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PATHOPHYSIOLOGY OF GALLSTONE PANCREATITIS

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1. ABSTRACT

Gallstone pancreatitis was first recognized as an entity by Opie in 1901 (1), and since then has generated volumes of literature which have attempted to explain its pathophysiology. Multiple animal experiments and human clinical studies in the past thirty years have led to a better understanding of both macro- and microscopic events which lead to pancreatic inflammation in the setting of a passing or impacted gallstone. Evidence suggests that pancreatic duct outflow obstruction is the initial event. Several possible sequelae of duct obstruction, including refluxed biliary-pancreatic secretions, pancreatic duct hypertension, and/or aberrant acinar cell secretion may result in pancreatic duct injury and release of pancreatic enzymes into the glandular interstitium, thus triggering a bout of acute pancreatitis.

The details of many events related to gallstone pancreatitis remain unclear; this chapter attempts to present the pathophysiology of this disease as it is known today. Additionally, clinical presentation and treatment of gallstone pancreatitis will be reviewed briefly.

2. INTRODUCTION

Gallstone, or biliary, pancreatitis refers to an episode of acute pancreatitis which is presumed to have been caused either by the passage of one or more gallstones through the intrapancreatic common bile duct and into the duodenum, or by the temporary or long-term impaction of a gallstone within the ampulla of Vater. While gallstones are one of the two most common causes of acute pancreatitis in the United States (the other being heavy alcohol consumption), only 3-8% of patients with symptomatic gallstones suffer from acute pancreatitis during their lifetimes (2,3). Gallstones are more common in women than men, which likely accounts for the finding that more than 70% of patients with biliary pancreatitis are female (4).

These patients usually present for medical attention with complaints of mid-epigastric pain, which may radiate to the back, nausea, vomiting, abdominal distention, fever, and occasionally jaundice. Laboratory findings of elevations in serum amylase and lipase typically confirm the diagnosis of acute pancreatitis. Elevated liver function tests, especially aspartate aminotransferase (5) and alanine aminotransferase (6) may also occur. The presence of gallstones on abdominal sonography, in the absence of a history of binge drinking, is highly suggestive of gallstone pancreatitis. Patients with small gallstones, a large number of gallstones, or an enlarged cystic duct may be predisposed to bouts of gallstone pancreatitis (2,7).

Establishing the diagnosis of gallstone pancreatitis is usually straightforward. In the majority of patients, this is a self-limited disease; however, in 10-15% of patients, it is severe and sometimes fatal (3,8). Gaining a better understanding of the pathophysiology of gallstone pancreatitis is critical to the success of our efforts to improve survival in this disease.

3. THE PATHOPHYSIOLOGY OF GALLSTONE PANCREATITIS

3.1. The inciting event: pancreatic duct outflow obstruction

3.1.1. Opie's common channel hypothesis

In 1900, Johns Hopkins pathologist E.L. Opie performed an autopsy on a patient who died of acute pancreatitis. Upon finding a gallstone impacted at the ampulla of Vater, he theorized that it was related to the pancreatitis, presumably by causing reflux of bile through the common channel (junction of main pancreatic and common bile duct) and back into the main pancreatic duct (1). The ampulla of Vater, the slightly bulbous termination of the common channel, lies within the wall of the second part of the duodenum and terminates in the major duodenal papilla. It is a logical place for a gallstone to lodge, given its distal location and the small diameter of the papilla (mean 2.1-2.5 mm)(7,9) relative to the common channel (mean 3.9 mm)(9). Opie's common channel hypothesis is also supported by autopsy studies in which a common channel was found in 74-89% of the general population (9,10). Recent evidence continues to support the importance of impacted ampullary stones in some patients. Kelly and colleagues found that 26% of patients undergoing early operation (within 48 hours of presentation) for gallstone pancreatitis had an impacted ampullary stone (11). These findings are consistent with those of Isogai, who reported that 57% of patients who underwent emergent surgery had an ampullary stone present at exploration (12). These studies provide compelling circumstantial evidence that impacted stones at the level of the ampulla contribute to the development of gallstone pancreatitis in some patients.

Obstruction of a common channel by an impacted stone does not explain the occurrence of gallstone pancreatitis in all patients. Autopsy studies indicate that *separate* ductal openings into the duodenum for the common bile duct and pancreatic duct are found in 18-19% of patients (9,10). Jones and colleagues found that 33% of patients with gallstone pancreatitis who underwent intraoperative cholangiography had separate ductal openings (13). Also, for reflux to occur, the common channel would have to be of sufficient length for bile to pass from the common duct into the pancreatic duct proximal to an impacted stone. Common channels are usually relatively short; Hand found that 50% of patients had a common channel length of 4-7 mm (9), and 42% of common channels studied by DiMagno *et al.* were less than 3 mm in length (10). Stone size in gallstone pancreatitis ranges from 1-15 mm (14). Furthermore, Elliott, Williams, and Zollinger in 1957 (15) noted that pancreatic ductal pressure is uniformly higher than common bile duct pressure, making simple reflux of bile alone after stone impaction (and in the absence of other factors) unlikely to occur. Thus, it seems probable that ampullary stones contribute to, but may not be a sufficient condition for, the development of biliary pancreatitis in some patients.

