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TREATMENT Marfan and Loeys-Dietz Syndromes Patients should be advised that vascular risks are increased by severe physical exertion, smoking, emotional stress, and pregnancy. Low-level moderate aerobic exercise and limits on isometric exercise are recommended. Prophylactic beta blocker and/or angiotensin II receptor blocker therapy are prescribed in normotensive individuals, and blood pressure control is important for those with hypertension. Surgical correction of the aorta, aortic valve, and mitral valve has been successful in many patients, but tissues are frequently friable. The scoliosis tends to be progressive, and surgical stabilization may be required. Dislocated lenses rarely require surgical removal, but patients should be followed closely for retinal detachment. Acknowledgment Darwin J. Prockop and John F. Bateman contributed to this chapter in the 20th edition and some material from that chapter has been retained here. ■ ■ **FURTHER READING** Besio R et al: Bone biology: Insights from osteogenesis imperfecta and related rare fragility syndrome. *FEBS J* 286:3033, 2019. De Backer J et al: Genetic testing for aortopathies: Primer for the nongeneticist. *Curr Opin Cardiol* 34:585, 2019. Jovanovic M et al: Osteogenesis imperfecta: Mechanisms and signaling pathways connecting classical and rare OI types. *Endocr Rev* 12:61, 2022. Loeys BL et al: The revised Ghent nosology for the Marfan syndrome. *J Med Genet* 47:476, 2010. Malfait F et al: The Ehlers-Danlos syndromes. *Nat Rev Dis Primers* 6:64, 2020. Marini JC et al: Osteogenesis imperfecta. *Nat Rev Dis Primers* 3:17052, 2017. Marzin P, Cormier-Daire V: New perspectives on the treatment of skeletal dysplasia. *Ther Adv Endocrinol Metab* 11:2042018820904016, 2020. Unger S et al: Nosology and classification of genetic skeletal disorders: 2023 revision. *Am J Med Genet A* 191:1164, 2023. Darrell H. G. Crawford, David M. Frazer

Hemochromatosis ■ ■ **DEFINITION** Hemochromatosis is a relatively common inherited disorder of iron metabolism more prevalent in European populations. It is now known to be an iron-storage disorder with underlying genetic heterogeneity that, in nearly all cases, causes inappropriately high cellular release of iron from iron exporting cells such as enterocytes and macrophages. The increase in intestinal iron absorption results in the deposition of excess iron in parenchymal cells with eventual cellular injury, tissue fibrosis, and organ failure. Cirrhosis of the liver, diabetes mellitus, arthritis, cardiomyopathy, and hypogonadotropic hypogonadism are the most important clinical consequences. The term hemochromatosis describes the unique genetic clinical/pathologic condition with features of increased serum transferrin saturation, iron overload in the liver but not the spleen, prevalent involvement of periportal hepatocytes with iron sparing of Kupffer

cells, and/or signs and symptoms of iron overload. These characteristics should occur in the absence of a primary/predominant red blood cell disorder to distinguish hemochromatosis from other iron overload conditions, which are also often genetic in origin.

The condition is most often caused by a mutation in the homeostatic iron regulator (HFE) gene, which is tightly linked to the HLA-A locus on chromosome 6p. Persons who are homozygous for the mutation are at increased risk of iron overload and account for 80–90% of hemo chromatosis in persons of northern European descent. In such subjects, the presence of hepatic fibrosis, cirrhosis, arthropathy, or hepatocel lular carcinoma constitutes iron overload-related disease. Rarer forms of non-HFE hemochromatosis are caused by mutations in other genes involved in iron metabolism (Table 426-1). The disease is now often diagnosed during its early stages when iron overload and organ dam age are minimal. Hemochromatosis CHAPTER 426 Secondary iron overload occurs as a result of an iron-loading anemia, such as thalassemia or sideroblastic anemia, in which erythropoiesis is ineffective and causes increased intestinal iron absorption. In the acquired iron-loading disorders, massive iron deposits in parenchy mal tissues can lead to the same clinical and pathologic features as in hemochromatosis. ■ ■PREVALENCE The prevalence of HFE-associated hemochromatosis mutations varies among different ethnic groups. It is most common in populations of northern European extraction in whom ~1 in 10 persons are hetero zy gous carriers and 0.3–0.5% are homozygotes, with even higher per centages in some Celtic populations such as those residing in Ireland and Brittany. The expression of the disease is variable and modified by several factors, especially alcohol consumption, dietary iron intake, blood loss associated with menstruation and pregnancy, and blood donation. Recent population studies indicate that ~40% of homozy gous men develop iron overload-related complications and about 6% develop hepatic cirrhosis. For women, iron overload-related complica tions occur in ~10%. In addition, there are as yet unidentified modify ing genes responsible for variable disease expression. Nearly 70% of untreated patients develop the first symptoms between ages 40 and 60. The disease is rarely evident before age 20, although with family screening (see “Screening for Hemochromatosis,” below) and periodic

