Anemias of Diminished Erythropoiesis

Although the anemias that stem from the inadequate production of red cells are heterogeneous, they can be classified into several major categories based on pathophysiology (Table 14-1). The most common and important anemias associated with red cell underproduction are those caused by nutritional deficiencies, followed by those that arise secondary to renal failure and chronic inflammation. Also included are less common disorders that lead to generalized bone marrow failure, such as aplastic anemia, primary hematopoietic neoplasms (Chapter 13), and infiltrative disorders that lead to marrow replacement (e.g., metastatic cancer and disseminated granulomatous disease). We first discuss the extrinsic causes of diminished erythropoiesis, which are more common and clinically important, and then nonneoplastic intrinsic causes.

Megaloblastic Anemias

The common theme among the various causes of megaloblastic anemia is an impairment of DNA synthesis that leads to ineffective hematopoiesis and distinctive morphologic changes, including abnormally large erythroid precursors and red cells. The causes of megaloblastic anemias are given in Table 14-5. The following discussion first describes the common features and then turns to the two principal types: pernicious anemia (the major form of vitamin B_{12} deficiency anemia) and folate deficiency anemia.

Some of the metabolic roles of vitamin B_{12} and folate are considered later. For now it suffices that vitamin B_{12} and folic acid are coenzymes required for the synthesis of thymidine, one of the four bases found in DNA. A deficiency of these vitamins or impairment in their metabolism results in defective nuclear maturation due to deranged or inadequate DNA synthesis, with an attendant delay or block in cell division.

Table 14-5 Causes of Megaloblastic Anemia

Vitamin B_{12} Deficiency
Decreased Intake
Inadequate diet, vegetarianism
Impaired Absorption
Intrinsic factor deficiency
Pernicious anemia
Gastrectomy
Malabsorption states
Diffuse intestinal disease (e.g., lymphoma, systemic sclerosis)
Ileal resection, ileitis
Competitive parasitic uptake
Fish tapeworm infestation
Bacterial overgrowth in blind loops and diverticula of bowel
Folic Acid Deficiency
Decreased Intake
Inadequate diet, alcoholism, infancy
Impaired Absorption
Malabsorption states
Intrinsic intestinal disease
Anticonvulsants, oral contraceptives
Increased Loss
Hemodialysis
Increased Requirement
Pregnancy, infancy, disseminated cancer, markedly increased hematopoiesis
Impaired Utilization
Folic acid antagonists
Unresponsive to Vitamin B_{12} or Folic Acid Therapy
Metabolic Inhibitors of DNA Synthesis and/or Folate Metabolism (e.g., Methotrexate)

Modified from Beck WS: Megaloblastic anemias. In Wyngaarden JB, Smith LH (eds): Cecil Textbook of Medicine, 18th ed. Philadelphia, WB Saunders, 1988, p. 900.

MORPHOLOGY

Certain peripheral blood findings are shared by all megaloblastic anemias. The presence of red cells that are macrocytic and oval **(macro-ovalocytes)** is highly characteristic. Because they are larger than normal and contain ample hemoglobin, most macrocytes lack the central pallor of normal red cells and even appear "hyperchromic," but the MCHC is not elevated. There is marked variation in the size (anisocytosis) and shape (poikilocytosis) of red cells. The reticulocyte count is low. Nucleated red cell progenitors occasionally appear in the circulating blood when anemia is severe. Neutrophils are also larger than normal (macropolymorphonuclear) and show **nuclear hypersegmentation**, having five or more nuclear lobules instead of the normal three to four (Fig. 14-16).

The marrow is usually markedly hypercellular as a result of increased hematopoietic precursors, which often completely replace the fatty marrow. **Megaloblastic changes** are detected at all stages of erythroid development**.** The most primitive cells (promegaloblasts) are large, with a deeply basophilic cytoplasm, prominent nucleoli, and a distinctive, fine nuclear chromatin pattern (Fig. 14-17). As these cells differentiate and begin to accumulate hemoglobin, the nucleus retains its finely distributed chromatin and fails to develop the clumped pyknotic chromatin typical of normoblasts. While nuclear maturation is delayed, cytoplasmic maturation and hemoglobin accumulation proceed at a normal pace, leading to nuclear-to-cytoplasmic asynchrony. Because DNA synthesis is impaired in all proliferating cells, granulocytic precursors also display dysmaturation in the form of **giant metamyelocytes and band forms**. Megakaryocytes, too, can be abnormally large and have bizarre, multilobate nuclei.

The marrow hyperplasia is a response to increased levels of growth factors, such as erythropoietin. However, the derangement in DNA synthesis causes most precursors to undergo apoptosis in the marrow (an example of ineffective hematopoiesis) and leads to pancytopenia. The anemia is further exacerbated by a mild degree of red cell hemolysis of uncertain etiology.

Anemias of Vitamin B_{12} Deficiency: Pernicious Anemia

Pernicious anemia is a specific form of megaloblastic anemia caused by an autoimmune gastritis that impairs the production of intrinsic factor, which is required for vitamin B_{12} uptake from the gut.

Normal Vitamin B_{12} Metabolism. Vitamin B_{12} is a complex organometallic compound also known as cobalamin. Under normal circumstances humans are totally dependent on dietary vitamin B_{12}. Microorganisms are the source of cobalamin in the food chain. Plants and vegetables contain little cobalamin, save that contributed by microbial