

Neurological Damage and Duodenopancreatic Reflux in the Pathogenesis of Alcoholic Pancreatitis

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Objective: To present a new theory on the pathogenesis of acute alcoholic pancreatitis based on experimental data, the significance of which has not been recognized, and on evidence from the current literature.

Hypothesis: That chronic alcoholism damages muscarinic receptors in the pancreas, duodenum, and Oddi sphincter, producing heightened sensitivity to acetylcholine, stimulation of protein-rich pancreatic juice, hypertonicity of the duodenum and esophagus, relaxation of the Oddi sphincter, and intraduodenal pressures exceeding those shown to cause duodenopancreatic reflux and acute pancreatitis in humans and experimental animals.

Outcome: The duodenopancreatic reflux mechanism can explain all of the clinical features of acute alcohol pan-

creatitis, including the intraductal site and rapid activation of zymogens by enterokinase, the recurrent episodes of pancreatitis, the precipitation of protein plugs by partial proteolytic hydrolysis, the severe vascular changes, the relation to infection by the most direct route, and the progression to chronic pancreatitis via the necrosis-fibrosis sequence.

Conclusions: Damage to the nervous system, with a time lag of 5 to 15 years between the onset of heavy drinking and the development of neurological disorders (peripheral neuropathy and cerebellar degeneration), is a characteristic complication of chronic alcoholism. The similarity to events in alcoholic pancreatitis is striking.

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DAMAGE to the nervous system, with a time lag between the onset of heavy drinking and the development of neurological disorders (peripheral neuropathy and cerebellar degeneration), is a characteristic complication of chronic alcoholism.¹ The similarity to events in alcoholic pancreatitis (AP) is striking, and the time lag is 5 to 15 years.

Grönroos and others²⁻⁴ proposed a new theory of the pathogenesis of AP based on the fact that the hypersecretion of pancreatic juice protein in patients with AP is due to increased cholinergic tone; supramaximal stimulation by the cholecystokinin (CCK) analogue, cerulein, causes acute edematous "pancreatitis" in animals; poisoning by anticholinesterase insecticides in humans precipitates acute pancreatitis; and a 60% decrease in rat pancreatic muscarinic receptors was demonstrated after 8 months of alcohol intake.⁴

However, acute AP and gallstone-associated pancreatitis are characterized by the inappropriate, intrapancreatic activation of pancreatic zymogens; the release of active enzymes into the interstitial space, pancreatic circulation, and peritoneal and

pleural effusions⁵⁻⁸; and evidence of marked vascular damage and pancreatic necrosis.⁹⁻¹² These major changes are not explained by Grönroos' theory.

First, cerulein "pancreatitis" is benign and edematous; marked vascular damage does not occur; the pathological process is mainly apoptosis rather than necrosis¹³⁻¹⁵; there is no general release of active enzymes into the circulation or interstitial space; there is no activation of the kinin system¹³⁻¹⁷; enzyme release into the pancreatic duct (PD) ceases; unactivated secretion accumulates in the interstitial space; and instillation of enterokinase into the PD transforms mild cerulein pancreatitis into lethal necrohemorrhagic pancreatitis.¹⁸ Cerulein pancreatitis is grossly unphysiological and despite evidence of activation of trypsinogen by cathepsin B in isolated rat acini exposed to supramaximal cerulein and additional calcium, cell viability was unaffected,¹⁶⁻¹⁷ consistent with the essentially benign nature of cerulein pancreatitis.

Second, the central role of enzyme-induced vascular damage in the pathogenesis of pancreatitis, now called "ischemia reperfusion injury," was summarized 30 years ago,^{19,20} beginning with the classic descrip-

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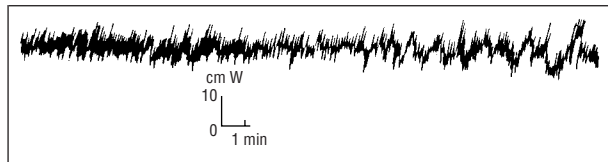


Figure 1. Normal duodenal motility. Reproduced with permission from Springer-Verlag, Berlin, Germany.³⁴ W indicates water.