TABLE 426-1 Classification of Iron Overload States

Hereditary Hemochromatosis	Hemochromatosis, HFE-related (type 1)	C282Y homozygosity	C282Y/H63D compound heterozygosity
Hemochromatosis, non-HFE-related	Juvenile hemochromatosis (type 2A) (hemojuvelin mutations)	Juvenile hemochromatosis (type 2B) (hepcidin mutation)	Mutated transferrin receptor 2, TFR2 (type 3)
Mutated ferroportin 1 gene, SLC40A1 (type 4)	Acquired Iron Overload	Iron-loading anemias	Thalassemia major
Sideroblastic anemia	Chronic hemolytic anemias	Transfusional and parenteral iron	Chronic liver disease
Hepatitis C	Alcoholic cirrhosis, especially when advanced	Nonalcoholic steatohepatitis	Porphyria cutanea tarda
Dysmetabolic iron overload syndrome	Post-portacaval shunting overload	Dietary iron overload	Miscellaneous
Iron overload in sub-Saharan Africa	Neonatal iron overload	Aceruloplasminemia	Congenital atransferrinemia

health examinations, asymptomatic subjects with iron overload can be identified, including young menstruating women.

Mutations in other genes involved in iron metabolism are respon sible for non-HFE-associated hemochromatosis. In contrast to HFE-associated hemochromatosis, the non-HFE-associated forms of hemochromatosis (Table 426-1) are rare, but they affect all populations and may affect young people (juvenile hemochromatosis). These con ditions result from mutations in one or more of the genes encoding proteins in the hepcidin pathway (Fig. 426-1), including hepcidin, hemojuvelin, and transferrin receptor 2 (TFR2). The resultant clinical disease is very similar to HFE-related disease because they all lead to hepcidin deficiency via a final common pathway (Fig. 426-1).

PART 12 Endocrinology and Metabolism A rare autosomal dominant form of hemochromatosis results from two types of mutations in the gene for the iron transporter ferroportin. Loss-of-function mutations

decrease the cell surface localization of ferroportin in certain tissues, thereby reducing its ability to export iron ("ferroportin disease") and causing cellular iron retention, particularly DCYTB DMT1 Liver FPN Heph TMPRSS6 Villus HFE/TFR1 TFR2 Crypt Hepcidin Duodenum

FIGURE 426-1 Pathways of normal iron homeostasis. Dietary inorganic iron traverses the brush border membrane of duodenal enterocytes via divalent metal-ion transporter 1 (DMT1) after reduction of ferric (Fe^{3+}) iron to the ferrous (Fe^{2+}) state by intestinal ferrireductases such as duodenal cytochrome B (DCYTB). Iron then moves from the enterocyte to the circulation via a process requiring the basolateral iron exporter ferroportin (FPN) and the iron oxidase hephaestin (Heph). In the circulation, iron binds to plasma transferrin and is thereby distributed to sites of iron utilization and storage. Much of the diferric transferrin supplies iron to immature erythrocyte cells in the bone marrow for hemoglobin synthesis. At the end of their life, senescent red blood cells (RBCs) are phagocytosed by macrophages, and iron is returned to the circulation after export through ferroportin. The liver-derived peptide hepcidin represses basolateral iron transport in the gut as well as iron released from macrophages and other cells and serves as a central regulator of body-iron traffic. At least two separate signals regulate hepcidin production in response to changes in body-iron requirements. The first involves the detection of circulating diferric transferrin by HFE and TFR2. A second relies on hepatic iron stores activating the hemojuvelin (HJV)-dependent bone morphogenetic protein (BMP)/SMAD pathway. This pathway is modified by erythroferrone released from erythroid precursor cells, which binds to BMP6 and inhibits its function. TMPRSS6 is a protease that regulates hepcidin production, possibly by modulating HJV activity. Heme is metabolized by heme oxygenase within the enterocytes, and the released iron then follows the same pathway. Mutations in the genes encoding HFE, TFR2, HJV, and hepcidin all lead to decreased hepcidin release and increased iron absorption, resulting in hemochromatosis (Table 426-1).

in macrophages. A second mutation abolishes the hepcidin-induced ferroportin internalization and degradation resulting in a "gain of function." Here the tissue iron distribution is similar to that in HFE-related disease (e.g., in parenchymal cells).

