CHAPTER 30

Etiology and Pathophysiology of Acute Pancreatitis

Michael L. Steer

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Our knowledge of the etiology of acute pancreatitis is limited to identifying the processes that, on epidemiological grounds, are associated with the development of the disease. The incidence of these various associated diseases among patients with acute pancreatitis, however, is not entirely clear because 1) the distinction between acute and chronic pancreatitis may be difficult or even impossible to make on clinical grounds, 2) many individuals with mild or only moderately severe pancreatitis may not be identified in any population being studied, and 3) a number of nonpancreatic diseases may be clinically indistinguishable from pancreatitis unless surgery or autopsy is performed. Our knowledge of the pathophysiology of pancreatitis is also limited. In this case, however, it is the protean nature of pancreatitis as well as the real difficulty encountered during attempts to study patients with this complex disease that account for the limited information that has been collected. Many investigators have turned to experimental models of acute pancreatitis to overcome these limitations, but the relevance of the various models developed has remained open to question (79).

ETIOLOGY

The processes most commonly associated with pancreatitis are biliary tract disease and alcoholism. Together, they account for 80 to 90% of patients given the diagnosis of acute pancreatitis, and the individual contribution of each appears to be related to the patient population being studied; i.e., alcoholism is most common in inner-city populations, especially in Scandinavia and the United States; biliary tract disease is more common in the more affluent suburban areas. The remaining 10 to 20% of patients with acute pancreatitis have this disease either in the absence of any other known associated process ("idiopathic") or in association with a variety of processes, with their incidences varying greatly among the many clinical series reported (Table 1).

Biliary Tract Disease

The recent recognition that most acute episodes of alcohol-related pancreatitis are in reality acute manifestations of chronic pancreatitis (vide infra) leaves biliary
tract disease as the condition most often associated with the development of acute pancreatitis. For the most part, it is calculous biliary tract disease (usually choledocholithiasis) that is found in patients with acute pancreatitis, although in some patients only cholecystolithiasis or acalculous disease may be documented. Presumably, in those patients, the offending common-duct stone either has evaded detection within the biliary tree or has already been passed through the sphincter of Oddi into the duodenum. An association between acute pancreatitis and either cholesterosis of the gallbladder or acute cholecystitis without choledocholithiasis has been claimed (18) but is not well documented.

The mechanism by which common-duct stones trigger acute pancreatitis is not known with certainty, although most students of this problem would agree that obstruction to flow caused by the stone is of fundamental importance. It is not clear if the relevant obstruction involves outflow from the pancreatic ductal system alone or if combined biliary and pancreatic outflow obstructions are required. In 1901, the finding of a stone impacted in the ampulla of Vater of a patient dying of acute pancreatitis prompted Opie (60) to propose the so-called common-channel hypothesis as an explanation for the mechanism by which stones cause acute pancreatitis. He reasoned that obstruction to outflow below a combined biliary duct and pancreatic duct (i.e., a common channel) would permit bile to flow into the pancreas. He presumed that bile, because of its detergent properties, could initiate pancreatic injury once reflux into the pancreatic duct had occurred. Subsequent experimental studies (79) have demonstrated that the forceful retrograde injection of bile into the pancreatic duct can, indeed, cause pancreatic injury reminiscent of pancreatitis. Furthermore, recent experimental observations have suggested that bile salts can alter the integrity of the pancreatic duct mucosal barrier and allow digestive enzymes to diffuse from the ductal space into the parenchyma of the pancreas (69). As yet, however, it is not clear whether or not these phenomena contribute to the development of acute clinical pancreatitis.

A number of objections to the common-channel hypothesis have been raised, based on the following observations: 1) a common channel, which is present in the majority of individuals (35), is usually so short that an obstructing stone impacted in the ampulla would obstruct the pancreatic duct as well as the bile duct (52), thus isolating the pancreatic ductal system from the biliary tract; 2) bile duct pressure normally is less than pancreatic duct pressure (53) and, therefore, pancreatic juice flow into the biliary system rather than bile flow into the pancreas is favored; 3) passage of normal bile through an unobstructed pancreatic ductal system in experimental animals does not precipitate acute pancreatitis (72).

Rather than causing bile to flow into the pancreatic duct, it is more likely that common-duct stones precipitate acute pancreatitis by obstructing the pancreatic duct. This might result either from direct pressure on the pancreatic duct exerted by a stone lodged in the terminal common duct or from the peripancreatic inflammatory response and/or sphincteric spasm induced by a stone passing through the ampulla and sphincter into the duodenum. The act of stone passage, itself, may be the most common inciting event in so-called gallstone pancreatitis, as indicated by the recent reports of Acosta et al. (1,2) and Kelly (41). These workers screened the feces of two types of patients: those with gallstones alone and those with gallstones as well as acute pancreatitis. Eighty-eight percent of the patients with pancreatitis had stones recovered from their feces within 10 days of the onset of their attack, whereas only 11% of patients with gallstones who did not have pancreatitis were found to have stones on fecal screening during a similar period of observation.

