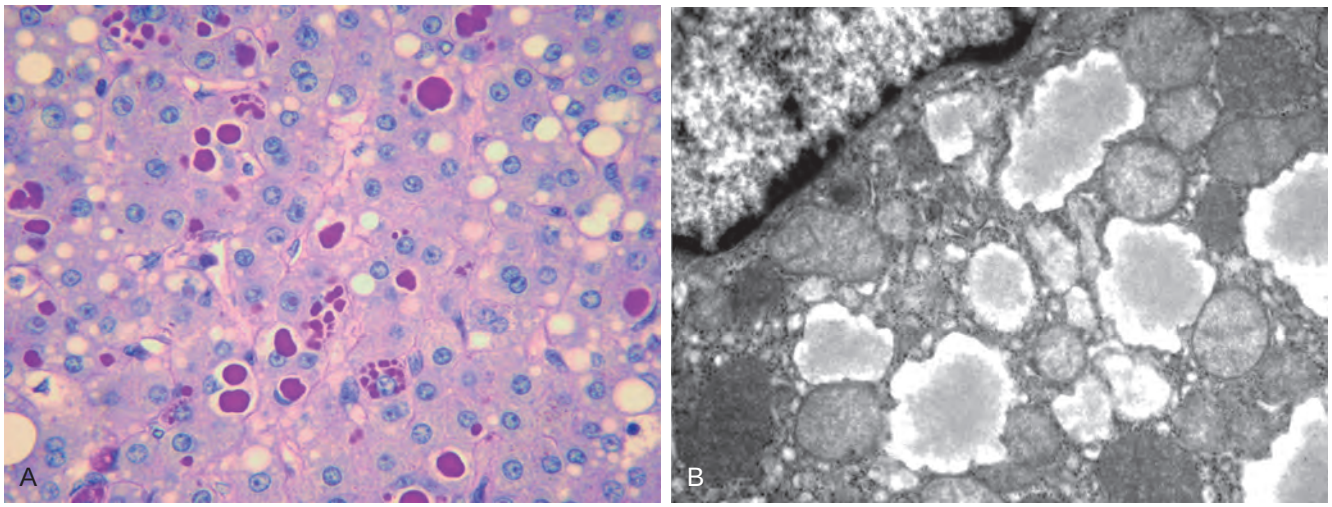

Figure 18-26 α_1-Antitrypsin deficiency. **A,** Periodic acid–Schiff (PAS) stain after diastase digestion of the liver, highlighting the characteristic magenta cytoplasmic granules. **B,** Electron micrograph showing endoplasmic reticulum dilated by aggregates of misfolded protein.

least 75 α_1AT forms have been identified, denoted alphabetically by their relative migration on an isoelectric gel. The general notation is "Pi" for "protease inhibitor" and an alphabetic letter for the position on the gel; two letters denote the genotype of an individual's two alleles. The most common genotype is PiMM, occurring in 90% of individuals (the "wild-type"). Most allelic variants show substitutions in the polypeptide chain but produce normal levels of functional α_1AT. Some deficiency variants, including the PiS variant, result in a moderate reduction in serum concentrations of α_1AT without clinical manifestations. Rare variants termed *Pi-null* have no detectable serum α_1AT.

The most common clinically significant mutation is PiZ; homozygotes for the PiZZ protein have circulating α_1AT levels that are only 10% of normal. These individuals are at high risk for developing clinical disease. Expression of alleles is autosomal codominant, and consequently, PiMZ heterozygotes have intermediate plasma levels of α_1AT. Among people of northern European descent, the PiS frequency is 6% and the PiZ frequency is 4%; the PiZZ state affects 1 in 1800 live births. Because of its early presentation with liver disease, α_1AT deficiency is the most commonly diagnosed inherited hepatic disorder in infants and children.

Pathogenesis. With most allelic variants, the protein is synthesized and secreted normally. Deficiency variants show a selective defect in migration of protein from endoplasmic reticulum to Golgi apparatus; this is particularly characteristic of the PiZ polypeptide, resulting from a single amino acid substitution of Glu342 to Lys342. *The mutant polypeptide (α_1AT-Z) is abnormally folded and polymerized, creating endoplasmic reticulum stress and triggering the unfolded protein response, a signaling cascade that may lead to apoptosis* (Chapter 2). *All individuals with the PiZZ genotype accumulate α_1AT-Z in the endoplasmic reticulum of hepatocytes, but only 10% to 15% of PiZZ individuals develop overt clinical liver disease.* Other genetic factors or environmental factors are thus posited to play a role in the development of liver disease.

MORPHOLOGY

α_1AT deficiency is characterized by the presence of round-to-oval **cytoplasmic globular inclusions in hepatocytes,** which on routine hematoxylin and eosin stains are acidophilic, but are strongly periodic acid–Schiff (PAS)-positive and diastase-resistant (Fig. 18-26). The globules are also present, but in diminished size and number in the PiMZ and PiSZ genotypes. Periportal hepatocytes contain the mutant proteins in early and mild forms of the disease with accumulation involving progressively more central hepatocytes with duration and more severe forms like the PiZZ variant. However, the number of globule-containing hepatocytes in a patient's liver is not correlated with the severity of pathologic findings.

The hepatic pathology associated with PiZZ homozygosity is extremely varied, ranging from neonatal hepatitis without or with cholestasis and fibrosis (discussed later), to childhood cirrhosis, to a smoldering chronic hepatitis or cirrhosis that becomes apparent only late in life. The diagnostic α_1AT globules may be absent in the young infant, although steatosis may be present as a tip-off to the possibility of α_1AT deficiency.

Clinical Features. Neonatal hepatitis with cholestatic jaundice appears in 10% to 20% of newborns with the deficiency. In adolescence, presenting symptoms may be related to hepatitis, cirrhosis or pulmonary disease. Attacks of hepatitis may subside with apparent complete recovery, or they may become chronic and lead progressively to cirrhosis. Alternatively, the disease may remain silent until cirrhosis appears in middle to later life. Hepatocellular carcinoma develops in 2% to 3% of PiZZ adults, usually, but not always, in the setting of cirrhosis. The treatment, indeed the cure, for severe hepatic disease is orthotopic liver transplantation. In patients with pulmonary disease the single most important preventive measure is avoidance of cigarette smoking, because smoking markedly accelerates emphysema and the destructive lung disease associated with α_1AT deficiency.