GENETIC BASIS The most common mutation in the HFE gene is a homozygous G to A transition that leads to a cysteine to tyrosine substitution at position 282 (C282Y) of the HFE protein. It has been identified in 85–90% of patients with hereditary hemochromatosis in populations of northern European descent but is found in only 60% of cases from Mediterranean populations. A second, relatively common HFE variant (H63D) results in a substitution of aspartic acid for histidine at residue 63 of the HFE protein. Homozygosity for H63D is not associated with clinically significant iron overload. Some compound heterozygotes (i.e., one copy each of C282Y and H63D) have mild to moderately increased body-iron stores but develop clinical disease only in association with Plasma Transferrin Bone marrow Erythroferrone RBC FPN BMP6 HJV BMPR Macrophage Hepcidin P ? SMAD P P Hepcidin

cofactors such as heavy alcohol intake or hepatic steatosis. HFE-associated hemochromatosis is inherited as an autosomal recessive trait, and heterozygotes have no, or minimal, increase in iron stores. However, this slight increase in hepatic iron can act as a cofactor that may modify the expression of other diseases such as porphyria cutanea tarda (PCT) or metabolic dysfunction associated steatohepatitis (MASH).

PATHOPHYSIOLOGY AND THE

ROLE OF HEPCIDIN Normally, the body-iron content of 3–4 g is maintained as a result of intestinal mucosal absorption of iron being equal to iron loss. This amount is ~1 mg/d in men and 1.5 mg/d in menstruating women. In hemochromatosis, intestinal iron absorption is greater than body

requirements and amounts to ≥ 4 mg/d. The progressive accumulation of iron increases plasma iron concentration and saturation of transferrin and results in a progressive increase of plasma ferritin (Fig. 426-2). Hepcidin is a key regulatory hormone that allows the bone marrow and other tissues to communicate their iron requirements. It was called hepcidin based upon its antibacterial activity ("HEPatic bacterioCIDal protein"). This liver-derived peptide represses basolateral iron export from intestinal enterocytes and iron release from macrophages and other cells by binding to ferroportin. Hepcidin, in turn, responds to signals in the liver mediated by HFE, TFR2, and hemojuvelin (Fig. 426-1). The development of hepcidin agonists represents a promising new therapeutic approach for iron overload disorders caused by low hepcidin levels. The HFE gene encodes a 343-amino-acid protein that is structurally related to MHC class I proteins. The basic defect in HFE-associated hemochromatosis is a lack of cell surface expression of HFE (due to the C282Y mutation). The normal (wild-type) HFE protein forms a complex with $\beta 2$ -microglobulin and transferrin receptor 1 (TFR1), and the C282Y mutation completely abrogates this interaction. As a result, the mutant HFE protein remains trapped intracellularly. Although the precise function of HFE at the cell surface is not known, mutations in this protein reduce hepcidin production leading to increased dietary iron absorption (Fig. 426-1). In advanced disease, the body may contain 20 g or more of iron, which is deposited mainly in parenchymal cells of the liver, pancreas, and heart. Iron deposition in the pituitary

Serum ferritin concentration ($\mu\text{g/L}$)

Age (yrs.)

Cirrhosis, organ failure Progressive tissue injury Increased total body iron Increased hepatic iron Increased serum iron Increased iron absorption

FIGURE 426-2 Sequence of events in genetic hemochromatosis and their correlation with the serum ferritin concentration. Increased iron absorption is present throughout life. Overt, symptomatic disease usually develops between ages 40 and 60, but latent disease can be detected long before this.

causes hypogonadotropic hypogonadism in both men and women. Tissue injury results from disruption of iron-laden lysosomes, lipid peroxidation of subcellular organelles by excess iron, and stimulation of collagen synthesis by activated hepatic stellate cells.