Continued pancreatic secretion into an obstructed pancreatic ductal system would be expected to produce pancreatic ductal hypertension. In this respect, the primary disturbance underlying gallstone pancreatitis may be similar to that responsible for some of the less common causes of pancreatitis, such as the presence of periampullary diverticulum, obstructing pancreatic and periampullary tumors (21), helminthic infestations of the pancreatic duct (21), and the acute pancreatitis that occurs after endoscopic retrograde pancreatography (13). Only the events leading to pancreatic ductal hypertension would seem to differ among these various etiologies of pancreatitis. The suggestion that pancreatic duct hypertension is an important early event in the development of acute pancreatitis is also supported by the large number of experimental studies that have demonstrated that acute experimental pancreatitis can be induced by injection of a variety of agents, under supraphysiological pressure, retrogradely into the pancreatic duct in experimental animals (79).

Although these various observations support the concept that ductal hypertension is an important early event in the development of acute pancreatitis, they do not define the mechanism by which the resulting pancreatitis is actually triggered. It has been generally presumed that ductal hypertension leads to rupture of small pancreatic ductules, extravasation of secretions into the pancreatic parenchyma, digestive enzyme activation, and subsequent pancreatitis. The lack of a clear understanding of how ductal rupture might cause digestive enzyme activation has resulted in an alternative hypothesis—i.e.,
that ductal hypertension might prevent discharge of digestive enzymes from acinar cells into the ductal space and that this secretory block could lead to intracellular events that precipitate pancreatitis (82).

Alcohol

Attacks of pancreatitis are frequently associated with ethanol abuse, but it is not clear if these episodes represent attacks of acute or chronic pancreatitis. Acute pancreatitis is, by definition, an acute inflammatory process involving a pancreas that, prior to the attack, had been both structurally and functionally normal (75). Because the status of the gland prior to the attack is almost never known, most have presumed that the first attack of pancreatitis in a previously asymptomatic patient is “acute” pancreatitis, unless evidence of chronic injury (e.g., calcifications) can be documented. Recent evidence, however, has clearly shown that the exocrine pancreas possesses great functional reserve. Close to 90% of secretory function can be lost before clinically apparent steatorrhea develops (17). In addition, loss of pancreatic function may be insidious. It may occur in the absence of clinically apparent attacks of pancreatitis, especially in patients with associated ethanol abuse. It is likely, therefore, that many, if not all, patients presenting clinically with a first acute attack of alcohol-related pancreatitis do, in fact, have chronic rather than acute pancreatitis. Typically they have consumed large quantities of ethanol for prolonged periods (8–10 years) (84) prior to their first attack of pancreatitis, and recurrent attacks can be anticipated if alcohol abuse continues.

Some individuals, however, manifest evidence of acute pancreatitis after only one or several exposures to alcohol. Some of these patients have another identifiable process that might explain the attack of pancreatitis (e.g., choledocholithiasis). However, for the remainder, no cause other than ethanol may be found, and the disease can then truly be considered alcohol-associated acute pancreatitis. The frequency with which acute pancreatitis is caused by alcohol as well as the mechanism by which ethanol might precipitate acute pancreatitis are not known. Oral administration of ethanol causes a transient stimulation of pancreatic exocrine secretion, followed by a later period of inhibition (55,89). Pirola and Davis (64) noted that ethanol caused contraction of the sphincter of Oddi. Thus, the combined effects of secretory stimulation and outflow obstruction might explain the association between ethanol ingestion and acute pancreatitis. Alternatively, ethanol may have some as yet unidentified toxic effect on the pancreas. Recent in vitro experiments have shown that high concentrations of ethanol can alter the balance between proteolytic enzymes and protease inhibitors in pancreatic juice, occasionally leading to secretion of activated proteolytic enzymes such as trypsin (81). Whether or not similar events occur in vivo and whether or not they can lead to the development of acute pancreatitis have not been shown.

Tumors

Acute pancreatitis may be the first clinical manifestation of a periampullary tumor originating in the duodenum, distal bile duct, or pancreatic head (21). For the most part, these tumors are malignant, and this diagnosis should be considered when dealing with a nonalcoholic patient whose attack of acute pancreatitis is not associated with demonstrable biliary tract disease. Pancreatic carcinoma is found in 1 to 2% of all patients with acute pancreatitis (21). Presumably the acute pancreatitis results from obstruction to the flow of pancreatic juice, and a similar phenomenon probably accounts for the frequent microscopic finding of areas of pancreatitis surrounding tumors of the pancreas even in the absence of clinical evidence of pancreatitis.

