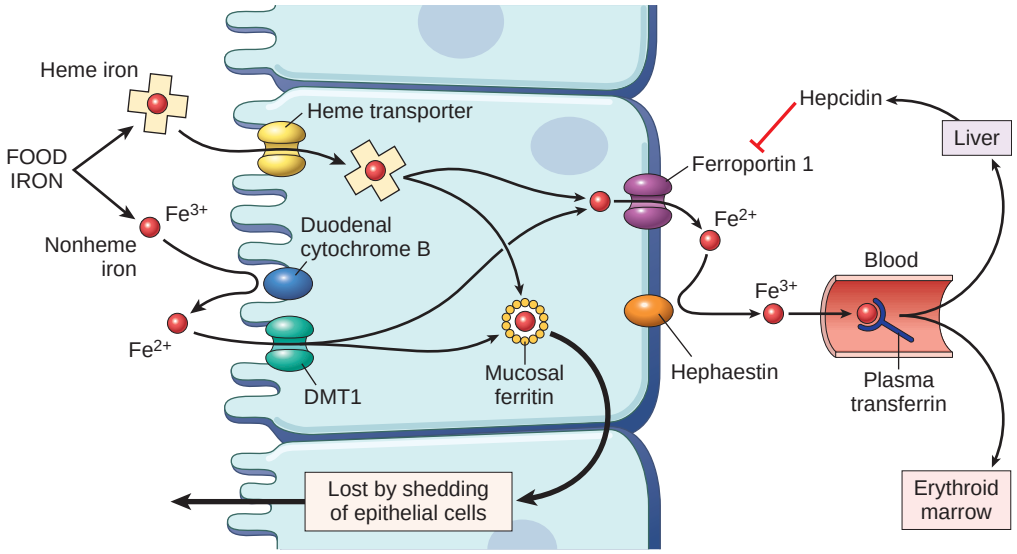

Figure 14-22 Regulation of iron absorption. Duodenal epithelial cell uptake of heme and nonheme iron is depicted. When the storage sites of the body are replete with iron and erythropoietic activity is normal, plasma hepcidin levels are high. This leads to down-regulation of ferroportin and trapping of most of the absorbed iron, which is lost when duodenal epithelial cells are shed into the gut. Conversely, when body iron stores decrease or when erythropoiesis is stimulated, hepcidin levels fall and ferroportin activity increases, allowing a greater fraction of the absorbed iron to be transferred to plasma transferrin. *DMT1*, Divalent metal transporter 1.

- As will be described subsequently, the *anemia of chronic disease* (perhaps more accurately referred to as the anemia of chronic inflammation) is caused in part by inflammatory mediators that increase hepatic hepcidin production.
- A rare form of microcytic anemia is caused by mutations that disable TMPRSS6, a hepatic transmembrane serine protease that normally suppresses hepcidin production when iron stores are low. Affected patients have high hepcidin levels, resulting in reduced iron absorption and failure to respond to iron therapy.
- Conversely, hepcidin activity is inappropriately low in both primary and secondary *hemochromatosis*, a syndrome caused by systemic iron overload.
- Secondary hemochromatosis can occur in diseases associated with *ineffective erythropoiesis*, such as β-thalassemia major and myelodysplastic syndromes (Chapter 13). Through incompletely understood mechanisms, ineffective erythropoiesis suppresses hepatic hepcidin production, even when iron stores are high. As discussed in Chapter 18, the various inherited forms of primary hemochromatosis are associated with mutations in hepcidin or the genes that regulate hepcidin expression.

Etiology. **Iron deficiency can result from (1) dietary lack, (2) impaired absorption, (3) increased requirement, or (4) chronic blood loss.** To maintain a normal iron balance, about 1 mg of iron must be absorbed from the diet every day. Because only 10% to 15% of ingested iron is absorbed, the daily iron requirement is 7 to 10 mg for adult men and 7 to 20 mg for adult women. Because the average daily dietary intake of iron in the Western world is about 15 to 20 mg, most men ingest more than adequate iron, whereas many women consume marginally adequate amounts of iron. The bioavailability of dietary iron is as important as the overall content. Heme iron is much more absorbable than inorganic iron, the absorption of which is influenced by other dietary contents. Absorption of inorganic iron is enhanced by ascorbic acid, citric acid, amino acids, and sugars in the diet, and inhibited by tannates (found in tea), carbonates, oxalates, and phosphates.

Dietary lack is rare in developed countries, where on average about two thirds of the dietary iron is in the readily absorbed heme form provided by meat. The situation is different in developing countries, where food is less abundant and most iron in the diet is found in plants in the poorly absorbable inorganic form. Dietary iron inadequacy occurs in even privileged societies in the following groups:

- *Infants*, who are at high risk due to the very small amounts of iron in milk. Human breast milk provides only about 0.3 mg/L of iron. Cow's milk contains about twice as much iron, but its bioavailability is poor.
- *The impoverished*, who can have suboptimal diets for socioeconomic reasons at any age
- *Older adults*, who often have restricted diets with little meat because of limited income or poor dentition
- *Teenagers* who subsist on "junk" food

Impaired absorption is found in sprue, other causes of fat malabsorption (steatorrhea), and chronic diarrhea. Gastrectomy impairs iron absorption by decreasing the acidity of the proximal duodenum (which enhances uptake), and also by increasing the speed with which gut contents pass through the duodenum. Specific items in the diet, as is evident from the preceding discussion, can also affect absorption.

Increased requirement is an important cause of iron deficiency in growing infants, children, and adolescents, as well as premenopausal women, particularly during pregnancy. Economically deprived women having multiple, closely spaced pregnancies are at exceptionally high risk.

Chronic blood loss is the most common cause of iron deficiency in the Western world. External hemorrhage or bleeding into the gastrointestinal, urinary, or genital tracts depletes iron reserves. Iron deficiency in adult men and postmenopausal women in the Western world must be