Secondary iron overload with iron deposition in parenchymal cells occurs in chronic disorders of erythropoiesis, particularly in those with defects in hemoglobin synthesis and ineffective erythropoiesis such as sideroblastic anemia and thalassemia (Chap. 103). In these disorders, iron absorption is increased. Moreover, these patients require blood transfusions and are frequently treated inappropriately with iron. PCT, a disorder characterized by a defect in porphyrin biosynthesis (Chap. 428), can also be associated with excessive parenchymal iron deposits. The magnitude of the iron load in PCT is usually insufficient to produce tissue damage. However, some patients with PCT also have mutations in the HFE gene, and some have associated hepatitis C virus (HCV) infection. Although the relationship between these disorders remains to be clarified, iron overload accentuates the inherited enzyme deficiency in PCT and should be avoided along with other agents (alcohol, estrogens, halo aromatic compounds) that may exacerbate PCT. Another cause of hepatic parenchymal iron overload is hereditary aceruloplasminemia. In this disorder, impairment of iron mobilization due to deficiency of ceruloplasmin (a ferroxidase) causes iron

overload in hepatocytes and a range of other cell types. Hemochromatosis CHAPTER 426 Excessive iron ingestion over many years rarely results in hemochromatosis. An important exception has been reported in South Africa among groups who brew fermented beverages in vessels made of iron. Hemochromatosis has been described in apparently normal persons who have taken medicinal iron over many years, but such individuals probably had genetic disorders. The common denominator in all patients with hemochromatosis is excessive amounts of iron in parenchymal tissues. Parenteral administration of iron in the form of blood transfusions or iron preparations results predominantly in reticuloendothelial cell iron overload. This appears to lead to less tissue damage than iron loading of parenchymal cells. In the liver, parenchymal iron is in the form of ferritin and hemosiderin. In the early stages, these deposits are seen in the periportal parenchymal cells, especially within lysosomes in the pericanalicular cytoplasm of the hepatocytes. This stage progresses to perilobular fibrosis and the formation of fibrous septa due to activation of hepatic stellate cells. In the advanced stage, a macronodular or mixed macro- and micronodular cirrhosis develops. The underlying hepatic iron concentration is an important determinant of the risk of the development of hepatic fibrosis and cirrhosis. Histologically, iron is increased in many organs, particularly in the liver, heart, and pancreas, and, to a lesser extent, in the endocrine glands. The epidermis of the skin is thin, and melanin is increased in the cells of the basal layer and dermis. Deposits of iron are present around the synovial lining cells of the joints. ■ ■CLINICAL MANIFESTATIONS C282Y homozygotes can be characterized by their stage in the progression of disease as follows: (1) a genetic predisposition without biochemical or clinical abnormalities; (2) iron overload without symptoms; (3) iron overload with symptoms (e.g., arthritis and fatigue); and (4) iron overload with organ damage—in particular, cirrhosis. Many subjects with significant iron overload are asymptomatic. For example, in a study of 672 asymptomatic C282Y homozygous subjects (identified by either family screening or routine health examinations), there was hepatic iron overload (grades 2–4) in 56% and 34.5% of male and female subjects, respectively, hepatic fibrosis (stages 2–4) in 18.4% and 5.4%, respectively, and cirrhosis in 5.6% and 1.9%, respectively. Normal range Initial symptoms of hemochromatosis are often nonspecific and include lethargy, arthralgia, skin pigmentation, loss of libido, and features of diabetes mellitus. Hepatomegaly, increased pigmentation, spider angiomas, splenomegaly, arthropathy, ascites, cardiac arrhythmias, congestive heart failure, loss of body hair, testicular atrophy, and jaundice are prominent in advanced disease.

Hepatocellular carcinoma develops in ~30% of patients with cirrhosis, and it is the most common cause of death in treated patients with cirrhosis—hence the importance of early diagnosis and therapy. The incidence increases with age, it is more common in men, and it occurs almost exclusively in cirrhotic patients.