Infections

Rising antibody titers to mumps virus and coxsackievirus and to Mycoplasma pneumoniae have been noted in up to 30% of patients with acute pancreatitis in whom no other factor has been identified as possibly causing the episode of pancreatitis (28,38). While it is generally assumed that these agents may induce pancreatitis by infecting pancreatic acinar cells, to date no studies in humans have shown that the offending organisms can be recovered from the pancreas. Thus, although these agents may cause pancreatitis, it remains possible that the rising antibody titers noted in these patients represent a nonspecific or anamnestic response to the pancreatitis. Acute pancreatitis has also been reported to be associated with parasitic infestations. Ascaris lumbricoides and Clonorchis sinensis have been recovered from the pancreatic duct in patients with pancreatitis, and it is believed that duct obstruction caused by the parasites triggers the episode of acute pancreatitis (21).

Drugs

Many drugs cause hyperamylasemia and/or abdominal pain, but it is not clear which, if any, actually cause acute pancreatitis. Most studies of drug-induced pancreatitis have been case reports involving relatively few patients. Usually, an illness resembling acute pancreatitis is observed during administration of the suspect drug, and the symptoms resolve after drug withdrawal. For practical as well as ethical reasons, rechallenge with the suspect drug is not always undertaken, and the conclusion that the drug caused the pancreatitis may be, at best, tenuous.
In spite of these limitations, a number of drugs are generally considered to be capable of causing pancreatitis (Table 2). Included in this group are the thiazide diuretics, furosemide, estrogens, azathioprine, L-asparaginase, 6-mercaptopurine, methyldopa, sulfonamides, tetracycline, pentamidine, and procainamide (88). Epidemiological studies have indicated that 1 to 4% of patients with Crohn's disease treated with azathioprine (85,87) and 7% of patients with leukemia treated with asparaginase (51) develop pancreatitis, but the incidences of pancreatitis among patients taking the other drugs mentioned earlier are considerably lower. Pancreatitis has been noted in up to 20% of AIDS patients treated with the drug dideoxyinosine (43). It is not entirely clear, however, whether the drug or the underlying AIDS is the cause of pancreatitis in these patients.

The mechanisms by which drugs induce pancreatitis are unknown, and most likely the phenomenon is multifactorial. For example, the thiazides may act directly on the pancreas or indirectly by altering calcium metabolism. Similarly, estrogens may have direct effects on the pancreas or may act indirectly by inducing hypertriglyceridemia. Tetracycline-induced fatty metamorphosis of the liver usually accompanies evidence of pancreatitis, but pancreatitis without evidence of liver disease has also been observed after administration of tetracycline. Finally, pancreatitis after procainamide administration may be the result of drug-induced lupus erythematosus.

Two commonly administered types of drugs are frequently considered as being capable of causing acute pancreatitis. These are the steroids and the H2-receptor antagonists such as cimetidine. Considerable controversy surrounds the question of whether or not either agent can induce pancreatitis, and, in addition, there have been claims that each may be useful in the treatment of acute pancreatitis (83,88). Although the evidence that either steroids or cimetidine can cause pancreatitis is, at present, weak, it would seem prudent to discontinue treatment with these drugs in patients with pancreatitis, especially if the drug is not absolutely required and if no other cause for pancreatitis can be identified.

**Lipid Abnormalities**

Patients with types I and V familial hyperlipoproteinemia experience frequent attacks of abdominal pain that are believed to represent episodes of acute pancreatitis (27). These attacks, which usually are associated with marked hypertriglyceridemia and the finding of lacteal serum, can be prevented by dietary manipulations that control serum triglyceride levels. These observations indicate that in these patients, hypertriglyceridemia may trigger acute pancreatitis. Havel (36) suggested that free fatty acids liberated from triglycerides by lipase in the pancreatic microcirculation can damage small vessels and produce ischemic pancreatic injury.

Ethanol ingestion can also alter lipid metabolism and on occasion, lead to hypertriglyceridemia with lacteal serum. Cameron et al. (11) have suggested that this may be one mechanism by which ethanol ingestion precipitates acute pancreatitis. However, hypertriglyceridemia may also be the result, rather than the cause, of pancreatitis, and much additional work in this area will be needed before we gain a clear understanding of the role that lipid abnormalities play in the pathogenesis of pancreatitis (16).

