patients do not demonstrate other features of cystic fibrosis, despite the presence of bi-allelic *CFTR* mutations; these patients are classified as having *nonclassic* or *atypical cystic fibrosis*. Identifying these individuals is important not only for subsequent management, but also for genetic counseling.

Genetic and Environmental Modifiers. **Although cystic fibrosis remains one of the best-known examples of the "one gene, one disease" axiom, there is now considerable evidence that genes other than CFTR modify the frequency and severity of certain organ-specific manifestations, especially pulmonary manifestations and neonatal meconium ileus.** Not surprisingly, polymorphisms in genes whose products modulate neutrophil function in response to bacterial infections act as modifier loci for the severity of pulmonary disease in cystic fibrosis. Examples of such modifier genes include *mannose binding lectin 2* (*MBL2*), *transforming growth factor β1* (*TGFB1*) and *interferon related developmental regulator 1* (*IFRD1*). It is postulated that polymorphisms in these genes regulate the resistance of the lungs to exogenous infections with virulent microbes (see later), thus modifying the natural history of cystic fibrosis. Similarly, several other genetic modifiers appear to influence the incidence of meconium ileus in cystic fibrosis, although the degree of association is less stringent than that observed for pulmonary manifestations.

Environmental modifiers may also explain the significant phenotypic differences between individuals who share the same *CFTR* genotype. This is best exemplified in pulmonary disease, where *CFTR* genotype and phenotype correlations can be perplexing. As stated earlier, defective mucociliary action because of deficient hydration of the mucus results in an inability to clear bacteria from the airways. *Pseudomonas aeruginosa* species, in particular, colonize the lower respiratory tract, first intermittently and then chronically. Concurrent viral infections predispose to such colonization. The static mucus creates a hypoxic microenvironment in the airway surface fluid, which in turn favors the production of *alginate*, a mucoid polysaccharide capsule, by the colonizing bacteria. Alginate production permits the formation of a biofilm that protects the bacteria from antibodies and antibiotics, allowing them to evade host defenses, and produce a chronic destructive lung disease. Antibody- and cell-mediated immune reactions induced by the organisms result in further pulmonary destruction, but are ineffective against the organism. It is evident, therefore, that in addition to genetic factors (e.g., class of mutation), a plethora of environmental modifiers (e.g., virulence of organisms, efficacy of therapy, intercurrent and concurrent infections by other organisms, exposure to tobacco and allergens) can influence the severity and progression of lung disease in cystic fibrosis.

MORPHOLOGY

The anatomic changes are highly variable in distribution and severity. In individuals with nonclassic cystic fibrosis, the disease is quite mild and does not seriously disturb their growth and development. In others, the pancreatic involvement is severe and impairs intestinal absorption because of the pancreatic insufficiency (Chapter 19), and so malabsorption stunts development and post-natal growth. In others, the mucus secretion defect leads to defective mucociliary action, obstruction of bronchi and bronchioles, and crippling fatal pulmonary infections. In all variants, the **sweat glands are morphologically unaffected.**

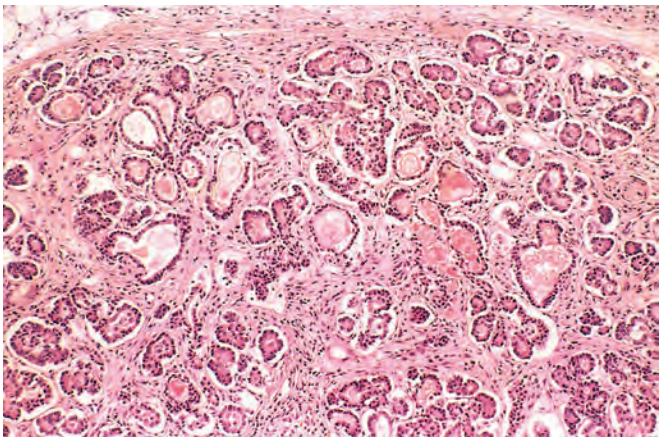

Figure 10-20 Pancreas in cystic fibrosis. The ducts are dilated and plugged with eosinophilic mucin, and the parenchymal glands are atrophic and replaced by fibrous tissue.

Pancreatic abnormalities are present in approximately 85% to 90% of patients with cystic fibrosis. In the milder cases, there may be only accumulations of mucus in the small ducts with some dilation of the exocrine glands. In more severe cases, usually seen in older children or adolescents, the ducts are completely plugged, causing atrophy of the exocrine glands and progressive fibrosis (Fig. 10-20). Atrophy of the exocrine portion of the pancreas may occur, leaving only the islets within a fibrofatty stroma. The loss of pancreatic exocrine secretion impairs fat absorption, and the associated avitaminosis A may contribute to squamous metaplasia of the lining epithelium of the ducts in the pancreas, which are already injured by the inspissated mucus secretions. Thick viscid plugs of mucus may also be found in the small intestine of infants. Sometimes these cause small-bowel obstruction, known as **meconium ileus**.

The **liver involvement** follows the same basic pattern. Bile canaliculi are plugged by mucus material, accompanied by ductular proliferation and portal inflammation. Hepatic **steatosis** is not an uncommon finding in liver biopsies. Over time, **focal biliary cirrhosis** develops in approximately a third of patients (Chapter 18), which can eventually involve the entire liver, resulting in diffuse hepatic nodularity. Such severe hepatic involvement is encountered in less than 10% of patients.

The **salivary glands** frequently show histologic changes similar to those described in the pancreas: progressive dilation of ducts, squamous metaplasia of the lining epithelium, and glandular atrophy followed by fibrosis.

The **pulmonary changes** are the most serious complications of this disease (Fig. 10-21). These stem from the viscous mucus secretions of the submucosal glands of the respiratory tree leading to secondary obstruction and infection of the air passages. The bronchioles are often distended with thick mucus associated with marked hyperplasia and hypertrophy of