3.1.2. Migrating stones

Seminal studies by Acosta and Ledesma in 1974 (14) and by Kelly in 1976 (16) supported the concept that either passage of a stone through the ampulla, or temporary stone impaction followed by passage, might cause acute pancreatitis. Acosta and Ledesma compared stool samples from 36 patients with gallstone pancreatitis to those from 36 patients having other biliary tract conditions (colic, cholecystitis, jaundice) without acute pancreatitis. The feces of 94% of the biliary pancreatitis cohort contained gallstones, versus only 8% of the controls (14). Comparable proportions of 84% and 11% were reported by Kelly (16). Additionally, patients with gallstone pancreatitis who undergo surgery earlier in the course of their disease (17 hours – 7 days after presentation) have a higher percentage of common bile duct stones detected at the time of surgery (64-75%) than those in whom surgery is delayed (22 days – 3 months after presentation; 12-18%)(2,17). This would suggest that a greater percentage of stones have passed into the gastrointestinal tract in the delayed cohort.

Acosta and Ledesma were the first to characterize stones in patients with gallstone pancreatitis. In stool studies they found a single stone in 24 of 34 (71%) patients, whereas multiple stones were found in 29% (14). Kelly's results were in agreement with these findings and he also found that stones ranged in size from 1-12 mm (16).

Several studies have shown that patients with gallstone pancreatitis tend to have a greater number of small stones (<5 mm diameter)(7,18,19,20). Two of these studies showed that mulberry-shaped gallstones were more common (18,19), and one (18) indicated that they tended to be lighter in weight. In theory, stones might also be able to migrate more easily if "escape" from the gallbladder and cystic duct into the common bile duct was facilitated. Supporting this concept, data from an extracorporeal shock wave lithotripsy (ESWL) study (21) indicates that clearance of gallstone fragments from the gallbladder is increased when the fragment size is <3 mm in diameter. Moreover, Kelly reported that patients with gallstone pancreatitis had larger-diameter cystic ducts than matched controls (3.8 mm vs. 2.4 mm, respectively) (7), and Armstrong *et al*. (2) substantiated these findings (4.9 vs. 3.7 mm, respectively). Whether a wider cystic duct facilitates gallstone passage, or rather cystic duct dilatation is the result of gallstone passage, is unknown.

Although migrating stones are accepted as a likely inciting event in many patients with gallstone pancreatitis, this theory does have some potential weaknesses. If the presence of migrating stones was a sufficient condition to produce pancreatitis, one would have predicted that pancreatitis should have affected the majority of patients after ESWL for symptomatic gallstones, rather than the observed 1.5-2% (21). The goal of this therapy was to render the stone fragments small enough to pass out of the gallbladder via the cystic duct and into the common bile duct. Migrating stone theories also rely on a common channel for the drainage of bile and pancreatic juice into the duodenum. As noted above (section 3.1.1), a common channel is not present in 18-33% of patients. Furthermore, in some cases, stones may have difficulty migrating to the orifice of the common channel and into the gastrointestinal tract. In an autopsy study that focused on the choledochoduodenal junction, Hand described a thickened portion, or "notch", in the common bile duct just proximal to its junction with the pancreatic duct and entry into the duodenum. The average diameter here was only 1.9 mm, and the author noted that "gallstones are usually held up above the notch" (9). The above considerations suggest that additional conditions, besides migrating stones, may be necessary for the development of pancreatitis.

3.1.3. Sludge and microlithiasis

Many cases of acute pancreatitis, primarily those in which a diagnosis of gallstone or alcohol-induced pancreatitis is not made, are called "idiopathic". Two studies from the early 1990s suggest that many of these idiopathic cases may be related to gallbladder sludge and microlithiasis. Ros *et al.* (22) examined stimulated duodenal bile from 51 patients, 4-8 weeks after discharge from hospital for idiopathic acute pancreatitis. They found "abnormal biliary sediment" (cholesterol monohydrate crystals, calcium carbonate microspheroliths, and calcium bilirubinate granules) in 67% of these patients, compared to zero percent in controls (alcohol- and triglyceride-induced pancreatitis). They also noted that sludge or small stones were present in most of the "idiopathic" patients on follow-up ultrasound.

A similar study done by Lee, Nicholls and Park (23) showed that 74% of patients convalescing from idiopathic acute pancreatitis had sludge (a suspension of cholesterol monohydrate crystals or calcium bilirubinate granules) detected by bile sampling or ultrasound. Long-term follow-up revealed that the patients with sludge who had either cholecystectomy or papillotomy had fewer episodes of recurrent acute pancreatitis.

These studies indicate that sludge or abnormal gallbladder sediment is another potential cause of gallstone pancreatitis. How sludge might cause pancreatic duct outflow obstruction is unknown. Possible explanations include inflammation of the sphincter during passage, or stasis of flow within a very narrow common channel.

