TABLE 367e-4 PHYSICAL FINDINGS IN HEREDITARY HEMOCHROMATOSIS

Finding	%
Hepatomegaly	60–85
Cirrhosis	50–95
Skin pigmentation	40–80
Arthritis (second, third metacarpophalangeal joints)	40–60
Clinical diabetes	10–60
Splenomegaly	10–40
Loss of body hair	10–30
Testicular atrophy	10–30
Dilated cardiomyopathy	0–30

TREATMENT HEREDITARY HEMOCHROMATOSIS

Treatment of HH is relatively straightforward with weekly phlebotomy aimed to reduce iron stores, recognizing that each unit of blood contains 200–250 mg of iron. If patients are diagnosed and treated before the development of hepatic fibrosis, all complications of the disease can be avoided. Maintenance phlebotomy is required in most patients and usually can be achieved with 1 unit of blood removed every 2–3 months. Family studies should be performed with transferrin saturation, ferritin, and genetic testing offered to all first-degree relatives.

Wilson's Disease Wilson's disease is an inherited disorder of copper homeostasis first described in 1912 (Chap. 429). The Wilson's disease gene was discovered in 1993, with the identification of *ATP7B*. This P-type ATPase is involved in copper transport and is necessary for the export of copper from the hepatocyte. Thus, in patients with mutations in *ATP7B*, copper is retained in the liver, leading to increased copper storage and ultimately liver disease as a result.

The clinical presentation of Wilson's disease is variable and includes chronic hepatitis, hepatic steatosis, and cirrhosis in adolescents and young adults. Neurologic manifestations indicate that liver disease is present and include speech disorders and various movement disorders. Diagnosis includes the demonstration of a reduced ceruloplasmin level, increased urinary excretion of copper, the presence of Kayser-Fleischer rings in the corneas of the eyes, and an elevated hepatic copper level, in the appropriate clinical setting. The genetic diagnosis of Wilson's disease is difficult because >500 mutations in *ATP7B* have been described with different degrees of frequency and penetration in certain populations.

TREATMENT WILSON'S DISEASE

Treatment consists of copper-chelating medications such as D-penicillamine and trientine. A role for zinc acetate has also been established. Medical treatment is lifelong, and severe relapses leading to liver failure and death can occur with cessation of therapy. Liver transplantation is curative with respect to the underlying metabolic defect and restores the normal phenotype with respect to copper homeostasis.

α_1 Antitrypsin Deficiency α_1AT deficiency was first described in the late 1960s in patients with severe pulmonary disease. α_1AT is a 52-kDa glycoprotein produced in hepatocytes, phagocytes, and epithelial cells in the lungs, which inhibits serine proteases, primarily neutrophil elastase. In α_1AT deficiency, increased amounts of neutrophil elastase can result in progressive lung injury from degradation of elastin, leading to premature emphysema. In the 1970s, α_1AT deficiency was discovered as a cause of neonatal liver disease, so-called "neonatal hepatitis." It is now known to be a cause of liver disease in infancy, early childhood, and adolescence, and in adults.

In α_1AT deficiency, variants in the proteinase inhibitor (Pi) gene located on chromosome 14 alter α_1AT structure, interfering with hepatocellular export. Aggregated, deformed polymers of α_1AT accumulate in the hepatocyte endoplasmic reticulum. There are over 75 different α_1AT variants. Conventional nomenclature identifies normal variants as PiMM; these individuals have normal blood levels of α_1AT. The most common abnormal variants are called S and Z. Individuals homozygous for the Z mutation (PiZZ) have low levels of α_1AT (about 15% of normal), and these patients are susceptible to liver and/or lung disease, yet only a proportion (about 25%) of PiZZ patients develop disease manifestations. Null variants have undetectable levels of α_1AT and are susceptible to premature lung disease.

α_1AT deficiency has been identified in all populations; however, the disorder is most common in patients of northern European and Iberian descent. The disorder affects about 1 in 1500 to 2000 individuals in North America. The natural history of α_1AT deficiency is quite variable because many individuals with the PiZZ variant never develop disease, whereas others can develop childhood cirrhosis leading to liver transplantation.

In adults, the diagnosis often comes in the course of evaluation of patients with abnormal liver test abnormalities or in a workup for cirrhosis. A hint to diagnosis may be coexistent lung disease at a relatively young age or a family history of liver and/or lung disease. Patients may have symptoms of pulmonary disease with cough and dyspnea. Liver disease may be asymptomatic other than fatigue, or patients may present with complications of decompensated liver disease.

Diagnosis of α_1AT deficiency is confirmed by blood tests showing reduced levels of serum α_1AT, accompanied by Pi determinations. Most patients with liver disease have either PiZZ or PiSZ; occasionally, patients with PiMZ have reduced levels of α_1AT, but they usually do not have a low enough level to cause disease. Liver biopsy is often performed to determine stage of hepatic fibrosis and shows characteristic PAS-positive, diastase-resistant globules in the periphery of the hepatic lobule.

TREATMENT α_1 ANTITRYPSIN DEFICIENCY

Treatment of α_1AT deficiency is usually nonspecific and supportive. For patients with liver involvement, other sources of liver injury, such as alcohol, should be avoided. Evidence for other liver diseases (e.g., viral hepatitis B and C, hemochromatosis, NAFLD) should be sought and treated if possible. Smoking can worsen lung disease progression in α_1AT deficiency and should be discontinued. Patients with lung disease may be eligible to receive infusions of α_1AT, which has been shown to halt further damage to the lungs. If liver disease becomes decompensated, transplantation should be pursued and is curative. Following transplant, patients express the Pi phenotype of the donor. Finally, risk of hepatocellular carcinoma is significantly increased in patients with cirrhosis due to α_1AT deficiency.

Cystic Fibrosis CF should also be considered as an inherited form of chronic liver disease, although the principal manifestations of CF include chronic lung disease and pancreatic insufficiency (Chap. 313). A small percentage of patients with CF who survive to adulthood have a form of biliary cirrhosis characterized by cholestatic liver enzyme abnormalities and the development of chronic liver disease. Ursodeoxycholic acid is occasionally helpful in improving liver test abnormalities and in reducing symptoms. The disease is slowly progressive.

METABOLIC LIVER DISEASES

Nonalcoholic Fatty Liver Disease NAFLD and NASH are common liver diseases causing abnormal liver test results and progressing to cirrhosis. **NAFLD and NASH are discussed in detail in Chap. 364.**

Lipid Storage Diseases There are a number of rare lipid storage diseases that involve the liver, including the inherited disorders of Gaucher's disease and Niemann-Pick disease (Chap. 433e). Other rare disorders