tion by Rich and Duff in 1936 of a “peculiar and rapid necrosis of the walls of the pancreatic vessels in all of their cases of hemorrhagic pancreatitis,”⁹ which proved to be due to the destruction of elastic tissue by free elastase, augmented by substantial trypsinlike activity²¹; similar lesions were produced in dogs by injecting commercial trypsin,⁹ which must have contained some elastase. Discrete areas of coagulative fat necrosis were produced also by activated enzymes in the peritoneal cavity of dogs, and small vessels plugged with thrombi were closely related to the areas of fat necrosis.²²

Trypsin, phospholipase A₂, elastase, and lipase gain access to the interstitial space, lymphatics, and blood vessels via basolateral gaps in acinar cells and increased ductular permeability,^{23,24} causing widespread thromboses, hemorrhage,⁹⁻¹² infarction, and fat necrosis²² by activation of the thrombin, complement, and kinin systems^{7,25,26}; and liberation of inflammatory cytokines,²⁷ platelet activating factors,²⁸ and possibly endothelin.²⁹ These factors may contribute to death from renal failure, shock, and adult respiratory distress syndrome in 10% to 20% of patients with severe pancreatitis.²⁶

The essential question in pathogenesis is “how” and “where” are the pancreatic zymogens activated in AP? So far, only one mechanism of rapid enzyme activation has been demonstrated in man, which involves the specific physiological action of duodenal enterokinase and bile salts on trypsinogen during normal digestion and via the reflux of duodenal contents into the PD from an obstructed duodenal loop (in dogs and in man), which precipitates severe acute pancreatitis.³⁰ A study of the sequential changes developing in closed duodenal loop pancreatitis has shown also that blood vessels were affected first, followed by hemorrhagic necrosis of the parenchyma.³¹ Duodenopancreatic reflux (D-PR) therefore provides an answer to the previously mentioned questions and there is now a rational explanation for the development of recurrent D-PR in patients with AP.

Basic studies in dogs showed that D-PR occurred only during phase 3 of the interdigestive motor migrating complex in which mean duodenal pressures exceeded mean pancreatic pressure and minimal reflux was observed in 2 of 5 dogs.³² However, the increased cholinergic stimulation in AP²⁻⁴ also affects cholinergic receptors in the duodenum and Oddi sphincter (OS). Stimulation of these receptors increases duodenal tone and the amplitude of duodenal contractions and relaxes the OS.³³ The net effect is to increase the duodenal/pancreatic pressure gradient and the possibility of D-PR.

HYPOTHESIS

Excessive alcohol intake for years damages muscarinic cholinergic receptors, initially leading to reduced cholinesterase activity; increased sensitivity to acetylcho-

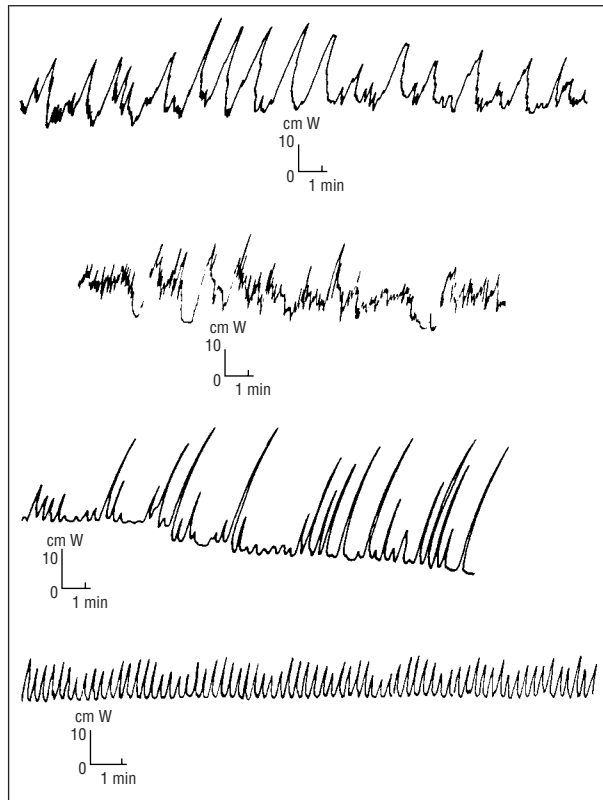


Figure 2. Duodenal motility in patients with acute pancreatitis. Reproduced with permission from Springer-Verlag, Berlin, Germany.³⁴ W indicates water.

line (ACH); duodenal hypertonicity; relaxation of the OS in response to food, fat, and alcohol; and subsequently leading to recurrent episodes of D-PR and pancreatitis, hypersecretion of protein-rich pancreatic juice, and precipitation of protein plugs. The evidence is as follows:

Motility Disturbances

Müller-Wieland³⁴ showed that the duodenal motility pattern in normal people consisted of small rhythmic contractions in rapid sequence with an amplitude of 5 to 15 cm H₂O (**Figure 1**). In patients with acute AP, irregular duodenal contractions of high amplitude (10-50 cm H₂O) alternated with relatively atonic phases (**Figure 2**).