3.1.4. Functional obstruction at the sphincter of Oddi

It is clear that most patients with gallstone pancreatitis pass stones into the gastrointestinal tract. The ability of these stones to generate pancreatic ductal outflow obstruction via short- or long-term impaction at the major duodenal papilla seems to require that multiple other factors, related to physical characteristics of gallstones and the choledochoduodenal junction, are present. An understanding that all of these circumstances might not exist simultaneously led some investigators to question whether characteristics of the (ampullary) sphincter of Oddi sometimes account for pancreatic ductal obstruction in gallstone pancreatitis. Stone *et al*., in 1981, found that 89% of their 36 patients who underwent early (<36 hours after admission) operation for biliary pancreatitis had inflamed ampullary regions at exploration (17). This percentage dropped to 17% in the cohort who had late (>3 months after admission) surgery. These findings led them to hypothesize that gallstones generate inflammation as they pass through the ampulla. In theory, an inflamed ampulla could cause ductal outflow obstruction, even in the absence of an impacted stone. Hernandez and Lerch (24) also proposed that the ampulla is sometimes functionally stenosed after gallstone passage. In their 17 patients who had cholecystectomy for a variety of conditions, those with gallstone pancreatitis and those with choledocholithiasis (and no pancreatitis) had meal-stimulated reflux of amylase into their T-tubes. The authors speculated that this pancreatic enzyme refluxed into the common bile duct, rather than exiting into the duodenum, because the sphincter of Oddi was obstructing its outflow. Common bile duct, duodenal, and sphincteric pressures were studied by Guelrud and colleagues in 1983 (25). They used endoscopic manometry to evaluate six patients at least one month after an episode of biliary pancreatitis, and compared them to 58 patients without a history of pancreatitis. The patients with a history of biliary pancreatitis had a higher mean pressure gradient between the common bile duct and duodenum, as well as a higher basal sphincter of Oddi pressure. Since the study was done after the episodes of pancreatitis, one cannot conclude whether such differences in sphincteric pressure were caused by a passing or impacted gallstone, or whether such differences might have predisposed patients to pancreatic duct outflow obstruction. Nevertheless, the idea that motor dysfunction at the sphincter might contribute to gallstone pancreatitis is intriguing.

These studies all demonstrate that abnormalities at the sphincter of Oddi, in the form of edema, inflammation, or unduly high basal pressure, may contribute to pancreatic ductal outflow obstruction. In fact, in the small percentage of patients in whom impacted or fecal gallstones are not found, or in whom there is no common channel, these sphincteric characteristics might make a definitive contribution to biliary pancreatitis.

3.1.5. Focus on the pancreatic duct

It seemed conceivable, then, that one or more stones impacting within and/or passing through the biliary tree could cause acute pancreatitis; however, as early as the 1960s, investigators recognized that these events likely required several concomitant circumstances related to anatomy, timing, pressure, and secretions. Examinations of the pancreatic duct were initiated to determine whether characteristics of the duct or actions of certain agents upon it might allow for a more inclusive view of the pathogenesis of biliary pancreatitis.

Was reflux of bile into the pancreatic duct even necessary? Lerch and colleagues (26), in 1993, attempted to answer this question by ligating the opossum's extrahepatic ductal system at various locations. They found that parameters of acute pancreatitis were essentially equivalent among all groups with pancreatic ductal outflow obstruction, including the group with isolated pancreatic duct obstruction (no reflux of bile possible). This led them to conclude that bile reflux and/or common bile duct obstruction might not be required in the pathogenesis of gallstone pancreatitis; in other words, pancreatic duct obstruction might be the critical initial event. Arendt *et al.* (27) substantiated the importance of main pancreatic duct obstruction in 1997 when they developed a rabbit model in which they created a duct of Santorini. They noted that obstruction of the main pancreatic duct caused pancreatic edema, but that this effect was not seen when pancreatic juice was allowed to egress via the duct of Santorini. In 1999, the same group showed that separate obstruction of the common bile and pancreatic ducts did not cause acute pancreatitis, but that temporary obstruction of the pancreatic duct, followed by decompression and flow of infected bile at high pressure into the pancreatic duct, did generate the disease (28). They surmised that pancreatic duct obstruction was necessary, but was not the only step required, for the genesis of acute pancreatitis.

3.2. Sequelae of pancreatic duct obstruction

Pancreatic duct outflow obstruction is thought to be a pivotal initial event in the pathogenesis of biliary pancreatitis. Since pancreatic duct injury follows outflow obstruction, investigators have focused on identifying an injurious "agent" that could induce pancreatic damage. In this section, the normal physiology of the pancreatic duct is briefly reviewed and potential mediators of ductal compromise are discussed.

3.2.1. Normal physiology: the pancreatic duct mucosal barrier

Intact pancreatic duct epithelial cells serve three important functions: (A) they line the duct and thereby serve as a conduit for pancreatic acinar and duct cell secretions; (B) they secrete water, bicarbonate (via an active transport mechanism), and electrolytes into the duct, following stimulation by the gut hormone secretin (3); and (C) they secrete mucus, which is thought to serve a protective function (29). Indeed, the pancreatic duct epithelium is relatively impermeable to sterile bile and bicarbonate (30).

