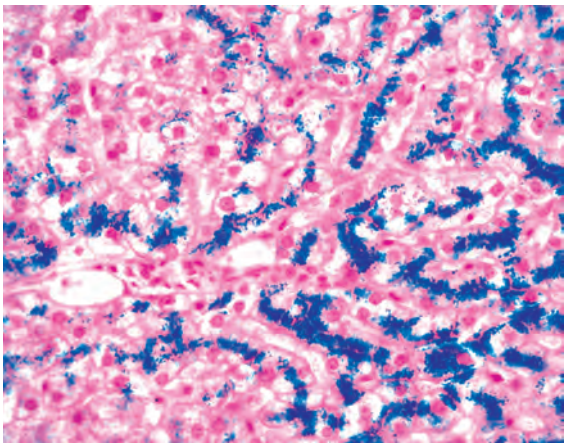

Figure 18-25 Hereditary hemochromatosis. In this Prussian blue-stained section, hepatocellular iron appears blue. The parenchymal architecture is normal.

content. In normal individuals, the iron content of liver tissue is less than 1000 μg per gram dry weight of liver. Adult patients with hereditary hemochromatosis exhibit more than 10,000 μg iron per gram dry weight; hepatic iron concentrations in excess of 22,000 μg per gram dry weight are associated with the development of fibrosis and cirrhosis. However, **with newly available genetic testing for these diseases, quantitative assessment of tissue iron content is no longer necessary for confirmation of a suspected diagnosis.**

The **pancreas** becomes intensely pigmented, has diffuse interstitial fibrosis, and may exhibit some parenchymal atrophy. Hemosiderin is found in both the acinar and the islet cells, and sometimes in the interstitial fibrous stroma. The **heart** is often enlarged and has hemosiderin granules within the myocardial fibers, producing a striking brown coloration to the myocardium. A delicate interstitial fibrosis may appear.

Although skin pigmentation is partially attributable to hemosiderin deposition in dermal macrophages and fibroblasts, most of the pigmentation results from increased epidermal melanin production, the mechanism of which in unknown. The combination of these pigments imparts a characteristic slate-gray color to the skin. With hemosiderin deposition in the synovial joint linings, an **acute synovitis** may develop. Excessive deposition of calcium pyrophosphate damages the articular cartilage, producing a disabling polyarthritis referred to as **pseudogout**. The **testes may be small and atrophic**, secondary to a derangement in the hypothalamic-pituitary axis resulting in reduced gonadotropin and testosterone levels.

Clinical Features. **The principal manifestations of classic hemochromatosis include hepatomegaly, abdominal pain, abnormal skin pigmentation (particularly in sun-exposed areas), deranged glucose homeostasis or diabetes mellitus due to destruction of pancreatic islets, cardiac dysfunction (arrhythmias, cardiomyopathy), and atypical arthritis.** In some patients, the presenting complaint is hypogonadism (e.g., amenorrhea in the female, impotence and loss of libido in the male). It is more often a disease of males, for reasons described earlier, and rarely becomes evident before age 40. The classic tetrad of cirrhosis with hepatomegaly, abnormal skin pigmentation, diabetes mellitus, and cardiac dysfunction might not develop until late in the course of the disease. Death may result from cirrhosis or cardiac disease. *A significant cause of death is hepatocellular carcinoma; the risk is 200-fold greater than in the general population.* Treatment for iron overload does not fully remove the cancer risk presumably because of DNA alterations that occur prior to the time of diagnosis and treatment initiation.

Fortunately, hemochromatosis can be diagnosed long before irreversible tissue damage has occurred. Screening involves demonstration of very high levels of serum iron and ferritin, exclusion of secondary causes of iron overload, and liver biopsy if indicated. *Screening of family members of probands is important.* Heterozygotes also accumulate excessive iron, but not to a level that causes significant tissue damage. Currently most patients with hemochromatosis are diagnosed in the subclinical, precirrhotic stage due to routine serum iron measurements (as part of other diagnostic workup). Treatment by regular phlebotomy steadily depletes tissue iron stores. With treatment, life expectancy is normal.

Neonatal hemochromatosis (also called congenital hemochromatosis) is a disease of unknown origin manifested by severe liver disease and extrahepatic hemosiderin deposition. Neonatal hemochromatosis is not an inherited disease; liver injury, leading to hemosiderin accumulation, occurs in utero, and might be related to maternal alloimmune injury to the fetal liver. Extrahepatic hemosiderin deposition, detected by buccal biopsy, needs to be documented for the correct diagnosis. There is no specific treatment, except for supportive care and liver transplantation in severe cases.

The most common causes of secondary (or acquired) hemochromatosis are disorders associated with ineffective erythropoiesis, such as severe forms of thalassemia (Chapter 14) and myelodysplastic syndromes (Chapter 13). In these disorders, the excess iron results not only from transfusions, but also from increased absorption. Transfusions alone, when given repeatedly over a period of years (e.g., in patients with chronic hemolytic anemias), can also lead to systemic hemosiderosis and parenchymal organ injury.

Cirrhosis caused by chronic liver diseases in which hepatitis is the predominant form of injury (e.g., chronic viral hepatitis, autoimmune hepatitis) can lead to diminished hepcidin production from loss of hepatocyte mass and, therefore, to cirrhosis-associated increased iron uptake from the gut. However, the increase in stainable iron in alcoholic cirrhosis, cannot be readily explained by decrease in hepcidin production alone. It is suspected that other, yet to be discovered, mechanisms are involved.

Wilson Disease

Wilson disease is an autosomal recessive disorder caused by mutation of the *ATP7B* gene, resulting in impaired copper excretion into bile and a failure to incorporate copper into ceruloplasmin. This disorder is marked by the accumulation of toxic levels of copper in many tissues and organs, principally the liver, brain, and eye. Normally, 40% to 60% of ingested copper (2 to 5 mg/day) is absorbed in