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 about 15% of symptomatic patients. The most common manifestation is congestive heart failure, which occurs in about 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. Adrenal insufficiency, hypothyroidism, and hypoparathyroidism are rare manifestations.

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 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; alcohol ingestion; iron intake; and ingestion of large doses of ascorbic acid, which promotes iron absorption (Chap. 96e). 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 and calculation of the hepatic iron index (Table 428-2), and (4) magnetic resonance imaging (MRI) of the liver. 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 = approximately 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; in this situation, however, the hepatic iron index is usually not increased as in hemochromatosis (Table 428-1). In otherwise healthy persons, a fasting serum transferrin saturation greater than 45% is abnormal and suggests homozygosity for hemochromatosis.

The serum ferritin concentration is usually a good 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 about 5 mg in body stores. In most untreated patients with hemochromatosis, the serum ferritin level is significantly increased (Fig. 428-2 and Table 428-1), and a serum ferritin level >1000 μg/L is the strongest predictor of disease expression among individuals homozygous for the C282Y mutation. However, in patients with inflammation and hepatocellular necrosis, 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. 428-3).

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 less than 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 only 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. Increased density of the liver due to iron deposition can be demonstrated by computed tomography (CT) or MRI, and with improved technology, MRI has become more accurate in determining hepatic iron concentration.

SCREENING FOR HEMOCHROMATOSIS

When the diagnosis of hemochromatosis is established, it is important to counsel and screen other family members (Chap. 84). 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 the iron stores are greatly increased (Fig. 428-2). All adult first-degree relatives of patients with hemochromatosis should be tested for the C282Y and H63D mutations and counseled appropriately (Fig. 428-3). 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* of the other parent is helpful because if

TABLE 428-2 REPRESENTATIVE IRON VALUES IN NORMAL SUBJECTS, PATIENTS WITH HEMOCHROMATOSIS, AND PATIENTS WITH ALCOHOLIC LIVER DISEASE

Determination	Normal	Symptomatic Hemochromatosis	Homozygotes with Early, Asymptomatic Hemochromatosis	Heterozygotes	Alcoholic Liver Disease
Plasma iron, μmol/L (μg/dL)	9–27 (50–150)	32–54 (180–300)	Usually elevated	Elevated or normal	Often elevated
Total iron-binding capacity, μmol/L (μg/dL)	45–66 (250–370)	36–54 (200–300)	36–54 (200–300)	Elevated or normal	45–66 (250–370)
Transferrin saturation, %	22–45	50–100	50–100	Normal or elevated	27–60
Serum ferritin, μg/L		1000–6000	200–500	Usually <500	10–500
Men	20–250				
Women	15–150				
Liver iron, μg/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