3.2.2. Refluxed fluid

Refluxed fluid was the first potentially injurious agent discussed in conjunction with biliary pancreatitis; the common channel and migrating stone theories both implicated it in the pathogenesis of the disease. Intraoperative cholangiography in patients with gallstone pancreatitis demonstrates reflux into the pancreatic duct in 43-67% (7,16,31). Whether fluid is able to flow retrograde into the pancreatic duct, and the nature of this fluid's composition, depends on numerous factors, including ductal pressure gradients, bacterial inoculum, and duration of duct outflow obstruction. Three types of fluid are reviewed below.

3.2.2.1. Bile-pancreatic juice mixture

Given that pancreatic duct pressure is usually higher than common bile duct pressure, it was assumed that obstructed pancreatic secretions would first mix with bile before conditions would change and reflux could occur. It thus seemed reasonable to test how a bile-pancreatic juice mixture might affect the pancreatic duct.

In 1957, Elliott, Williams, and Zollinger (15) obstructed the canine common bilio-pancreatic duct and measured pressures. They found that the pancreatic ductal pressure increased steadily for the first 12 hours, stabilized, and came into equilibrium with common bile duct pressure by about 24 hours. They concluded that this time period allowed secretions to mix. Further, they injected various solutions into the pancreatic duct and found that the duct exhibited different levels of resistance to infusion depending on the nature of the fluid. Bile-pancreatic juice mixtures, and bile mixed with trypsin, were allowed to incubate for at least 24 hours. They were then easy to instill and caused acute hemorrhagic pancreatitis. A lack of incubation time caused little damage, and bile alone caused little damage.

Joyeuse, Hallenbeck and McCaughey (32) sought to replicate the findings of Elliott *et al.* in experiments conducted in 1962, in which they infused solutions into the canine pancreatic duct. They, too, demonstrated that an incubated bile-activated pancreatic juice mixture tended to generate severe pancreatitis, while solutions that either were not activated (by enterokinase) or were not mixed caused very little damage. Studies on the feline pancreatic duct by Konok and Thompson (29) showed that an activated bile-pancreatic juice mixture yielded pancreatic interstitial edema, but they did not find evidence of necrosis.

The above animal experiments led to the conclusion that incubated (or activated) bile-pancreatic

juice could cause acute pancreatitis. This model seemed to be coincident with the human state of biliary pancreatitis, in which it was assumed (at that time) that an obstructing gallstone and a common channel would allow pancreatic secretions to mix with bile. Such a mixture appeared to be able to enter the pancreas at lower or equalized pressures and cause glandular damage.

3.2.2.2. Infected bile

Subsequently, many investigators sought to determine whether the presence of bacteria in bile might make bile alone, or a bile-pancreatic juice mixture, toxic to the pancreatic duct. *Escherichia coli*, a common gastrointestinal pathogen that is often found in the bile and stones of patients with cholangitis (33), was the organism used in most of these studies, although sometimes other enteric flora or mixed inocula were used.

Konok and Thompson, in their 1969 study (29) discussed above, demonstrated that bile infected with *E. coli* caused significant duct wall destruction, interstitial edema, and leukocyte infiltration. Arendt and his colleagues conducted three important studies on infected bile in the 1990s. In 1997 (27), they showed that infected bile caused acute interstitial pancreatitis in rabbits and, notably, that a patent duct of Santorini allowed this fluid to flow retrograde into the pancreas in a model of common channel obstruction. In 1998 (34), human bile inoculated with various bacterial species was instilled into ligated rabbit pancreatic ducts. Mixtures with each of the bacterial species used generated acute interstitial-edematous pancreatitis, as well as necrosis and loss of duct epithelial cells. In 1999 (35), they again found that ductal disruption and non-lethal acute pancreatitis resulted from infusion of infected human bile into the ligated rabbit pancreatic duct. One interesting aspect of the latter study was that the infected bile (>10,000 CFU/ml) was obtained via ERCP specimens from human patients with gallstone pancreatitis.

Other investigators did studies to determine how infected bile might cause damage to the pancreatic duct, and how the duct might be altered at a microscopic level. Enzymes produced by enteric flora were explored by Mizumoto and colleagues (36). Their infusion of bile-beta glucuronidase or trypsin-beta glucuronidase mixtures into the rabbit pancreatic duct caused severe necrotizing pancreatitis and destruction of the pancreatic duct. Reber *et al.* (30) later showed that perfusion of the feline pancreatic duct with infected bile increased ductal permeability. A 1991 experiment by Arendt (37) revealed that *E. coli*-infected human bile labeled with a tracer and infused into the feline pancreatic duct caused progressive changes in duct ultrastructure. Tracer was visualized to cross the ductal epithelial barrier as early as 15 minutes after infusion was begun, and tight junctions between duct epithelial cells failed to maintain their barrier function as time progressed.