**Postoperative Pancreatitis**

Acute pancreatitis occurs after a number of surgical procedures, most commonly, operations performed on or near the pancreas. It is generally believed that postoperative pancreatitis results from either iatrogenic injury to the gland or obstruction to the flow of pancreatic juice. The operations most frequently associated with postoperative pancreatitis include common bile duct exploration, sphincteroplasty, distal gastrectomy, and splenectomy (7,62,94). Cardiopulmonary bypass and cardiac transplantation have also been associated with pancreatitis (3,24), and in these cases hypoperfusion and/or atheromatous emboli to the pancreatic circulation may be the mechanism of pancreatic injury. Hyperamylasemia and pancreatitis have also been noted after cardiopulmonary bypass (68). Recently, Fernandez-del Castillo and coworkers have reported a high incidence of so-called pancreatic injury associated with cardiopulmonary bypass (25). These workers have claimed an association between pancreatic injury and administration of large doses of calcium in the perioperative period. Unfortunately, in that study hyperamylasemia was considered pancreatic injury. Since hyperamylasemia may be a non-specific phenomenon in such patients and more objective evidence of pancreatitis was lacking in most of the patients reported by Fernandez-del Castillo, the claim that perioperative calcium administration leads to pancreatic injury in bypass patients is far from convincing. The observation that acute pancreatitis can develop in cold-exposed patients with severe hypothermia (20,26,50) suggests that hypothermia may also contribute to the development of postoperative pancreatitis in patients undergoing cardiopulmonary bypass.

| **TABLE 2. Drugs associated with acute pancreatitis** |
|----------------|------------------|
| **Thiazide diuretics** | Sulfonamides |
| **Furosemide** | Tetracycline |
| **Estrogens** | Pentamidine |
| **Azathioprine** | Procainamide |
| **1-Asparaginase** | Nitrofurantoin |
| **6-Mercaptopurine** | Dideoxyinosine |
| **Methyldopa** | Valproic acid |
Acute pancreatitis has also been reported to follow a number of relatively minor procedures performed in areas remote from the pancreas (94). For example, it has been observed after parathyroidectomy, thyroidectomy, and inguinal hernia repair. The mechanism by which these procedures might induce pancreatitis is unknown.

Trauma

In view of the central and relatively unprotected location of the pancreas in the abdomen, it is surprising that pancreatic injury and traumatic pancreatitis are relatively uncommon. They can be associated with either penetrating or blunt trauma, in the latter case resulting from compression of the pancreas against the spine. The degree of injury may range from a relatively mild contusion to laceration and fracture. For the most part, pancreatic injury is associated with injury to surrounding organs and is diagnosed only at the time of operation. It has been estimated that only 1 to 3% of patients with severe abdominal trauma have significant pancreatic injury (37), but many patients not operated on may have mild unrecognized injury to the pancreas.

Controversial Causes of Pancreatitis

Until recently, pregnancy had been considered as a cause of acute pancreatitis. Indeed, there may be an increased incidence of pancreatitis during pregnancy. However, several reviews including large numbers of patients have revealed that most patients developing pancreatitis during pregnancy do so as a result of some other coincident process, most commonly cholelithiasis (49). Therefore, pregnancy itself should no longer be considered as a cause of acute pancreatitis (21). Similarly, posterior penetrating duodenal ulcers have long been considered as a cause of acute pancreatitis. Although microscopic evidence of both acute and chronic pancreatic inflammation is frequently noted in the ulcer bed and surrounding pancreas, true clinical pancreatitis is uncommon unless the inflammatory reaction produces pancreatic ductal obstruction.

Pancreatitis has generally been considered a common occurrence in patients with hyperparathyroidism. It has been reported in 6 to 7% of patients with hyperparathyroidism and 25% of patients with hyperparathyroid crisis (33). This frequency has prompted many to advocate a search for underlying hyperparathyroidism in all patients with otherwise unexplained pancreatitis. Recently, several studies that have surveyed large numbers of patients with hyperparathyroidism have suggested that the disease may only rarely, if at all, precipitate pancreatitis (9,90). For example, Bess et al. (9) reviewed 1,153 patients with primary hyperparathyroidism operated on at the Mayo Clinic and noted that only 17 (1.5%) had coexisting or prior attacks of pancreatitis—an incidence that approximated that of pancreatitis among hospital patient populations in general. Other factors that might have accounted for the pancreatitis, such as gallstones or alcohol abuse, were found in 11 of the 17 patients. Furthermore, cure of the hyperparathyroidism was not always associated with resolution of the pancreatitis unless these other factors were also corrected. Thus, pancreatitis that is caused by hyperparathyroidism must be rare, if it occurs at all.

