the duodenum and proximal small intestine, and is transported to the portal circulation complexed with albumin and histidine. Free copper dissociates and is taken up by hepatocytes. In the liver copper binds to an α_2-globulin (apoceruloplasmin) to form *ceruloplasmin*, which is secreted into the blood. Excess copper is transported into the bile. Ceruloplasmin accounts for 90% to 95% of plasma copper. Circulating ceruloplasmin is eventually desialylated, endocytosed by the liver, and degraded within lysosomes, after which the released copper is excreted into bile. This degradation/excretion pathway is the primary route for copper elimination. The estimated total body copper is only 50 to 150 mg.

Pathogenesis. Wilson disease results from mutations in the *ATP7B* gene. Located on chromosome 13, the *ATP7B* gene, encodes a transmembrane copper-transporting ATPase, expressed on the hepatocyte canalicular membrane. More than 300 mutations in the *ATP7B* gene have been identified, but not all cause the disease. *The overwhelming majority of patients are compound heterozygotes containing different mutations on each ATP7B allele.* The overall frequency of mutated alleles is 1:100, and the prevalence of the disease is approximately 1:30,000 to 1:50,000 (approximately 9000 patients in the United States). Deficiency in the ATP7B protein causes a decrease in copper transport into bile, impairs its incorporation into ceruloplasmin, and inhibits ceruloplasmin secretion into the blood. These changes cause copper accumulation in the liver and a decrease in circulating ceruloplasmin. The accumulated copper causes toxic liver injury by three mechanisms: 1) Promoting the formation of free radicals by the Fenton reaction (Chapter 2); 2) binding to sulfhydryl groups of cellular proteins; and 3) displacing other metals from hepatic metalloenzymes. Although there is a latent period of variable duration, there may be sudden onset of a severe systemic illness. This is triggered by spillage of non–ceruloplasmin-bound copper from the liver into the circulation, causing hemolysis and pathologic changes at other sites such as the brain, corneas, kidneys, bones, joints, and parathyroids. Concomitantly, urinary excretion of copper markedly increases from its normal miniscule levels.

MORPHOLOGY

The liver often bears the brunt of injury, but the disease may also present as a neurologic disorder. The hepatic changes are variable, ranging from relatively minor to massive damage, and mimic many other disease processes. **Fatty change (steatosis)** may be mild to moderate with focal hepatocyte necrosis. An acute, fulminant hepatitis can mimic acute viral hepatitis. Chronic hepatitis in Wilson disease exhibits moderate to severe inflammation and hepatocyte necrosis, admixed with fatty change and features of steatohepatitis (hepatocyte ballooning with prominent Mallory-Denk bodies). Eventually cirrhosis supervenes.

Excess copper deposition can often be demonstrated by special stains (rhodamine stain for copper, orcein stain for copper-associated protein). Because copper also accumulates in chronic obstructive cholestasis and because histology cannot reliably distinguish Wilson disease from viral- and drug-induced hepatitis, demonstration of hepatic copper content in excess of 250 μg per gram dry weight is most helpful for making a diagnosis. Unlike in hereditary hemochromatosis, where genetic testing has lessened the need for quantitative metal assessment, the vast range of genetic alterations in Wilson disease means that genetic testing is not yet a primary diagnostic modality; with the advent of next generation sequencing, however, this is likely to change in the near future.

Toxic injury to the brain primarily affects the basal ganglia, particularly the putamen, which shows atrophy and even cavitation. Nearly all patients with neurologic involvement develop eye lesions called **Kayser-Fleischer rings**, green to brown deposits of copper in Descemet membrane in the limbus of the cornea.

Clinical Features. The age at onset and the clinical presentation of Wilson disease are extremely variable (average age is 11.4 years), but the disorder usually manifests in affected individuals between 6 and 40 years of age. Initial presentation may either be with acute or chronic liver disease. Neurologic involvement presents as movement disorders (tremor, poor coordination, chorea or choreoathetosis) or rigid dystonia (spastic dystonia, mask like facies, rigidity and gait disturbances); these symptoms may be confused with Parkinsonism. Patients may also have psychiatric symptoms such as depression, phobias, compulsive behavior, and labile mood. Hemolytic anemia may occur due to toxicity of copper to red cell membranes. *The biochemical diagnosis of Wilson disease is based on a decrease in serum ceruloplasmin, an increase in hepatic copper content (the most sensitive and accurate test), and increased urinary excretion of copper (the most specific screening test).* Serum copper levels are of no diagnostic value, since they may be low, normal, or elevated, depending on the stage of evolution of the disease. Demonstration of Kayser-Fleischer rings further favors the diagnosis. Early recognition and long-term copper chelation therapy (with D-penicillamine or Trientine) or zinc-based therapy (which blocks uptake of copper in the gut) has dramatically altered the usual progressive downhill course. Individuals with hepatitis or unmanageable cirrhosis require liver transplantation, which can be curative.

α_1-Antitrypsin Deficiency

α_1-Antitrypsin deficiency is an autosomal recessive disorder of protein folding marked by very low levels of circulating α_1-Antitrypsin (α_1AT). The major function of this protein is the inhibition of proteases, particularly neutrophil elastase, cathepsin G, and proteinase 3, which are normally released from neutrophils at sites of inflammation. α_1AT deficiency leads to the development of pulmonary emphysema, because the activity of destructive proteases is not inhibited (Chapter 15). It also causes liver disease as a consequence of hepatocellular accumulation of the misfolded protein. Cutaneous necrotizing panniculits also occurs in a minor subset of patients.

α_1AT is a small 394–amino acid plasma glycoprotein synthesized predominantly by hepatocytes. It is a member of the serine protease inhibitor (serpin) family. The gene, located on chromosome 14, is very polymorphic, and at