Bacterial content and ductal pressure were addressed by Armstrong *et al.* (38) in 1985. They found that infected bile instilled into the rat pancreatic duct at either low (8 cm H2O) or high (35 cm H2O) pressure caused significant damage to the duct, including loss of cells into the ductal lumen and increase in ionic flux across the duct epithelium.

Several animal studies, then, have indicated that bile with a high bacterial content can compromise the barrier function of the duct, damage duct cells, and lead to histologic changes of the pancreas consistent with acute pancreatitis. While these studies seem conclusive, how often infected bile might be the damaging ductal "agent" is less certain. In their 1999 study (35) in which bile specimens from 21 biliary pancreatitis patients were obtained by ERCP, Arendt et al. noted that only 29% of these patients had bile which could be considered "infected" (>10,000 CFU/ml). Similarly, Acosta and colleagues reported infected bile in 26 of 78 (33%) patients (39).

3.2.2.3. Non-infected bile

Experiments using sterile bile or bile with a low bacterial count sought to demonstrate whether bile needed to be infected in order to impair pancreatic ductal integrity.

Mizumoto *et al.* (36) and Reber *et al.* (30) both showed that infusion of bile lacking bacterial enzymes, or of sterile bile, did not cause pancreatic duct destruction or increased ductal permeability in the same manner as infected solutions. In 1997, Arendt and colleagues (27) demonstrated that sterile bile flow along the rabbit pancreatic duct failed to produce inflammatory lesions of the pancreas. The same group documented in 1998 (34) and 1999 (35) that sterile human bile, or bile with less than 10,000 CFU/ml bacteria from biliary pancreatitis patients, instilled into a ligated rabbit pancreatic duct, caused either no effect or minimal edematous changes of the gland.

Despite the above studies, there is some evidence to indicate that non-infected bile may sometimes cause pancreatic duct damage. Armstrong *et al.* (38), in addition to their findings with infected bile (section 3.2.2.2), studied infusion of sterile human bile into the rat pancreatic duct at low and high pressures. Sterile bile did yield moderate increases in anionic flux and transductal potential difference at low pressure, but caused significantly greater changes when instilled at high pressure. The bile salt glycodeoxycholate, at physiologic pressures (7-28 cm H2O), was shown by the same group (38) to cause increased ionic flux and ductal ultrastructural damage. The damage worsened with higher concentrations of the bile salt. Alvarez, Fasano, and Bass (40) found that the bile salt taurodeoxycholic acid (TDCA) induced dose-related reductions in tissue resistance and short-circuit current across bovine pancreatic duct epithelium. Changes seemed to be reversible at low doses, but low doses of the bile salt also caused loss of response to a secretory agent (forskolin). The latter finding prompted these authors to propose that even small amounts of bile in the pancreatic duct could impair the normal secretory function of the duct.

There is considerable evidence, then, to indicate that exposure of the pancreatic duct to several fluid types might cause ductal compromise that in turn might lead to acute pancreatitis. Incubated bile-pancreatic juice mixtures,

bile with a high bacterial count, or sterile bile at high pressure seem to be the most likely candidates, although even sterile bile at physiologic pressures can cause aberrations in duct cell function and ultrastructure.

3.2.2.4. Duodenal secretions

The sphincter of Oddi normally serves as a barrier to the retrograde flow of duodenal secretions, which contain activated pancreatic enzymes, from the duodenum into the extrahepatic ductal system. In theory, reflux of duodenal secretions through an incompetent sphincter and into the pancreatic duct could result in acute pancreatitis (Steer, 41). Such a mechanism might result from sphincter stretching or injury after passage of a gallstone. In a model intended to replicate post-Billroth II pancreatitis in the dog, McCutcheon and Race in 1962 (42) created a blind duodenal loop and demonstrated that refluxed duodenal contents caused pancreatitis that ranged from mild to severe hemorrhagic in histologic appearance. Since acute pancreatitis is an uncommon complication following endoscopic sphincterotomy, protective mechanisms must exist which limit the incidence and/or severity of this phenomenon.

3.2.3. Persistent acinar cell secretion

Under normal conditions, fat and protein in the duodenum trigger cholecystokinin (CCK) secretion from mucosal endocrine I cells of the small intestine (43). CCK subsequently stimulates pancreatic zymogen release from acinar cells into the pancreatic duct. Yeo and Cameron (3) note that the normal human pancreas produces exocrine secretions (including water and electrolytes from duct cells) at a basal rate of 0.2-0.3 ml/min and a maximal rate of 5.0 ml/min. Samuel and colleagues (44) quantified acinar cell stimulation by measuring amylase activity in the zymogen-enriched subcellular fraction of rat pancreas homogenates. They found that acinar cells were hyperstimulated to secrete amylase when the common bile-pancreatic duct was ligated, a model of gallstone obstruction. Otsuki suggests that duodenal depletion of bile-pancreatic juice, as occurs in gallstone pancreatitis, may free CCK-releasing cells from tonic inhibition and thereby increase CCK-induced stimulation of acinar cells (43). Bile may provide tonic inhibition of CCK-releasing cells while proteases degrade and inactivate CCK releasing factors. In gallstone pancreatitis and pancreatic ductal obstruction, therefore, duct and acinar cells may secrete against a closed system and their products are unable to egress into the second portion of the duodenum. This generates a cycle in which increased CCK levels may cause hyperstimulation of the acinar cells, which could contribute to pancreatic duct hypertension and tissue damage.