Considerable controversy surrounds the question of whether pancreas divisum is a cause of acute pancreatitis. Failure of fusion between the dorsal and ventral ductal systems, which occurs in 9 to 10% of individuals (80), causes most of the pancreatic juice to drain into the duodenum via the lesser papilla rather than through the papilla of Vater. Proponents of the theory that pancreas divisum causes pancreatitis argue that this anatomical arrangement results in a relative obstruction to flow because the lesser papilla is too small to accommodate the bulk of pancreatic exocrine secretion. Indeed, some reports have indicated that the incidence of pancreatitis is increased among patients with pancreas divisum (14,70,73) although more recent studies based on larger numbers of patients have failed to confirm this association (15,86). The failure, in most hands, of procedures that improve drainage via the lesser papilla to eliminate attacks of pancreatitis in patients with pancreas divisum and the lack of ductal dilatation in patients with pancreas divisum and presumed pancreatitis have also been used as arguments against the suggestion that pancreas divisum causes pancreatitis (80). While the general consensus at the time of this writing is that pancreas divisum is rarely, if ever, the cause of pancreatitis (78), the entire issue remains unsettled and further studies are clearly needed.

Miscellaneous

In Trinidad, acute pancreatitis is frequently caused by the sting of a scorpion (8), and, experimentally, acute pancreatitis has been elicited by administration of scorpion venom on small animals. Recent studies have indicated that a toxin in scorpion venom stimulates the discharge of neurotransmitter from cholinergic terminals in the pancreas (30) and thereby causes massive exocrine pancreatic secretion. It is likely that the pancreatitis that develops both clinically and experimentally is the result of this massive secretory stimulation and may, in this way, be analogous to the acute clinical and experimental pancreatitis reported to follow intoxication with an antiacetylcholinesterase-containing insecticide (19). Acute pancreatitis can also be experimentally induced by supraphysiological pancreatic stimulation with cholecystokinin, as well as muscarinic cholinergic agonists (44),
but no clinical correlates for these forms of pancreatitis are known.

Acute pancreatitis has occasionally been reported to follow performance of translumbar aortography (39), especially when the injection is made at a relatively high level. It is not clear whether these cases of pancreatitis reflect direct trauma to the pancreas at the time of needle placement, atheromatous embolization to the pancreas, or pancreatographic of high concentrations of contrast material.

Acute pancreatitis has been associated with afferent loop obstruction following Billroth II gastrectomy and gastrojejunostomy (29). It is generally believed that increased duodenal pressure causes reflux of duodenal contents through the sphincter of Oddi and that pancreatitis results from retrograde flow of activated digestive enzymes into the pancreatic duct. Experimental pancreatitis can be induced by creation of a blind-loop duodenal obstruction (63) (the so-called Pfeiffer loop) and prevented by concomitant ligation of the pancreatic duct (48). Although these observations support the concept of duodenal reflux being an important early event in this form of pancreatitis, others have argued that the pancreatitis that develops after creation of a blind-loop duodenal obstruction results from pancreatic ischemia. The observation that sphincteroplasty of the sphincter of Oddi does not frequently lead to acute pancreatitis is perhaps the strongest argument against the hypothesis that duodenal reflux is an important precipitating factor in pancreatitis, because reflux is almost always noted after performance of a sphincteroplasty.

A variety of vascular lesions occasionally may be associated with acute pancreatitis. These include the so-called low-flow states, atheromatous embolization, mesenteric atherosclerosis, and thrombosis, but, in those cases, infarction of the pancreas is usually noted. Although many patients with pancreatitis also have significant atherosclerotic cardiovascular disease, the contribution that this disease makes to the development of pancreatitis is unclear. Similarly, pancreatitis has been noted in association with a variety of autoimmune diseases, and, on occasion, antipancreatic antibodies can be demonstrated in patients with pancreatitis (21). However, it is unclear whether or not immunologic factors actually induce pancreatitis. More likely, the coexistence of autoimmune diseases and pancreatitis may be merely a matter of chance, and antipancreatic antibodies may reflect pancreatic damage rather than explain its development.

Idiopathic Pancreatitis

In any group of patients with pancreatitis, some patients will have this disease in the absence of any process known to be capable of inducing pancreatitis. These patients are said to have idiopathic pancreatitis, and until recently this group represented 10 to 15% of all patients with acute pancreatitis. More recently, as patients have been more thoroughly evaluated and more apparent causes for pancreatitis have been identified, the idiopathic group has become smaller. At present, with careful study, only 5 to 7% of patients with acute pancreatitis have this disease in the absence of any known cause and are considered to have acute idiopathic pancreatitis (38,40,67).

