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BASIC FACTORS IN THE PATHOGENESIS OF PANCREATITIS

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IN the last fifty years many studies and observations, both clinical and experimental, have contributed to the knowledge of the pathogenesis of pancreatitis. From this work, it has become apparent that no single etiologic factor can explain all types of pancreatitis. This paper reviews the basic factors that have been shown to be pathogenic, and some of the clinical or experimental studies in which they have been observed.

Those basic pathogenic factors, which have been enumerated over the years, are: (1) obstruction of the pancreatic ductal system with a stimulus to secrete against the obstruction; (2) reflux of bile into the pancreatic ductal system via a "common channel"; (3) infection, secondary to the reflux of infected material into the pancreatic duct, or from systemic infection elsewhere; (4) trauma to the pancreas; (5) vascular ischemia of the pancreas; (6) circulating proteolytic enzymes; and (7) an allergic response to previous sensitization. An eighth potential factor is that of the effect of direct toxins on the pancreas, a factor that has been the subject of much speculation, but at the present time has no clinical or experimental support.

In dealing with the problems of pancreatitis, it should be recalled that the disease, in approximately 80 per cent of patients, is a secondary or associated condition. The primary problems with which pancreatitis is most often associated are those of biliary tract disease, alcoholism, the postoperative state, trauma, mumps or other infections, and metabolic disorders such as hyperparathyroidism or

hyperlipemia. In 20 per cent of patients no primary problem is recognizable, and the pancreatitis must be termed idiopathic.

Obstruction of the Pancreatic Duct

In 1901, Opie[1,2] reported the postmortem findings in two cases of pancreatitis, which were secondary to biliary tract disease. In one patient a stone had wedged in the terminal bile duct, obstructing the pancreatic duct. In the other patient a stone had wedged in the ampulla of Vater, so that the common bile duct and the pancreatic duct were united into a common channel behind the obstructed ampullary orifice. Although this second case captured the enthusiasm of the medical profession and became widely discussed, the principle of obstruction of the pancreatic ducts was not forgotten. In succeeding years, many other cases of pancreatitis were charged to the result of obstructing stones in the common bile duct. Stones have been found in only from 10 to 15 per cent of the cases reported at post mortem, but many surgeons and pathologists have continued to believe that when a stone could not be demonstrated, it must have been "passed."[3-5] Recently, the role of spasm or fibrosis of the choledochal sphincter has been emphasized as a mechanism whereby the terminal pancreatic duct may become obstructed.[6]

In 1936, Rich and Duff[7] emphasized the importance of partial obstruction of the pancreatic duct in the pathogenesis of pancreatitis, by reporting the presence of ductal metaplasia in a number of cases. Other pathologists have since found metaplasia present in the pancreatic ductal system in many cases of normal pancreas as well as in pancreatitis.[8] The importance of ductal metaplasia as an obstructing lesion is not established.

Many other pathologists have noted pancreatic ductal obstruction as a significant finding in postmortem studies of pancreatitis. Thal, Perry, and Egner[9] reported ductal obstruction in the majority of 42 fatal cases; Bell[10] believes it is a basic cause of pancreatitis. The importance of pancreatic ductal obstruction, complete or partial, has been reemphasized by the findings of pancreatographic studies in patients with chronic pancreatitis.[11] Puestow and Gillesby[12] have coined the term "chain-of-lakes" deformity to describe the multiple strictures with alternating ductal dilatation found in these patients.

A rare cause of pancreatitis in the United States is the infestation and partial obstruction of the pancreatic ductal system with roundworms; this is a more common etiologic factor in middle eastern countries.[13]

Experimental studies have further emphasized the importance of obstruction of the pancreatic duct. Complete obstruction has been used experimentally by Popper and Necheles[14] to create pancreatitis in dogs; and by Wangensteen, Leven, and Manson,[15] and Lium and Maddock[16] in cats. When secretin alone was used to stimulate the pancreas, an edematous pancreatitis ensued. The author and Davis[17] have shown that in dogs with incomplete pancreatic ductal obstruction and stimula-

tion of both enzymatic and ductal secretions, varying severities of pancreatitis can be created. With minimal stimulus over a short period, pancreatic edema occurred. Maximal stimulus for a three-hour period with the duct intermittently obstructed for four hours, created hemorrhagic pancreatitis. Enzymatic secretion must be maximally stimulated to achieve the severe forms of pancreatitis. Multiple episodes of recurrent pancreatitis from a partially or intermittently obstructed ductal system resulted in chronic pancreatitis.

Reflux of Bile

The concept of the "common channel," exemplified by the second case reported by Opie,[2] became the basis of one of the most popular theories for the cause of pancreatitis during the first half of the present century. One of the major reasons for its popularity was that the traditional method of creating pancreatitis in laboratory animals had been with the forced instillation of bile or other noxious material into the pancreatic ducts. Opie[18] stated that in 1856 Claude Bernard noted that the forced injection of bile or "sweet oil" up the pancreatic duct in dogs was capable of producing an acute pancreatic necrosis. In succeeding years, the forced instillation of bile has continued to be the most common method of producing experimental pancreatitis.