3.2.4. Duct hypertension

Resting pressure in the human pancreatic duct is approximately 8 cm H_2O and after maximal exocrine stimulation a hypertensive reading of 35 cm H_2O is recorded (Armstrong *et al*., 38). Animal models of duct hypertension (ligation of the pancreatic duct or infusion of fluid into the duct at high pressure) have shown consistently that hypertension alters the macro- and microscopic appearances of the pancreatic duct. For example, Metz *et al*. (45) found that ligation of the rat pancreatic duct resulted in ductal dilatation, a skewed arrangement and appearance of duct epithelial cells, and a compromised paracellular permeability barrier. Armstrong *et al.* (38) obtained similar results after ligation and perfusion of the rat bile-pancreatic duct, and noted that higher perfusion pressures led to more striking changes. Bockman and colleagues (46) examined the distribution of fluid which had been infused into the canine pancreatic duct at elevated pressures, and found that it disrupted the ductal epithelium and flowed into the periacinar space. Thus, it seems possible that duct hypertension may contribute to pancreatic injury via a breakdown in epithelial integrity and exposure of the pancreatic interstitium to enzyme-rich pancreatic juice.

3.3. Pathophysiologic consequences of pancreatic duct injury

As discussed in previous sections, many investigators have shown that changes in duct cell function and morphology can stem from a variety of injurious agents associated with biliary pancreatitis. The mechanism by which pancreatic duct obstruction leads to acute pancreatitis is not completely clear. Current thinking favors a pathway, described below, involving aberrant regulation of acinar cell secretion leading to cellular injury.

3.3.1. Acinar cell secretory blockade

In normal acinar cells, a secretory stimulus such as CCK causes the movement of zymogen granules (containing inactive pancreatic digestive enzymes such as trypsinogen and chymotrypsin) to the apex of the cell. Here, after the granules fuse with the plasma membrane, zymogens are released into the lumen of the pancreatic duct. They travel to the duodenum where enterokinase cleaves trypsinogen and begins a cascade of enzyme activation (3). Although pancreatic duct obstruction initially leads to increased acinar cell secretion (section 3.2.3), later in the course of acute pancreatitis secretory blockade occurs (41,47). The mechanism of secretory blockade is unknown. It is possible that hypertension or duct cell damage may inhibit the acinar cell's normal secretory mechanisms via a neural or other pathway. Alternatively, Luthen and colleagues (48) and Steer and Meldolesi (47) suggest that damaged duct cells and/or the outflow obstruction (elevated hydrostatic pressure) which initiated the disease might act as mechanical inhibitors to secretion. Secretory blockade is thought to promote co-localization of pancreatic digestive enzymes and lysosomal hydrolases (47), discussed below (section 3.3.2).

3.3.2. Co-localization of digestive enzymes and lysosomal hydrolases

Acinar cell lysosomes are normally in a different subcellular compartment from the zymogen granules, and this separation presumably functions to protect the cell from "premature" intracellular activation of destructive digestive enzymes. Lysosomal hydrolases are not, therefore, involved in zymogen activation under normal conditions. Steer and colleagues found large cytoplasmic vacuoles containing both pancreatic digestive enzymes and lysosomal hydrolases in the pancreas from many groups of

animals in which acute pancreatitis had been induced using several different techniques (41,47). These results were supported by those of Oshio *et al.* who showed that short-term ligation of the rat pancreatic-biliary duct led to redistribution of the lysosomal enzyme cathepsin B from the lysosomal fraction of the acinar cell to the zymogen granule-enriched fraction (49). In 1995, Luthen and colleagues (48) used retrograde infusion and ductal ligation models of biliary pancreatitis to document a similar shift of cathepsin B and beta-galactosidase, as well as increased activity of these lysosomal enzymes within the pancreas. In another model of gallstone pancreatitis, Hirano and Manabe (50) showed that cathepsin B redistribution, lysosomal and mitochondrial fragility, and increases in serum amylase and pancreatic water content were most pronounced in rats with repeated pancreatic-biliary duct obstruction and concomitant exocrine stimulation. Thus, aberrant trafficking of subcellular vesicles seems to result in co-localization of pancreatic digestive enzymes and lysosomal hydrolases.

3.3.3. Cytoplasmic activation of pancreatic enzymes

Co-localization of these enzymes (lysosomal and digestive) would be expected to result in intracellular activation of proteolytic enzymes. Trypsin, chymotrypsin, and other active pancreatic enzymes could then injure the acinar cells directly (41), and, presumably, invade the interstitium via basolateral extrusion or damaged cell membranes. Additionally, activated enzymes that are released into the pancreatic duct might gain access to the pancreatic interstitium via back-diffusion through a compromised duct epithelium (see section 3.2) (45). Indeed, activated pancreatic enzymes have been found in pancreatic duct fluid (51) and ascites (52) from patients with acute pancreatitis.

