deposition in endocrine organs, resulting in liver dysfunction, diabetes, and other endocrine abnormalities.

The most frequent cause of iron deficiency is occult blood loss. All men and postmenopausal women who are found to be iron deficient should have an evaluation for a source of gastrointestinal blood loss, regardless of the detection of occult blood. In premenopausal women, iron deficiency is most frequently related to loss of iron with menstruation (about 15 mg per month) and during pregnancy (about 900 mg per pregnancy). *Helicobacter pylori* infection can cause iron deficiency even in the absence of intestinal bleeding. Dietary deficiency of iron is most commonly seen in multiparous women of childbearing age, in young children whose growth outstrips their intake of iron, and in babies who drink mostly milk at the expense of an intake of iron-containing foods.

Laboratory Evaluation

As previously stated, early iron deficiency does not exhibit the hallmark microcytosis and hypochromia that characterize classic iron deficiency. Evaluation of the blood smear in advanced iron deficiency often demonstrates hypochromic RBCs, target cells, and pencil-shaped elongated cells. Iron deficiency is frequently associated with reactive thrombocytosis.

The mainstay of the diagnosis of iron deficiency is the peripheral blood iron indices. These include iron concentration, total iron-binding capacity (TIBC), transferrin saturation, and ferritin concentration. The transferrin saturation is the ratio of serum iron to transferrin concentration; it is normally at least 20%. Iron deficiency results in a decrease in serum iron and an increase in iron-binding capacity, decreasing this ratio to less than 10%. Chronic inflammatory conditions (e.g., infection, inflammation, malignancy) often decrease both iron and TIBC, but the transferrin saturation usually remains above 20%. The ferritin level is a reflection of total-body iron stores. The liver synthesizes ferritin in proportion to total-body iron, and a level of less than 12 ng/mL strongly supports a diagnosis of iron deficiency. Unfortunately, ferritin is an acute phase reactant, and levels rise in the setting of fever, inflammatory disease, infection, or other stresses. However, ferritin levels in response to stress do not often rise above 100 ng/mL, and levels higher than 100 ng/mL usually rule out iron deficiency.

If the indirect measurement of iron indices does not definitively confirm or refute a diagnosis of iron deficiency, a therapeutic trial of iron supplementation may be considered. Alternatively, a bone marrow examination can be performed to provide a direct assessment of marrow iron stores. Presence of iron in the marrow excludes iron deficiency anemia because marrow iron stores will be depleted before there is any fall in RBC production resulting from iron deficiency; conversely, complete absence of marrow iron confirms the diagnosis of iron deficiency.

Treatment

Oral iron supplementation, with administration of ferrous sulfate or ferrous gluconate two or three times daily, is the treatment for iron deficiency. Patients should be educated about the potential gastrointestinal side effects, including diarrhea or constipation, and some may benefit from a gradual increase in the dose based on tolerance. Iron should be administered for several months after resolution of anemia to allow for the reconstitution of iron stores.

In patients with malabsorption, a complete inability to tolerate oral iron, or iron demands that outstrip replacement with oral supplements, parenteral iron may be administered. The parenteral administration of iron, especially iron dextran, has been associated with anaphylaxis. However, newer preparations such as sodium ferric gluconate, iron sucrose, ferumoxytol, and ferric carboxymaltose are significantly safer. As previously stated, all male patients and postmenopausal women with iron deficiency require evaluation for a source of gastrointestinal bleeding.

Macrocytic Anemias

Two categories of hypoproductive macrocytic anemias exist: megaloblastic anemias and nonmegaloblastic macrocyctic anemias. Megaloblastic anemias arise from a failure of DNA synthesis and result in lack of synchrony between the maturation of the nucleus and the cytoplasm of hematopoietic cells. Nonmegaloblastic macrocytic anemias usually reflect membrane abnormalities resulting from defects in cholesterol metabolism and are most commonly found in patients with advanced liver disease or severe hypothyroidism. Reticulocytosis greater than 10% causes an elevated MCV on automated blood counts because reticulocytes are larger than mature RBCs.

Megaloblastic Anemias

Megaloblastic anemias result from a block in the synthesis of critical nucleotide precursors of DNA, which leads to a cell cycle arrest in S phase. Cytoplasmic maturation occurs, but maturation of the nucleus is arrested. Cells take on a bizarre appearance, with large immature nuclei surrounded by more mature-appearing cytoplasm. Interference with DNA synthesis affects all rapidly dividing cells, so patients with megaloblastic syndromes often have pancytopenia and gastrointestinal symptoms such as diarrhea and malabsorption. In women, megaloblastic changes of the cervical mucosa occur and may cause abnormal results on Papanicolaou smears. The most common causes of megaloblastic anemia are deficiencies of vitamin B_{12} or folate, medications that inhibit DNA synthesis or that block folate metabolism, and myelodysplasia.

Cobalamin Deficiency

Cobalamin (vitamin B_{12})is absorbed from animal protein in the diet. The process of cobalamin absorption and metabolism is complex because cobalamin is always bound to other proteins. In the stomach, protein-bound vitamins are released by digestion with pepsin and are bound to haptocorrin (transcobalamin I). Within the proximal duodenum, pancreatic proteases digest cobalamin away from haptocorrin, and cobalamin binds to intrinsic factor (IF), also known as transcobalamin III. IF is secreted by the parietal cells of the stomach and mediates absorption of cobalamin through the cubam receptor in the distal ileum. Within the ileal mucosal cell, the IF-cobalamin complex is again digested, and cobalamin is released into the plasma bound to haptocorrin and transcobalamin II.

Within the cell, cobalamin is a cofactor for two intracellular enzymes, L-methylmalonyl–coenzyme A (CoA) mutase and homocysteine-methionine methyltransferase (Fig. 47-3).