Excessive skin pigmentation is present in patients with advanced disease. The characteristic metallic or slate-gray hue is sometimes referred to as bronzing and results from increased melanin and iron in the dermis. Pigmentation usually is diffuse and generalized. Diabetes mellitus occurs in ~65% of patients with advanced disease and is more likely to develop in those with a family history of diabetes, suggesting that direct damage to the pancreatic islets by iron deposition occurs in combination with other risk factors. The management is similar to that of other forms of diabetes. PART 12 Endocrinology and Metabolism Arthropathy develops in 25–50% of symptomatic patients. It usually occurs after age 50 but may occur as a first manifestation or long after therapy. The joints of the hands, especially the second and third metacarpophalangeal joints, are usually the

first joints involved, a feature that helps to distinguish the chondrocalcinosis associated with hemochromatosis from the idiopathic form (Chap. 384). A progressive polyarthritides involving the wrists, hips, ankles, and knees may also ensue. Acute attacks of synovitis may be associated with deposition of calcium pyrophosphate (chondrocalcinosis or pseudogout), mainly in the knees. Radiologic manifestations include cystic changes of the subchondral bones, loss of articular cartilage with narrowing of the joint space, diffuse demineralization, hypertrophic bone proliferation, and calcification of the synovium. The arthropathy tends to progress despite removal of iron by phlebotomy. Although the relation of these abnormalities to iron metabolism is not known, the fact that similar changes occur in other forms of iron overload suggests that iron is directly involved. Cardiac involvement is the presenting manifestation in ~15% of symptomatic patients. The most common manifestation is congestive heart failure, which occurs in ~10% of young adults with the disease, especially those with juvenile hemochromatosis. Symptoms of congestive heart failure may develop suddenly, with rapid progression to death if untreated. The heart is diffusely enlarged. This may be misdiagnosed as idiopathic cardiomyopathy if other overt manifestations are absent. Cardiac arrhythmias include premature supraventricular beats, paroxysmal tachyarrhythmias, atrial flutter, atrial fibrillation, and varying degrees of atrioventricular block. Hypogonadism occurs in both sexes and may antedate other clinical features. Manifestations include loss of libido, impotence, amenorrhea, testicular atrophy, gynecomastia, and sparse body hair. These changes are primarily the result of decreased production of gonadotropins due to impairment of hypothalamic-pituitary function by iron deposition. ■ ■

DIAGNOSIS The association of (1) hepatomegaly, (2) skin pigmentation, (3) diabetes mellitus, (4) heart disease, (5) arthritis, and (6) hypogonadism should suggest the diagnosis. However, as stated above, significant iron overload may exist with none or only some of these manifestations. Therefore, a high index of suspicion is needed to make the diagnosis

TABLE 426-2
Representative Iron Values in Normal Subjects, Patients with Hemochromatosis, and Patients with Alcoholic Liver Disease

	Normal	Plasma iron, $\mu\text{mol/L}$ ($\mu\text{g/dL}$)	9–27 (50–150)	32–54 (180–300)	Usually elevated	Elevated or normal	Often elevated
Total iron-binding capacity, $\mu\text{mol/L}$ ($\mu\text{g/dL}$)	45–66 (250–370)	36–54 (200–300)	36–54 (200–300)	Normal	45–66 (250–370)	Transferrin saturation, %	22–45
50–100	50–100	Normal or elevated	27–60	Serum ferritin, $\mu\text{g/L}$	1000–6000	200–500	Usually <500
10–500	Men 20–250	Women 15–150	Liver iron, $\mu\text{g/g}$ dry wt	300–1400	6000–18,000	2000–4000	300–3000
300–2000	Hepatic iron index	<1.0					

“ 2 1.5–2 <2 <2

early. Treatment before permanent organ damage occurs can reverse the iron toxicity and restore life expectancy to normal. The history should be particularly detailed in regard to disease in other family members and should include information on alcohol ingestion; iron intake; and ingestion of large doses of ascorbic acid, which promotes iron absorption (Chap. 344). Appropriate tests should be performed to exclude iron deposition due to hematologic disease. The presence of liver, pancreatic, cardiac, and joint disease should be confirmed by physical examination, radiography, and standard function tests of these organs. The degree of increase in total body iron stores can be assessed by (1) measurement of serum iron and the percent saturation of transferrin (or the unsaturated iron-binding capacity), (2) measurement of serum ferritin concentration, (3) liver

