trimethoprim-sulfamethoxazole, and protease inhibitors. Incidence has been markedly reduced due to advances in therapy (Chap. 226).

CHRONIC PANCREATITIS AND PANCREATIC EXOCRINE INSUFFICIENCY

PATHOPHYSIOLOGY

Chronic pancreatitis is a disease process characterized by irreversible damage to the pancreas as distinct from the reversible changes noted in acute pancreatitis (Table 371-4). The events that initiate and then perpetuate the inflammatory process in the pancreas are becoming more clearly understood. Irrespective of the mechanism of injury, it is becoming apparent that stellate cell activation that results in cytokine expression and production of extracellular matrix proteins cause acute and chronic inflammation and collagen deposition in the pancreas. Thus, the condition is defined by the presence of histologic abnormalities, including chronic inflammation, fibrosis, and progressive destruction of both exocrine and eventually endocrine tissue (atrophy). A number of etiologies have been associated with chronic pancreatitis resulting in the cardinal manifestations of the disease such as abdominal pain, steatorrhea, weight loss, and diabetes mellitus (Table 371-5).

Although alcohol has been believed to be the primary cause of chronic pancreatitis, other factors contribute to the disease because not all heavy consumers of alcohol develop pancreatic disease. There is also a strong association between smoking and chronic pancreatitis. Cigarette smoke leads to an increased susceptibility to pancreatic autodigestion and predisposes to dysregulation of duct cell CFTR function.

TABLE 371-5 CHRONIC PANCREATITIS AND PANCREATIC EXOCRINE INSUFFICIENCY: TIGAR-O CLASSIFICATION SYSTEM

Toxic-metabolic
Alcoholic
Tobacco smoking
Hypercalcemia
Hyperlipidemia
Chronic renal failure
Medications—phenacetin abuse
Toxins—organotin compounds (e.g., dibutylin dichloride, DBTC)
Idiopathic
Early onset
Late onset
Tropical
Genetic
Cationic trypsinogen (*PRSS1*)
Cystic fibrosis transmembrane conductance regulator gene (*CFTR*)
Calcium-sensing receptor (*CASR*)
Chymotrypsin C gene (*CTRC*)
Pancreatic secretory trypsin inhibitor gene (*SPINK1*)
Autoimmune
Type 1 autoimmune chronic pancreatitis
IgG4 systemic
Type 2 autoimmune chronic pancreatitis
Recurrent and severe acute pancreatitis
Postnecrotic (severe acute pancreatitis)
Recurrent acute pancreatitis
Vascular diseases/ischemia
Radiation induced
Obstructive
Pancreas divisum
Duct obstruction (e.g., tumor)
Preampullary duodenal wall cysts
Posttraumatic pancreatic duct scars

Abbreviations: DBTC, dibutylin dichloride; TIGAR-O, toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, obstructive.

Smoking is an independent, dose-dependent risk factor for chronic pancreatitis and recurrent acute pancreatitis. Both continued alcohol and smoking exposure are associated with pancreatic fibrosis, calcifications, and progression of disease

Recent characterization of pancreatic stellate cells (PSCs) has added insight into the underlying cellular responses behind development of chronic pancreatitis. Specifically, PSCs are believed to play a role in maintaining normal pancreatic architecture that can shift toward fibrogenesis in the case of chronic pancreatitis. The sentinel acute pancreatitis event (SAPE) hypothesis uniformly describes the events in the pathogenesis of chronic pancreatitis. It is believed that alcohol or additional stimuli lead to matrix metalloproteinase–mediated destruction of normal collagen in pancreatic parenchyma, which later allows for pancreatic remodeling. Proinflammatory cytokines, tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), and interleukin 6 (IL-6), as well as oxidant complexes, are able to induce PSC activity with subsequent new collagen synthesis. In addition to being stimulated by cytokines, oxidants, or growth factors, PSCs also possess transforming growth factor β (TGF-β)–mediated self-activating autocrine pathways that may explain disease progression in chronic pancreatitis even after removal of noxious stimuli.

ETIOLOGIC CONSIDERATIONS

Among adults in the United States, alcoholism is the most common cause of clinically apparent chronic pancreatitis, whereas cystic fibrosis is the most frequent cause in children. As many as 25% of adults in the United States with chronic pancreatitis have the *idiopathic* form. Recent investigations have indicated that up to 15% of patients with idiopathic pancreatitis may have pancreatitis due to genetic defects (Table 371-5).

Whitcomb and associates studied several large families with hereditary chronic pancreatitis and were able to identify a genetic defect that affects the gene encoding for trypsinogen. Several additional defects of this gene have also been described. The defect prevents the destruction of prematurely activated trypsin and allows it to be resistant to the intracellular protective effect of trypsin inhibitor. It is hypothesized that this continual activation of digestive enzymes within the gland leads to acute injury and, finally, chronic pancreatitis. Since the initial discovery of the *PRSS1* mutation defect, other genetic diseases have been detected (Table 371-5).

Several other groups of investigators have documented mutations of *CFTR*. This gene functions as a cyclic AMP–regulated chloride channel. In patients with cystic fibrosis, the high concentration of macromolecules can block the pancreatic ducts. It must be appreciated, however, that there is a great deal of heterogeneity in relationship to the *CFTR* gene defect. More than 1000 putative mutations of the *CFTR* gene have been identified. Attempts to elucidate the relationship between the genotype and pancreatic manifestations have been hampered by the number of mutations. The ability to detect *CFTR* mutations has led to the recognition that the clinical spectrum of the disease is broader than previously thought. Two studies have clarified the association between mutations of the *CFTR* gene and another monosymptomatic form of cystic fibrosis (i.e., chronic pancreatitis). It is estimated that in patients with idiopathic pancreatitis, the frequency of a single *CFTR* mutation is 11 times the expected frequency and the frequency of two mutant alleles is 80 times the expected frequency. In these studies, the patients were adults when the diagnosis of pancreatitis was made; none had any clinical evidence of pulmonary disease, and sweat test results were not diagnostic of cystic fibrosis. The prevalence of such mutations is unclear, and further studies are certainly needed. In addition, the therapeutic and prognostic implication of these findings with respect to managing pancreatitis remains to be determined. Long-term follow-up of affected patients is needed. *CFTR* mutations are common in the general population. It is unclear whether the *CFTR* mutation alone can lead to pancreatitis as an autosomal recessive disease. A study evaluated 39 patients with idiopathic chronic pancreatitis to assess the risk associated with these mutations. Patients with two *CFTR* mutations (compound heterozygotes) demonstrated *CFTR* function at a level between that seen in typical cystic fibrosis and cystic