Müller-Wieland's findings were confirmed and extended by Anderson,³⁵ who measured duodenal pressures after the intraduodenal instillation of saline, dilute hydrochloric acid, and alkali in 6 patients with chronic biliary tract disease, 7 patients with chronic pancreatitis (excess alcohol intake in 6), and 2 normal patients. In normal patients and in patients with biliary tract disease, there was a rapid rise in duodenal pressure after the instillation of acid, which returned to normal rapidly with the addition of alkali. Patients with AP developed marked and prolonged duodenal hypertonicity after acid instillation, which was associated with abdominal pain that “accurately reproduced previous attacks of pancreatitis”; the hypertonicity settled slowly with the addition of alkali. The initial resting duodenal pressures were 0 to 10 cm H₂O in 4 of the 6 patients with alcoholism and 15 to 25 cm H₂O in 4 of the 7 patients with chronic pan-

creatitis. After instillation of dilute acid, duodenal pressure exceeded 75 cm H₂O in all patients, and in 1 patient, reached 130 cm. In 3 patients, the duodenal pressure remained high for more than 20 minutes even after the instillation of alkali. Implications as to “whether it was a cause or effect of pancreatitis” were not pursued.

THESE RESULTS are highly significant when compared with closed duodenal loop pancreatitis in monkeys³⁶ and dogs,³⁷ in which D-PR occurred at duodenal loop pressures of 40 cm H₂O and between 25 and 130 cm H₂O, respectively. When alcohol was used to distend the duodenal loop instead of saline, D-PR occurred at a lower pressure and was further lowered by chronic alcohol ingestion.³⁸ Trypsinogen, kallikreinogen, and proelastase are all rapidly activated in the duodenal loop model; all 3 pancreatic proteases induce reflux pancreatitis³⁹ and the destructive effect of elastase in the canine and human pancreas is well documented.^{21,39} Important articles by Müller-Wieland³⁴ and Anderson³⁵ have been neglected (one was in a German journal,³⁴ the other was not readily accessible³⁵), and their relevance to the pathogenesis of pancreatitis was not understood. Further motility studies need to be done.

A recent study showed that esophageal peristaltic dysfunction and reflux are common in chronic alcoholism; high amplitude contractions have been recorded in the middle third of the esophagus in 13 (57%) of 23 patients with chronic alcoholism; 14 (61%) had reflux symptoms and 10 (43%) had esophageal inflammation.⁴⁰ The instillation of alcohol into the stomach or duodenum of opossums while awake also produces intense bursts of spike potential (phase 3–like activity) in the duodenum and OS,⁴¹ and a recent study in humans showed that perfusion of the descending duodenum with various ethanol-containing solutions stimulated clustered contractions that migrated aborally.⁴²

There is evidence of severe damage to nerves and ganglia in patients with AP. Inflammatory foci of lymphocytes associated with nerves were observed in the pancreas in 57% and 35%, respectively, of patients with obstructive chronic pancreatitis and AP and only in 1 case of nonalcoholic idiopathic chronic pancreatitis.⁴³ Similar foci were more commonly found in association with ganglia than in nerves in patients with chronic pancreatitis. The mean diameter of nerves was increased and they showed disintegration of the perineurial sheath sufficient to affect its permeability.⁴⁴ Electron microscopy studies in patients with alcoholic myopathy have also revealed degeneration of axons and disruption of myelin sheaths.⁴⁵