PATHOPHYSIOLOGY

The pathophysiology of acute pancreatitis is even less well understood than is the etiology of the disease. It is customary for writers reviewing this subject to state that acute pancreatitis results from autodigestion of the gland. Indeed, a considerable amount of circumstantial evidence has been accumulated to suggest that pancreatic digestive enzymes may play an important role in the early stages of acute pancreatitis. The pancreas synthesizes a variety of enzymes, such as the proteases and phospholipases, that are capable of causing tissue damage. Activated forms of these enzymes have been detected in the pancreatic parenchyma, pancreatic juice, and ascitic fluid of some patients with acute pancreatitis (31,32,57,58). Experimental studies have shown that some of these enzymes (most notably elastase and the phospholipases) can induce pancreatitis in animals following injection into the pancreatic parenchyma or duct, especially when they are combined with bile or bile acids (76). Finally, the gross and microscopic appearances of the pancreas during acute pancreatitis suggest that cellular damage by agents such as digestive enzymes may have occurred. Diffuse edema is usually noted in association with evidence of inflammation that may be patchy or diffuse, and necrosis of glandular or peri glandular tissue may be seen. Furthermore, fat necrosis in the peripancreatic tissues is found, indicating damage to adipocytes by liberated lipases. Varying degrees of vascular injury, which has been attributed to the effect of digestive enzymes, have been observed, including thrombosis of small vessels and hemorrhage into the retroperitoneum and/or pancreatic parenchyma. These changes are especially prevalent in the most severe forms of the disease.

Although these observations certainly support the concept that acute pancreatitis may be an "autodigestive" disease, the issue is far from settled, because studies of cellular events that occur during the early stages of this disease in humans have not been possible. Thus, it remains entirely possible that intrapancreatic activation and release of digestive enzymes occur as a result, rather than as the cause, of pancreatitis and that some or all of the gross and microscopic changes noted earlier are in-
duced by some mechanism other than cell injury by digestive enzymes.

**Enzyme Activation**

Three features of normal pancreatic structure and function provide protection for the gland against the potentially harmful effects of the digestive enzymes that it synthesizes and secretes. These are 1) synthesis of enzymes as inactivezymogens, 2) the presence of protease inhibitors, and 3) segregation of digestive enzymes from the cytoplasmic space. If, indeed, acute pancreatitis is an autodigestive disease, an abnormality in one or more of these factors may play an important role in the initiation and evolution of the disease.

The digestive enzymes synthesized and secreted by the exocrine pancreas that are capable of inducing tissue injury are, normally, present within the pancreas only in the form of inactive proenzymes or zymogens. Activation of these zymogens (the trypsinosins, chymotrypsinosins, procarboxypeptidases, proelastase, and prophospholipases) occurs in the duodenum, where the brush-border enzyme enterokinase (enteropeptidase) catalyzes the conversion of trypsinosinogen to trypsin, and trypsin activates the other zymogens. Reflux of duodenal contents into the pancreatic duct could result in intraductal zymogen activation. Bile itself does not cause zymogen activation, and therefore reflux of bile (e.g., from common channel and reflux) would not by itself trigger enzyme activation. Recent experimental studies have suggested that bile, ethanol, and drugs such as aspirin may reduce the ductal barrier to diffusion and allow ductal contents to reach the gland parenchyma (69). Similarly, ductal rupture as a result of pancreatic duct hypertension (e.g., secretion into an obstructed duct) may also lead to extravasation of pancreatic juice into the parenchyma of the gland. It has been generally presumed that entry of digestive enzymes into the parenchyma of the gland leads to premature activation of these enzymes and subsequent cell injury, although no mechanism for intraparenchymal enzyme activation has been demonstrated. Recent experimental studies utilizing three dissimilar models of pancreatitis have supported an alternative hypothesis: that intrapancreatic activation of digestive enzymes occurs within the acinar cell itself as a result of the admixture of digestive enzyme zymogens and lysosomal hydrolases that are capable of activating trypsinosinogen. In these studies, experimental pancreatitis was induced either by feeding young female mice a choline-deficient ethionine-supplemented diet, by infusing rats with a supramaximally stimulating dose of the secretagogue cerulein, or by obstructing the rat or rabbit pancreatic duct. In all cases, large vacuoles appeared that contained both digestive enzymes and lysosomal hydrolases. In diet-induced pancreatitis, the large vacuoles appeared to arise as a result of fusion between zymogen granules and lysosomes (erinphagy), whereas following cerulein infusion the vacuoles appeared to reflect an arrest of the normal processes involved in condensing vacuole maturation that resulted in the segregation of lysosomal hydrolases away from digestive enzymes (42,59,74,82,92). Whether or not similar events occur in clinical pancreatitis remains to be established.