4. ACUTE PANCREATITIS: CLINICAL MANIFESTATIONS AND TREATMENT

Previous sections of this chapter have attempted to illustrate that there are probably many complex mechanisms by which gallstones can trigger acute pancreatitis. Once acute pancreatitis has begun, though, the histologic changes of the gland and its surrounding retroperitoneal area are fairly consistent regardless of etiology. Notable is that the extent of these changes does vary considerably among individual patients.

Parenchymal edema, secondary to local vasodilatation and leakage of pancreatic juice into the interstitium, is the most commonly seen change in acute pancreatitis. Infiltration of polymorphonuclear leukocytes and red blood cells into the pancreas are sometimes seen, and the disease progresses to gangrene and necrosis of the gland in some patients (3,47,53). Retroperitoneal fluid sequestration and fat necrosis are extra-pancreatic sequelae of pancreatic inflammation.

4.1. Clinical presentation

Patients with gallstone pancreatitis typically complain of midepigastric or upper abdominal pain (which may radiate to the upper back), nausea, and vomiting. Significant fever, tachycardia, or tachypnea, if present, may be harbingers of severe pancreatitis (3). Severe pancreatitis affects about 10% of patients and is characterized by hemodynamic instability, pulmonary decompensation, and altered mental status. About 2-7% of the western population with gallstone pancreatitis has concurrent cholangitis (8). Hospital mortality from gallstone pancreatitis is estimated at 10-25% (8,23).

Nearly all patients with acute pancreatitis have significant elevations in serum amylase and lipase (3). In contrast to those with alcoholic pancreatitis, patients with gallstone pancreatitis typically have amylase peaks within 24 hours of presentation in the 1000-1500 IU/dl range and the amylase decreases precipitously (often by 50% per day in the first 2-3 days) in most patients. Thus, if the patient presents for evaluation several days into the illness, the peak amylase may have already occurred, and this delay occasionally obscures the diagnosis. The frequent finding of elevated liver function tests (3,5,6) in patients with gallstone pancreatitis may be due to hepatocyte necrosis caused by common bile duct hypertension (12).

4.2. Variability in disease progression

It can be difficult to predict at the time of presentation which patients will progress to severe pancreatitis. The magnitude of increase in pancreatic enzyme levels does not correlate with disease severity (54). Recently, a group from Harbor-UCLA Medical Center has proposed using an admission serum glucose level of $\geq$150 mg/dl as a single predictor of those patients who will progress to severe biliary pancreatitis (55,56). They conclude that this test is superior to the biliary Ranson score (57,58), largely because one does not need to wait 48 hours to calculate the predictive score. Neoptolemos (59) observed that his biliary pancreatitis patients who had common bile duct stones present on ERCP were more likely to develop complications of the disease, and theorized that persistent, large gallstones present in the common bile duct predispose patients to severe forms of gallstone pancreatitis.

Why do some patients have mild self-limited pancreatic inflammation while others have hemorrhagic necrosis of the pancreas and surrounding fat accompanied by multisystem organ failure? Considerable controversy has surrounded this question. Some investigators maintain that the severity of the disease is determined early on in the course of gallstone pancreatitis, while others believe that certain factors may intercede to convert mild to severe inflammation.

Supporters of the theory that the degree of pancreatic disease is determined in the beginning stages of biliary pancreatitis rely on findings from animal studies that short-term ductal obstruction can yield significant changes in cellular and glandular morphology (49,60). In the clinical arena, patients with acute pancreatitis who have been treated with agents that quell pancreatic exocrine secretion have not experienced lower morbidity or mortality than untreated controls. Additionally, the use of

pancreatic enzyme inhibitors has not generated improved outcomes (3). These two findings lead some to assume that the course of the disease cannot be altered once past an as-yet undefined critical point. In a prospective, randomized trial of the timing of surgery for gallstone pancreatitis, Kelly and Wagner (11) provide evidence, based on 165 patients, that bolsters this assumption. They found that mild edematous or hemorrhagic necrotizing pancreatitis can develop in many situations: with or without impacted stones, early or late in the progression of disease, and with early or delayed surgery. These authors hypothesize that the quantities of activated digestive enzymes and digestive enzyme inhibitors present at inception of the disease decide the ultimate severity of a bout of pancreatitis.

Others disagree. They point to animal studies that have found that the level of pancreatic injury (61,62) and the degree of duct ultrastructural changes (37) are greater with longer duct obstruction time. Also, repeated short-term duct obstruction can cause disease in animals which is equivalent to or more severe than pancreatitis caused by a single, long-term obstruction (50, 63). The latter finding supports the theory that migration of multiple gallstones can lead to severe pancreatitis. Neoptolemos (59) hypothesized that persistent, large stones in the common bile duct block the flow of pancreatic juice that contains activated enzymes, thus worsening biliary pancreatitis that has already been initiated.