Cholecystokinin receptors on human OS tissue mediate sphincter relaxation,⁴⁶ consistent with the physiological effect of intraluminal fats and amino acids in releasing CCK, causing contraction of the gallbladder and prolonged relaxation of the OS^{47,48}; and CCK-stimulated duodenal contractions in one third of the patients tested.⁴⁸ Hypersensitivity to CCK in AP therefore should relax the OS, and Sarles and Sahel made the important observation in patients with chronic pancreatitis that “the OS was immobile and patulous, offering no resistance to the passage of contrast”⁴⁹; and in 150 patients with chronic pancreatitis and dystonia of the OS

assessed by radiological and manometric control, 133 were related to hypotonia and 17 to hypertonia.⁵⁰ Direct vision of the duodenum has also shown that anesthesia of common types causes dilatation of the papilla of Vater.⁵¹

Mean basal OS and PD pressures are similar in normal controls and in patients with AP in the basal fasting, unstimulated state.⁵²⁻⁵⁴ However, intragastric ethanol reduced peak OS pressure from 75 ± 26 mm Hg to 39 ± 19 mm Hg, and basal pressure from 30 ± 19 mm Hg to 11.8 ± 6 mm Hg.⁵³ No drugs were given before endoscopy. Several groups have also reported an excess of retrograde contractions in the OS with a corresponding fall in the percentage of antegrade phasic contractions in patients with idiopathic recurrent pancreatitis and AP, changes that could predispose to D-PR.⁵⁴⁻⁵⁶

Acute pancreatitis, abdominal pain, vomiting, and death have been reported after the ingestion of organophosphate insecticides⁵⁷⁻⁶¹ and from cutaneous exposure to these compounds.⁶⁰ Organophosphates bind irreversibly to acetylcholinesterase at acetylcholine receptors, which mediate relaxation of the OS,⁶⁰ thus producing an acute form of sensitivity to acetylcholine that mimics the more chronic alcoholic variety postulated for AP. A patulous OS in the presence of duodenal hypertonicity and D-PR would explain persistent symptoms of acute pancreatitis. In the patient with cutaneous exposure to insecticide, symptoms of pancreatitis persisted for 6 months.⁶⁰

Specific examples of D-PR include the following:

- the precipitation of severe acute pancreatitis in dogs and humans with an obstructed duodenal loop³⁰;
- the relatively common occurrence of D-PR during operative cholangiography⁶²⁻⁶⁴ and reflux occurs only when the OS is relaxed⁶⁵;
- the occurrence of reflux in 5 patients exhibiting D-PR and a hypotonic OS, and in 2 patients, one of whom had chronic pancreatitis, during gross segmental activity of the duodenum⁶⁶;
- the visibility of contrast in the common bile duct (CBD), duodenum, and PD after an intravenous infusion of cholegrafin and dextrose in a woman with gallstone-associated pancreatitis, indicating that D-PR may occur under more physiological conditions⁶⁷;
- the association of pancreatitis and D-PR, as reported in 6 patients with an incompetent papilla of Vater due to Crohn disease of the duodenum⁶⁸⁻⁷¹;
- the existence of separate openings of the PD and CBD into the duodenum, which also predispose the alcoholic patient to pancreatitis and to reflux of contrast material from the duodenum: 24 (86%) of 28 patients with AP at endoscopic retrograde cholangiopancreatography had separate openings of the ducts compared with 6 (20%) of 30 in chronic alcoholic patients without pancreatitis.⁶⁴

Pancreatitis and Lysolecithin

The combination of trypsin, bile salts, phospholipase A₂, and lecithin produces lysolecithin, which is lytic for acinar cells⁷² and which is found in the highest concentrations in the duodenum.⁷³ Lysolecithin infused at physiological pressures into the PD of rats produces severe hemorrhagic ne-

crisis,⁷⁴ and a high concentration of lysolecithin has been demonstrated in necrotic tissue of patients dying from acute pancreatitis,⁷⁵ consistent with the mechanism of D-PR.

Relation to Protein Plugs

Sarles et al⁷⁶⁻⁷⁸ attributed the precipitation of protein plugs in chronic calcific pancreatitis to an imbalance between protein hypersecretion in pancreatic juice; supersaturation of pancreatic secretion with calcium carbonate; a decreased concentration of a low-molecular-weight protein (pancreatic stone protein [PSP]), later named lithostathine, which helps to prevent the crystallization of calcium carbonate in the ducts; and an increase in the trypsinogen-trypsin inhibitor ratio, which would favor the calcification of precipitated protein.