biopsy with measurement of the iron concentration (Table 426-2), and (4) magnetic resonance imaging (MRI) of the liver to quantify hepatic iron stores. In addition, a retrospective assessment of body-iron storage is also provided by performing weekly phlebotomy and calculating the amount of iron removed before iron stores are exhausted (1 mL blood = ~0.5 mg iron). Each of these methods for assessing iron stores has advantages and limitations. The serum iron level and percent saturation of transferrin are elevated early in the course, but their specificity is reduced by significant false-positive and false-negative rates. For example, serum iron concentration may be increased in patients with alcoholic liver disease without iron overload (Table 426-2). In otherwise healthy persons, a fasting serum transferrin saturation >45% is abnormal and suggests homozygosity for hemochromatosis. The serum ferritin concentration is used as an index of body-iron stores, whether decreased or increased. In fact, an increase of 1 µg/L in serum ferritin level reflects an increase of ~8–10 mg in body stores. In most untreated patients with hemochromatosis, the serum ferritin level is significantly increased (Fig. 426-2 and Table 426-2), and a serum ferritin level >1000 µg/L is a strong predictor of cirrhosis among individuals homozygous for the C282Y mutation. However, in patients with hepatic necroinflammatory conditions such as alcoholic liver disease and metabolic dysfunction-associated steatotic liver disease, acute hepatocellular necrosis, or systemic inflammatory conditions, serum ferritin levels may be elevated out of proportion to body iron stores due to increased release from tissues. Therefore, a repeat determination of serum ferritin should be carried out after acute hepatocellular damage has subsided (e.g., in alcoholic liver disease). Ordinarily, the combined measurements of the percent transferrin saturation and serum ferritin level provide a simple and reliable screening test for hemochromatosis, including the precirrhotic phase of the disease. If either of these tests is abnormal, genetic testing for hemochromatosis should be performed (Fig. 426-3). The role of liver biopsy in the diagnosis and management of hemochromatosis has been reassessed as a result of the widespread availability of genetic testing for the C282Y mutation. The absence of severe fibrosis can be accurately predicted in most patients using clinical and biochemical variables. Thus, there is virtually no risk of severe fibrosis in a C282Y homozygous subject with (1) serum ferritin level HOMOZYGOTES WITH EARLY, ASYMPTOMATIC HEMOCHROMATOSIS HETEROZYGOTES ALCOHOLIC LIVER DISEASE

Subjects with unexplained liver disease Adult first-degree relative of patient with HH Individual with suggestive symptoms (see text) Reassure, possibly retest later Transferrin saturation and serum ferritin* TS <45% SF <300 TS ≥45% and/or SF >300 µg/L Normal Counsel and consider non-HFE hemochromatosis HFE genotype C282Y Homozygote C282Y/H63D (compound heterozygote) Serum ferritin >300–1000 µg/L LFT normal Serum ferritin

“ 1000 µg/L and/or LFT abnormal Serum ferritin <300 µg/L LFT normal Observe, retest in 1–2 years No iron overload Investigate and treat as appropriate Liver biopsy Confirmed iron overload Phlebotomy *For convenience both genotype and phenotype (iron tests) can be performed together at a single visit in first-degree relatives. FIGURE 426-3 Algorithm for screening for HFE-associated hemochromatosis. HH, hereditary hemochromatosis, homozygous subject (C282Y +/+); LFT, liver function test; SF, serum ferritin concentration; TS, transferrin saturation. <1000 µg/L, (2) normal serum alanine aminotransferase

values, (3) no hepatomegaly, and (4) no excess alcohol intake. However, it should be emphasized that liver biopsy is the most reliable method for establishing or excluding the presence of hepatic cirrhosis, which is the critical factor determining prognosis and the risk of developing hepatocellular carcinoma. Biopsy also permits histochemical estimation of tissue iron and measurement of hepatic iron concentration. Serum tests for liver fibrosis and transient elastography can guide decisions about the need for liver biopsy in affected patients. Increased density of the liver due to iron deposition can be demonstrated by computed tomography (CT) or MRI, and with improved technology, MRI can accurately determine hepatic iron concentration. ■