The pancreatic acinar cell synthesizes and secretes proteins capable of inactivating proteolytic enzymes such as trypsin (34). It is likely that these proteins are cotransported through the acinar cell along with digestive enzymes and that some are secreted by exocytosis of zymogen granule contents into the pancreatic ductal space. The protease inhibitors may function to inactivate trypsin that might be generated as a result of autoactivation of trypsinosinogen within acinar cells or the ductal space. Theoretically, trypsin inhibitor levels might be reduced under certain circumstances (postoperative states, shock, effect of drugs or alcohol, etc.), and this change could explain the intrapancreatic activation of zymogens, with subsequent pancreatitis. However, considerable further work in this area characterizing trypsin inhibitor levels in health and disease is needed before the importance of possible defects in this protective mechanism can be established. It is clear, however, that administration of exogenous trypsin inhibitors (i.e., Trasylol) does not alter the course of pancreatitis once the lesion has become established (56).

It is, most likely, no evolutionary accident that the potentially harmful digestive enzymes synthesized by pancreatic acinar cells are not normally present within the cell cytoplasm. These enzymes are synthesized on ribosomes attached to the endoplasmic reticulum, and the nascent polypeptide chains elongate within the cisternae of this endoplasmic reticulum. Following the completion of protein synthesis, they are transported to the Golgi complex and packaged into condensing vacuoles that mature into zymogen granules. The zymogen granules migrate to the luminal pole of the cell, where their contents are discharged into the ductal space by exocytosis following fusion-fission of the zymogen granule-limiting membrane and the luminal plasma membrane (61). As noted previously, recent evidence suggests that under certain circumstances, admixture of zymogens and lysosomal hydrolases capable of activating trypsinosinogen may occur, and this could result in intracellular zymogen activation. Theoretically, defects in the integrity of subcellular organelle membranes may also occur that could result in intracellular release of digestive enzymes, and this might explain the basis of some forms of pancreatitis. Clearly, further studies in this area are needed.
Local Manifestations

Cell injury is most likely one of the earliest events in the evolution of acute pancreatitis. Whereas this may be a result of premature digestive enzyme activation, it is also possible that the cell injury precedes enzyme activation. For example, Seelig and Seelig (77) demonstrated deposition of the C3 cytolytic component of complement in the pancreas during acute experimental pancreatitis and suggested that this may be the mechanism by which cell injury occurs.

Edema and inflammation are the basic lesions of acute pancreatitis. A number of investigators have suggested that the lesion may progress from this relatively mild form to a more severe form characterized by necrosis and hemorrhage. Presumably, changes in the pancreatic microcirculation lead to pancreatic ischemia, which favors progression of mild pancreatitis to severe pancreatitis. Alternatively, the severity of the lesion may be established at its inception, i.e., mild or severe. In this regard, the recent studies of Ranson et al. (65) and several other groups may be of great importance. They have shown that the severity of pancreatitis, and the potential for subsequent mortality and/or development of complications, can be determined by evaluating a carefully selected group of clinical and biochemical parameters that are available within a short time after onset of the disease. These observations therefore suggest that the severity of the lesion is established very early in its natural history and argue against the concept that mild pancreatitis progresses to the more severe form. Furthermore, if progression from mild to severe pancreatitis does occur, and if the disease is the result of intraparenchymal zymogen activation, it might be expected that the majority of patients would progress to the more severe forms of the disease, because it is not apparent what the turn-off mechanism for this process, once initiated, might be. These unresolved issues are of extreme clinical importance, as they have obvious therapeutic implication and certainly warrant further investigation.

Acute pancreatitis is frequently associated with three manifestations that are unlike those of any other disease process. These are fat necrosis, pseudocyst formation, and a phenomenon known as pancreatic abscess. Each appears to be related to the release of digestive enzymes originating in the pancreas. Release of lipases leads to adipose tissue injury and fat necrosis that usually is in the peripancreatic tissue but on occasion can be seen in tissues, such as subcutaneous fat, that are remote from the pancreas. Pseudocysts represent extraluminal collections of pancreatic juice, usually resulting from ductal rupture. They are more common in chronic pancreatitis but can also be seen in acute pancreatitis. These collections usually are contained within the pancreas itself, in the retroperitoneum, or in peripancreatic spaces such as the lesser peritoneal sac bounded by omentum, stomach, duodenum, colonic mesentery, and pancreas. Pseudocysts contain high concentrations of digestive enzymes, and a connection with the pancreatic duct can frequently be demonstrated. When leakage of pseudocysts into the free peritoneal cavity develops, or if ductal rupture without pseudocyst formation occurs, pancreatic ascites may be noted.