Allan and White,⁷⁹ however, found 2 types of precipitates in human pancreatic juice collected postoperatively: concentration-dependent fine precipitates in unactivated juice, chilled on ice, which redissolved on warming, and insoluble flocculent precipitates in activated pancreatic juice. They concluded that plug formation was due to a series of partial activations of zymogens in the ductule. This was supported by the following:

1. Large amounts of protein micro precipitates and free proteolytic activity were found by Rinderknecht and Renner⁸⁰ in a patient who subsequently died from pancreatitis; in contrast, pure pancreatic juice from 10 chronic alcoholic patients without evidence of pancreatic disease confirmed protein hypersecretion in these patients, but protein plugs were not seen⁸¹; pancreatic juice obtained from 11 patients with acute or resolving acute pancreatitis contained large amounts of active enzymes (trypsin, chymotrypsin, elastase, and carboxypeptidase) and a corresponding lack of natural trypsin inhibitor.^{82,83}

2. In 1 patient with AP treated by lateral pancreaticojejunostomy, thick material resembling toothpaste occluded the large and small PDs⁸⁴ and there are similar reports of ducts filled with inspissated fluid, without any stones, in patients with acute pancreatitis.^{76,85-87}

3. Figarella et al⁸⁸ found that precipitated protein X present in pancreatic juice of patients with chronic pancreatitis was immunologically identical with a degradation product of trypsinogen liberated by proteolysis. Limited tryptic hydrolysis of PSP yields a carboxy terminal polypeptide of 133 amino acids, stated to be the main component of ductal plugs, and an N-terminal undecapeptide that exerts the inhibitory effect on calcium carbonate crystal growth.⁷⁸ A recent study in which porcine enteropeptidase was added to human pancreatic juice demonstrated rapid conversion of PSP to PSP S₁ by tryptic cleavage of the N-terminal part of PSP, and PSP S₁ has been found in serum from a patient with pancreatic disease.⁸⁹ These findings are consistent with the role of active enzymes in the formation of ductal plugs by partial proteolytic hydrolysis, and the plugs add a marked obstructive element to the inflammatory process.

Obstruction of the main PD is not the cause of AP, as it is absent in the early stages of the disease,⁹⁰ and in 33 cases of chronic relapsing pancreatitis associated with alcoholism, most showed a normal-caliber PD even when the

disease was severe.⁹¹ Protein plugs may be found also in nonactivated pancreatic juices,⁹² but this is to be expected in the intervals between episodes of acute pancreatitis.

Relation to Infection

A study of the normal flora in the small bowel showed that one third of the jejunal aspirates were sterile, one half showed minimal growth, and 17% showed significant growth,⁹³ suggesting that refluxed duodenal contents could be sterile in most cases of human pancreatitis, but were infected in 10% to 20% of patients. This is supported by a series of 405 patients dying from acute pancreatitis (90% of whom were chronic alcoholics); 243 died within 7 days of admission and 67 (27.5%) were infected. In patients surviving more than 7 days, 80% were infected.⁹⁴ Similarly, in a recent study, 38 (76%) of 50 patients with severe pancreatitis who were not receiving antibiotic prophylaxis developed pancreatic infection.⁹⁵ The presence of infection in closed duodenal loop pancreatitis in rats changes mild or moderate pancreatitis to severe pancreatitis⁹⁶ and the findings are consistent with a direct route of enteric infection via D-PR in acute pancreatitis in contrast to the translocation of bacteria from distant sites.

Usual Arguments Against D-PR

The following arguments are made against the role of D-PR: (1) the pressure gradient of about 12 mm Hg between the PD and duodenum; (2) the finding of normal OS and PD resting pressures in most cases of acute pancreatitis; (3) that sphincteroplasty allows free reflux into the PD without causing pancreatitis; (4) that procedures that make the OS incompetent are not usually followed by pancreatitis.^{97,98}

The first 2 arguments no longer apply to AP because of the evidence of marked duodenal hypertonicity, a hypotonic OS, and intraduodenal pressures in patients with AP that exceed those necessary to precipitate D-PR in experimental animals. Normal resting OS and PD pressures are irrelevant; it is the exaggerated responses to food, fat, and alcohol in the OS and duodenum that determine whether D-PR occurs. The third argument, which is often used, is an incorrect assumption. After 247 sphincteroplasties, Jones et al⁹⁹ found that there was free reflux into the CBD but not into the PD; this was also noted by others.^{100,101} This was presumably due to the separate PD sphincter, the specialized mucosal folds in the papilla of Vater,^{32,62} and the resting pressure within the PD, which is 2 to 4 times that in the CBD.^{102,103} When the transampullary septum was excised in addition to sphincteroplasty, 8 (9.8%) of 81 of the patients developed postoperative pancreatitis and only 30% of patients with chronic pancreatitis had a good result.¹⁰⁴ In a recent report, 26 patients with episodes of recurrent idiopathic pancreatitis underwent sphincteroplasty and septectomy without developing significant pancreatitis postoperatively; the selection process excluded patients with alcohol dependence¹⁰⁵ and therefore excluded the abnormal responses to food and alcohol seen in patients with AP.