4.3. Treatment

The appropriate treatment of biliary pancreatitis, like many other aspects of the disease, has generated considerable debate over the years and is a subject about which an enormous amount has been written. The paragraphs below are not meant to be a comprehensive review of this topic, but rather a brief summary based on the most current literature.

4.3.1. Supportive care of acute pancreatitis

Irrespective of the etiology of acute pancreatitis, initial treatment involves aggressive supportive care. Careful monitoring of patients, particularly with respect to intravascular volume status, is critical. Fluid losses can be occult and massive resulting from intraabdominal inflammation, so patients generally require considerable fluid resuscitation. This should be titrated against measured endpoints of urinary output or central venous pressure. Bowel rest and appropriate pain management are also important, and patients who are more ill or appear to be deteriorating should be placed in an intensive care unit. Nasogastric tubes are reserved for patients with vomiting. The utility of antibiotics is controversial, although at present they are thought to be beneficial in patients with pancreatic necrosis and/or abscess.

4.3.2. Timing and scope of intervention

Patients who have suffered from biliary pancreatitis are likely to have recurrences of the disease if cholecystectomy is not performed. An estimated 35-50% will experience another bout of pancreatitis within 3-6 months of the first attack if the gallbladder is left *in situ* (3,8). Considerable debate has centered around two issues: the timing of gallbladder removal relative to the onset of symptoms, and the changing role of ERCP in the treatment of this disease.

Stelzner and Pellegrini (8) and Yeo and Cameron (3) present excellent reviews of these subjects. Current consensus is that most patients with biliary pancreatitis should be allowed to "cool down" from the acute episode (resolution of pain, return of bowel function, improvement in laboratory studies) prior to cholecystectomy, but that surgery should occur during the same hospital admission. Exceptions to this recommendation include patients who require either urgent ERCP to decompress the common bile duct or surgical debridement of necrotic pancreatic tissue.

Emergent ERCP with stent placement is thought to be beneficial in patients presenting with acute cholangitis concurrent with gallstone pancreatitis, and in some patients with early, severe gallstone pancreatitis (8,59). Biliary decompression may be life-saving and subsequent stone extraction can be achieved once the patient stabilizes. Semi-elective ERCP with stone extraction may be appropriate definitive therapy, leaving the gallbladder *in situ*, for patients deemed unfit for surgery.

Most patients with gallstone pancreatitis today undergo laparoscopic cholecystectomy prior to discharge from the hospital. As surgical experience with advanced laparoscopic procedures improves, we have seen increased use of intraoperative cholangiography to detect persistent common bile duct stones, with planned laparoscopic stone retrieval (common bile duct exploration) as needed. Common bile duct stones are present in a variable percentage of biliary pancreatitis patients at operation; the incidence is as high as 75% less than two days after hospital admission, and decreases markedly by four days after presentation (8). ERCP may also be performed prior to laparoscopic cholecystectomy to extract common bile duct stones. In patients with severe pancreatitis, surgical debridement of necrotic pancreatic or peri-pancreatic tissue may be necessary.

4.4. Pathology

The pancreas is left intact in patients with biliary pancreatitis, except in those who require pancreatic debridement. Gross appearance of the pancreas at surgery can range from a mildly edematous organ to a hemorrhagic and necrotic one.

Chitkara (64) examined 53 gallbladders that were removed from patients with biliary pancreatitis within 12 days of the start of the disease. He noted that "intraepithelial neutrophilic aggregates" were the most common (60%) histologic finding. An intact gallbladder epithelium and plasma cells in the lamina propria were also seen frequently.

Isogai *et al.* (12) studied hepatic histologic changes associated with biliary pancreatitis. Their specimens were 26 liver biopsies taken during emergent surgery. Ninety-six percent showed hepatocyte necrosis and 65% acute cholangitis within the liver. These

percentages would be expected to drop after ductal decompression, and likely would parallel clinical decline in transaminase levels.

5. PERSPECTIVE

Elucidating the pathogenesis of gallstone pancreatitis has challenged many investigators. While certain correlations have become apparent, causal relationships have remained elusive. Pancreatic duct outflow obstruction seems to be a requisite inciting event. Duct obstruction can be achieved by an impacted ampullary stone(s), one or more migrating gallstones, or functional obstruction of the sphincter of Oddi. Damage to the pancreatic duct epithelium can be caused by refluxed secretions, elevated pancreatic duct pressure, or persistent acinar cell secretion. Pancreatic duct epithelial damage leads to a breakdown in epithelial integrity. Cellular events that follow duct compromise may include impairment of normal exocrine function, co-localization of pancreatic enzymes and lysosomal hydrolases within acinar cell vesicles, and aberrant activation of pancreatic enzymes resulting in tissue damage.

While the scenario presented above seems plausible, most authors who have reviewed this subject comment that simple explanations regarding the pathogenesis of biliary pancreatitis are almost certainly inadequate. In reality, there are probably multiple ways the disease can arise. Its initiation, severity and duration may well depend on a patient's anatomy, duration of duct obstruction, stone size, number of migrating stones, level of bacterobilia, or host response to the inflammatory insult.

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