 0.5-1.0% of adult Hb	$\alpha_2\gamma_2$
Gower 1	Embryonic	$\zeta_2\varepsilon_2$
Gower 2	Embryonic	$\alpha_2\varepsilon_2$
Portland	Embryonic	$\zeta_2\gamma_2$