It is axiomatic that D-PR would not precipitate acute pancreatitis unless refluxed material was retained for suf-

ficient time to activate pancreatic zymogens within the ducts. The complex system of mucosal folds in the papilla of Vater reacts to chemical irritation by producing a marked hyperemia and a significant increase in papillary pressure.¹⁰⁶ Initially, this mechanism would aid retention of refluxed material and also prevent further reflux. Sphincteroplasty would destroy this mechanism, increase drainage from the ducts, and therefore prevent retention of refluxed material. The balance between retention, degree of activation of zymogens, and drainage of refluxed material would determine the severity (or absence) of ensuing pancreatitis in each case. This is illustrated by the classic experiment in which bile and active proteases were continually perfused through the pancreas of a goat without causing pancreatitis¹⁰⁷: there were no barriers to drainage; there was no retention of active enzymes; the serum amylase was not altered; and the experiment was a wash-through procedure in which pancreatic secretions were continuously drained from the pancreas; therefore, although expected, pancreatitis did not ensue.

Consideration of these principles helps to answer the question of why sphincterotomy and sphincteroplasty appear to be helpful in gallstone-associated pancreatitis when these procedures increase the risk of pancreatitis.¹⁰⁸ In gallstone-associated pancreatitis, pancreatitis has already occurred and sphincterotomy aids drainage from the bile duct without substantially increasing the risk of reflux into the PD. However, there is not complete agreement about the value of endoscopic sphincterotomy (ES) in biliary pancreatitis.

In a recent study of 238 patients with acute biliary pancreatitis, 126 patients had early endoscopic retrograde cholangiopancreatography and ES, 14 of whom died (10 from acute pancreatitis); the other 112 were treated conservatively, which resulted in 7 deaths (4 from acute pancreatitis). Patients in the ES group had more severe complications.¹⁰⁹ Two hundred fourteen patients were investigated for choledocholithiasis, by transduodenal sphincterotomy in 108 patients and by exploration of the CBD only in 106. Long-term results were available in 31 patients in each group. In the ES group, 10 (32%) developed recurrent cholangitis and 7 (23%) developed chronic pancreatitis, compared with 3 (10%) and 3 (10%), respectively, in the CBD exploration group.¹¹⁰ Forty-five patients with a diagnosis of stenosis of the OS had sterile bile initially; after sphincterotomy or sphincteroplasty, 70% and 76%, respectively, had bile colonized by enteric organisms. There were no symptoms of infection, due presumably to adequate drainage of the CBD.¹¹¹ The loss of sterility in the biliary tract is permanent after these procedures. Whether this is a satisfactory situation has yet to be determined, but recent articles have documented recurrent stones, sphincter stenosis, cholangitis, and bile duct cancer as possible long-term results of ES and sphincteroplasty.^{112,113}

Endoscopic sphincterotomy, sphincteroplasty, endoscopic retrograde cholangiopancreatography, and endoscopic manometry of the papilla of Vater are all procedures that temporarily or permanently breach the normal defense mechanisms that prevent duodenal reflux, and that are associated with an increased risk of D-PR, acute pancreatitis, and death.