■ **SCREENING FOR HEMOCHROMATOSIS** When the diagnosis of hemochromatosis is established, it is important to counsel and screen other family members (Chap. 480). Asymptomatic and symptomatic family members with the disease usually have an increased saturation of transferrin and an increased serum ferritin concentration. These changes occur even before iron stores are greatly increased (Fig. 426-2). All adult first-degree relatives of patients with hemochromatosis should be tested for the C282Y and H63D mutations and counseled appropriately (Fig. 426-3). In affected individuals, it is important to confirm or exclude the presence of cirrhosis and begin therapy as early as possible. For children of an identified proband, testing for HFE mutations in the other parent is helpful because if normal, the child is an obligate heterozygote and at no risk. Otherwise, for practical purposes, children need not be checked before they are 18 years old. The role of population screening for hemochromatosis is controversial. Recent studies indicate that it is highly effective for primary care physicians to screen subjects using transferrin saturation and serum ferritin levels. Such screening also detects iron deficiency. Genetic screening of the normal population is feasible but remains controversial in terms of cost-effectiveness.

TREATMENT Hemochromatosis The therapy of hemochromatosis involves removal of the excess body iron and supportive treatment of damaged organs. Iron removal is best accomplished by weekly or, with gross iron loading, twice-weekly phlebotomy of 500 mL. Although there is an initial modest decline in the volume of packed red blood cells to about 35 mL/dL, the level stabilizes after several weeks. The plasma transferrin saturation remains increased until the available iron stores are depleted. In contrast, the plasma ferritin concentration falls progressively, reflecting the gradual decrease in body-iron stores. One 500mL unit of blood contains 200–250 mg of iron, and ≥ 25 g of iron may have to be removed. Therefore, in patients with advanced disease, weekly phlebotomy may be required for 1–2 years, and it should be continued until the serum ferritin level is ≤ 100 μ g/L. Thereafter, phlebotomies are performed at appropriate intervals to maintain ferritin levels at ≤ 100 μ g/L. The transferrin saturation fluctuates and may still be elevated but should not dictate further therapy unless it is persistently at 100% when free unbound iron may circulate. Usually, one phlebotomy every 3 months will suffice. It is important, however, not to overtreat and render the patient iron deficient. Hemochromatosis CHAPTER 426 Chelating agents such as deferoxamine, when given parenterally, remove 10–20 mg of iron per day, which is much less than that mobilized by once-weekly phlebotomy. Phlebotomy is also less expensive, more convenient,

and safer for most patients. However, chelating agents may be indicated when anemia or hypoproteinemia is severe enough to preclude phlebotomy. Effective oral iron chelating agents, deferasirox (Exjade) and deferiprone, are now available. These agents are effective in thalassemia and secondary iron overload but are expensive and carry the risk of significant side effects. Alcohol consumption should be severely curtailed or eliminated because it increases the risk of cirrhosis in hereditary hemochromatosis nearly tenfold. Dietary adjustments are unnecessary, although vitamin C and iron supplements should be avoided. The management of hepatic failure, cardiac failure, and diabetes mellitus is similar to conventional therapy for these conditions. Loss of libido and change in secondary sex characteristics are managed with testosterone replacement or gonadotropin therapy (Chap. 403). End-stage liver disease may be an indication for liver transplantation, although results are improved if the excess iron can be removed beforehand. The available evidence indicates that the fundamental metabolic abnormality in hemochromatosis is reversed by successful liver transplantation. ■ ■

PROGNOSIS The principal causes of death are cardiac failure, hepatocellular failure, or portal hypertension and hepatocellular carcinoma. Life expectancy is improved by removal of excessive iron stores and maintenance of these stores at near-normal levels. The 5-year survival rate with therapy increases from 33 to 89%. With repeated phlebotomy, the liver decreases in size, liver function improves, pigmentation of skin decreases, and cardiac failure may be reversed. Diabetes improves in ~40% of patients, but removal of excess iron has little effect on hypogonadism or arthropathy. Hepatic fibrosis may decrease, and cirrhosis may regress with adequate phlebotomy therapy. Hepatocellular carcinoma occurs as a late sequela in patients who are cirrhotic at presentation. The apparent increase in its incidence in treated patients is probably related to their increased life span. Hepatocellular carcinoma rarely develops if the disease is treated in the precirrhotic stage. Indeed, the life expectancy of homozygotes treated before the development of cirrhosis is normal. The importance of family screening and early diagnosis and treatment cannot be overemphasized. Asymptomatic individuals detected by family studies should have phlebotomy therapy if iron stores are moderately to severely increased. Assessment of iron stores at appropriate intervals is also important. With this management approach, most manifestations of the disease can be prevented.

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