Pancreatic abscess is perhaps the most dreaded local manifestation of acute pancreatitis, because it is associated with significant morbidity and mortality. Characteristically, pancreatic abscesses are composed of necrotic peripancreatic connective tissue and contain both activated digestive enzymes and a mixed flora of bacteria. These latter two components act synergistically to promote progression of the lesion. Erosion into adjacent organs may occur. True loculation of liquid pus is uncommon, and the material usually has a pastelike consistency that makes it impossible to drain, requiring frequent as well as vigorous debridement.

Distant Manifestations

Acute pancreatitis is frequently associated with evidence of intravascular hypovolemia. Transudation as well as exudation of intravascular fluid into the peripancreatic retroperitoneum are common and may be of great magnitude. In addition, there is frequently evidence of a diffuse capillary-leak phenomenon in which fluid is lost into the extravascular space in areas remote from the pancreas (subcutaneous tissues, pulmonary interstitium, peritoneal cavity, etc.). The mechanism by which this leak occurs is not known. It may, in part, reflect a hypoalbuminemia-related decrease in intravascular colloid osmotic pressure. In addition, it has been suggested that vasoactive agents released into the circulation from the inflamed pancreas may play an important role in this process (23, 87). The latter hypothesis, although not yet supported by conclusive evidence, is intriguing, as it suggests that the diffuse capillary leak noted in pancreatitis might be specific for that disease rather than a nonspecific manifestation of septic or nonseptic shock.

Hypotension can also occur in severe attacks of acute pancreatitis. Most studies have suggested that there is a hyperdynamic cardiovascular state in severe pancreatitis that is similar to that noted in cirrhosis and septicemia (10). Hypotension, when it occurs, is usually related to an inadequate cardiac response to diminished peripheral resistance (10). As with other manifestations of pancreatitis, a role for vasoactive agents, including activated enzymes released from the pancreas, has been proposed in the pathophysiology of this hypotension, and various myocardial depressant factors have been sought (45–47, 66). In experimental animals, hypotension can be induced by infusion of hemorrhagic ascitic fluid
obtained from patients or experimental animals with pancreatitis (5,91).

Hypocalcemia, sometimes severe enough to cause tetany, may occur in pancreatitis. For the most part, the decrease in serum calcium is merely a reflection of the hypoalbuminemia that occurs, and in these cases ionized (i.e., nonprotein-bound) calcium levels remain at normal or near-normal levels (4). Occasionally, however, a reduction in the level of ionized calcium may occur, and the decrease in total serum calcium can exceed that attributable to the effects of hypoalbuminemia. It is not clear why ionized calcium levels fall in these patients, and several explanations have been proposed, including 1) loss of calcium by precipitation of calcium salts into areas of fat necrosis (22), 2) a decrease in parathormone release from the parathyroid glands (12,71), 3) failure of bony tissues to respond to released parathormone (93), and 4) enhanced release of thyrocalcitonin (6). The issue remains unsettled, but currently it is generally believed that calcium precipitation into areas of fat necrosis, although it does occur, is insufficient to explain the hypocalcemia that sometimes occurs. Most investigators have noted normal or only slightly elevated levels of parathormone, suggesting that the hypocalcemia may involve both a diminished end-organ (i.e., bone) response to parathormone and a decreased parathyroid response to hypocalcemia.

Severe attacks of acute pancreatitis may be associated with pulmonary failure and/or renal failure. The mechanism by which the lungs and/or kidneys fail in this disease is not obvious. It is likely that both phenomena are, at least in part, related to sepsis and/or hypotension. Thus, the pulmonary failure may be similar to that of the adult respiratory distress syndrome (ARDS), and the uraemia may be on a prerenal basis. On the other hand, these lesions may be more specific to the process of pancreatitis, resulting from injury induced by circulating activated digestive enzymes or vasoactive agents. For example, the pulmonary lesion may result from surfactant changes caused by circulating phospholipases (54), and the renal lesion may reflect basement membrane injury caused by circulating enzyme/enzyme-inhibitor complexes, immune complexes, circulating activated proteolytic enzymes, or other proteins specific to the process of acute pancreatitis. Clearly, further work in this area will be needed before an understanding of these phenomena can emerge.

CONCLUDING COMMENTS

In this chapter, the etiology and pathophysiology of acute pancreatitis have been reviewed. Although large amounts of epidemiological and physiological data have been accumulated, it is clear that our understanding of this disease remains, at best, limited. The most important questions remain unanswered: What is the cause, in cell physiological terms, of acute pancreatitis? What processes are involved in the progression of the disease following its inception? What mechanisms explain the distant manifestations of acute pancreatitis? Answers to these questions probably will be required before effective methods of preventing and treating this disease can be developed.

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REFERENCES


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