Relationship Between Acute and Chronic Pancreatitis

Once the pathogenetic process has started, episodes of acute AP, gallstone-associated pancreatitis, and idiopathic pancreatitis are clinically indistinguishable,^{2,114,115} particularly at the time of the first attack.¹¹⁵ The age and sex difference between the patients in the study by Sarles,¹¹⁶ who had alcoholic or gallstone-associated pancreatitis, was due to the fact that the alcoholics were mostly young men, and patients with gallstones are more often female and middle-aged.¹¹⁶

Sarles¹¹⁶ claimed that acute AP was an early manifestation of chronic AP. This view was challenged by a study of the morphologic changes in 73 patients with AP (mean follow-up, 12 years) that supported the development of chronic pancreatitis from severe acute pancreatitis (necrosis leading to fibrosis sequence),^{117, 118} and a criticism of the article¹¹⁹ was answered by the authors.¹²⁰

In addition, in a retrospective study of 247 chronic alcoholic patients dying from acute pancreatitis, 131 (53%) showed no histological evidence of chronic pancreatitis; the other 116 had evidence of both acute and chronic pancreatitis. Early chronic pancreatitis was also found in 8, 12, and 8 patients, respectively, in the miscellaneous, postoperative, and CBD stone groups.⁹⁴ Of 67 patients with acute AP and no other symptoms, 11 died and 54 had severe necrotic pancreatitis; 48 of the 56 survivors had complete clinical, morphologic, and biochemical follow-up (median, 9 years), and 7 of the 48 died after another 2 to 17 years. The authors found no evidence of chronic pancreatitis in these patients and concluded that the acute episode was not a first attack of pancreatitis in already existing chronic pancreatitis.¹²¹ Nonalcoholic acute pancreatitis may also progress to chronic pancreatitis: recurrent episodes of acute necrotic pancreatitis induced by a closed duodenal loop in rats healed with scarring.¹²² Two genetic variants of coxsackievirus B4 affect the mouse pancreas differently: one variant induces acute pancreatitis, which is followed by repair of the exocrine tissue (suggesting apoptosis rather than necrosis); the other variant caused marked destruction of exocrine tissue and chronic pancreatitis.¹²³ Acute hereditary pancreatitis is clinically indistinguishable from acute AP and gallstone-associated pancreatitis, and recurrent acute episodes of hereditary pancreatitis progress to chronic pancreatitis, which is indistinguishable from other forms of chronic pancreatitis.¹²⁴ Functional exocrine impairment was present in 9 (30%) and structural abnormalities were present in 4 (13%) of the 30 patients studied. In 4 patients (13%) who suffered multiple attacks of severe acute pancreatitis and in whom cholecystectomy was not performed, enzyme supplements were required and pancreatic calcifications were observed.¹²⁵

These observations provide convincing evidence for the necrosis-fibrosis sequence in pancreatitis, which has been widely accepted for years,¹²⁶ and suggest that the development of pancreatic fibrosis depends on the number and severity of acute attacks of pancreatitis rather than whether they are alcoholic, gallstone associated, idiopathic, or "other" in origin.

Role of Oxidative Stress and Inflammatory Mediators

Sulfhydryl compounds, particularly glutathione, protect cells from injury by oxygen-derived free radicals that are generated in a variety of models of experimental pancreatitis including cerulein pancreatitis in rats,¹²⁷⁻¹²⁹ and there is evidence that antioxidant therapy relieves pain in patients with chronic pancreatitis.¹³⁰ However, human¹³¹ and rat¹³² pancreatic zymogens are not activated by oxygen-free radicals, and the role of the latter in pathogenesis appears to be secondary to the mechanism that initiates pancreatic inflammation by activating the pancreatic proenzymes.

Inflammatory mediators (cytokines) have been recognized only in the last 10 years. Interleukin (IL-1), tumor necrosis factor α , and interleukin 6 appear in the pancreatic parenchyma within 30 minutes of induction of acute pancreatitis; in turn, they release other cytokines including platelet-activating factor and interleukin 8 and their cumulative actions may contribute to shock, renal failure, and the adult respiratory distress syndrome.²⁷ Perfusion experiments using IL-1 and tumor necrosis factor α alone do not precipitate acute pancreatitis, "colocalization, activation, or release of enzymes,"²⁷ and their production is also secondary to the mechanism initiating pancreatic inflammation. Cytokine determinations may be helpful in assessing the severity and prognosis of episodes of acute pancreatitis and, in theory, cytokine antagonists could be useful therapeutic agents, but anti-tumor necrosis factor α has so far been ineffective in clinical trials.¹³³

Role of Intra-acinar Calcium Ions

The stimulation of zymogen secretion by CCK is mediated by the mobilization and release of calcium ions into the acinar cytosol,¹³⁴ and a high level of cytosolic calcium has been suggested as the trigger for all forms of acute pancreatitis.¹³⁵ This theory is based on the cerulein pancreatitis model in which the earliest changes occur within the acinar cytosol, accompanied by a marked increase in intracellular calcium ions; the assumption that, in human pancreatitis, the earliest changes also occur within the acinar cell; and that these changes precipitate pancreatitis, which mimics clinical acute pancreatitis.

However, a sharp rise in cytosolic calcium ions is part of the normal stimulus for enzyme secretion, which returns to near-resting concentrations with continued stimulation.¹³⁴ The intra-acinar changes in cerulein pancreatitis, which include the activation of trypsinogen, are consistently benign and cell viability appears to be unaffected.^{16,17} Colocalization of lysosomal enzymes and zymogens occurs after PD ligation¹³⁶ and the pancreatitis is also benign. There is no hard evidence that the earliest changes in human acute pancreatitis occur in the acinar cytosol, and in severe experimental pancreatitis, which mimics clinical pancreatitis, the earliest changes are vascular.³¹ Although there is increased muscarinic stimulation in AP, there is no evidence that it can reach a "supramaximal" level (40 times the maximal dose) and maximal stimulation does not cause the intra-acinar changes. In clinical pancreatitis associated with gallstones or alcoholism, the serum cal-

cium concentration is normal or reduced, and most patients with hyperparathyroidism diagnosed at an early stage do not develop pancreatitis.¹³⁷

By contrast, severe hypercalcemia (whether due to multiple myeloma,¹³⁸ vitamin D intoxication,¹³⁹ or hyperparathyroidism)¹⁴⁰ does cause acute pancreatitis, although the mechanism is uncertain. Autoactivation of trypsinogen is unlikely; it is a slow *in vitro* process that takes hours, and the high content of natural trypsin inhibitor would neutralize slow activation *in vivo*.¹⁴¹ In a recent study of 1224 patients with hyperparathyroidism, 40 had pancreatitis (acute in 18, subacute in 8, and chronic in 14) and the serum calcium level was significantly higher in the patients with pancreatitis than in those without.¹⁴⁰

Episodes of severe abdominal pain unrelated to peptic ulceration or acute pancreatitis occur in cases of untreated hyperparathyroidism and chronic AP, consistent with duodenal spasm¹⁴² or hyperstimulation of nerves and ganglia. Hypercalcemia is known to stimulate pancreatic secretion,¹⁴³ and it may have other cholinergic actions including increased duodenal tone, a relaxed OS, and a pressure gradient favoring D-PR, which could explain the association between all forms of hypercalcemia and acute pancreatitis. This alternative hypothesis is open to testing by motility studies of the duodenum and OS in patients with marked hypercalcemia.

CONCLUSIONS

The proposed model of pathogenesis can explain, to our knowledge for the first time, all of the typical features of AP, including the following:

- The time lag between the onset of heavy drinking and neurological damage, which is typical of slow poisoning by alcohol abuse in other neurological disorders, and why only a proportion of heavy drinkers are affected.
- The recurrent episodes of acute AP, precipitated by D-PR, and associated with a pressure gradient from the duodenum to the PD that exceeds that proven to cause D-PR and pancreatitis in man, monkeys, dogs, and rats.³³⁻³⁸
- The rapid activation of pancreatic zymogens by the physiological action of enterokinase and bile salts, and the neutralization of protease inhibitors.
- The site of zymogen activation—intraductal—shown by the presence of active enzymes within the ducts.^{78,80,82,83}
- The precipitation of protein plugs by partial proteolytic hydrolysis of lithostathine at an appropriate pH for tryptic activity.
- The central role of enzyme-induced vascular damage via the actions of trypsin, elastase, phospholipase A₂, and the activation of the thrombin, complement, kinin systems, and platelet-activating factors.
- The pathogenesis of fat necrosis by vascular damage and coagulative necrosis.²²
- The relationship between recurrent episodes of D-PR and acute necrohemorrhagic pancreatitis leading to the development of chronic AP via the necrosis-fibrosis sequence.
- The relationship between acute pancreatitis and exposure to insecticides through damage to cholinergic receptors in the duodenum and OS as well as in the pancreatic parenchyma.

- The reason why infection by enteric organisms complicates pancreatitis in some patients and not in others via the most direct route from the duodenum.
- The relationship between marked hypercalcemia (due to a variety of factors) and pancreatitis, via muscarinic stimulation of duodenal tonicity and associated relaxation of the OS.

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