Two primary objections to the bile-reflux factor as the major cause of pancreatitis have been enumerated. The first objection has to do with the anatomic incidence of a "common channel." Many anatomic studies and observations have demonstrated that in only from 20 to 40 per cent of studies the pancreatic and biliary ducts were noted to enter the ampulla of Vater together with an ampullary chamber sufficiently large for a stone to lodge and to allow a common passageway behind the stone.[19] In from 40 to 60 per cent of dissections the ducts united so closely to the ampullary orifice that it is unlikely that reflux of bile could occur.[20] In from 5 to 15 per cent of dissections the ducts opened side by side into the duodenum. Other studies, however, in which the papillary orifice was clamped with a small hemostat, have shown that material irrigated into the common duct will reflux into the pancreatic duct in a much higher percentage of cases than would appear possible from inspection or dissection of the ampullary chamber. In studies performed in this fashion, the potential for reflux could be demonstrated in as high as 60 to 70 per cent of postmortem cases.[21]

Doubilet and Mulholland[6] have emphasized the role of the ampullary sphincter in creating an obstruction of the terminal ducts, and in uniting the bile and pancreatic ducts into a common system behind the obstruction. They[22] have come to believe so strongly that sphincter spasm or fibrosis creates a common channel that they state this is the cause of pancreatitis in 100 per cent of their cases. This belief has been challenged by many surgeons.

The second major objection to the common channel theory has been that

pancreatic ductal pressures measured in both experimental animals and in man are invariably higher than the pressures of the biliary system.[23,24] Thus, although reflux of pancreatic juice into the biliary system could occur commonly, reflux in an opposite direction would appear to be less feasible. Further, the pressures required to instill bile into the pancreatic ductal system are higher than those that might develop physiologically.[19]

Elliott, Williams, and Zollinger[25] in 1957 demonstrated that in dogs in which the biliary system was obstructed for several days, ductal pressures rose comparably to those of the obstructed pancreatic ductal system. Furthermore, an incubated bile and pancreatic juice mixture could be instilled into the pancreatic ductal system at elevated pressures, comparable to those developed by the obstructed biliary system. They[25] theorized that when an obstructed common channel exists, pancreatic juice might flow into the biliary system, where incubation with bile could occur in the gallbladder. After a time, as long as the system remained obstructed, a reversal of flow might then occur with reflux of the mixed bile and pancreatic juice into the pancreas.

In recent studies, the author and Knowles[26] have united the biliary and pancreatic ductal systems of dogs into an obstructed, common system and found that after from 24 to 30 hours bile reflux actually occurs. Bile can be demonstrated to flow into the pancreatic duct, and in some of the dogs bile has been found in the tissues of the pancreas at postmortem examinations. This supports the theory of Elliott, Williams, and Zollinger,[25] and indicates that when an anatomic common channel exists, and becomes obstructed, the reflux of bile is a definite factor in the pathogenesis of pancreatitis.

Infection

Infectious agents have been associated with the pathogenesis of pancreatitis in two ways: first, by the occasional association of pancreatitis with mumps, and other systemic infections; and secondly, by the pancreatitis created experimentally by the reflux of infected materials up the pancreatic duct.

Mumps pancreatitis has been well documented in many published cases.[27,28] This form is almost invariably a mild edematous pancreatitis. Other infections, such as typhoid, scarlet fever, viral hepatitis, and infectious mononucleosis,[29] have been associated with pancreatitis, and these also have usually been mild.

The reflux of infected material up the pancreatic duct has been studied experimentally by many investigators. Thal, Tansathithaya, and Egner[30] demonstrated that the reflux of a bacterial filtrate of *Escherichia coli* produced an edematous pancreatitis. When after the instillation of this infected material the pancreatic duct was ligated, a more severe infection supervened, resulting in a necrotizing pancreatitis. Persky, Schweinburg, Jacob, and Fine[31] showed that in experimental bile-reflux pancreatitis the administration of antibiotics considerably decreased the

mortality. This observation has been supported by improvement in clinical morbidity and mortality when antibiotics are used. An occasional pancreatic abscess still occurs late in the disease, in spite of the increased use of antibiotics.

Recent studies by Pfeffer, Safadi, Mixter, and Hinton[32] have emphasized that an overwhelming necrotizing pancreatitis is associated with a closed obstruction of the duodenal loop. One of the factors involved in this preparation may be the reflux of infected duodenal contents up the pancreatic ductal system. It has been suggested that reflux of duodenal contents may be a prime etiologic factor in the pancreatitis associated with the postgastrectomy state if an afferent loop obstruction occurs.[33]

Trauma

Direct trauma, most commonly blunt trauma, to the pancreas in humans has been well documented as a precipitating cause of pancreatitis.[34,35] A frequent injury in children is that of a bicycle handlebar injury, or, in adults, that associated with automobile steering wheel accidents. These injuries compress the pancreas in its retroperitoneal position against the spinal column. The occurrence of pancreatic pseudocysts is not uncommon after this type of pancreatitis.[36]

Penetrating abdominal injuries have also been associated with pancreatitis, and pancreatic duct injuries. These injuries have occurred at surgery from manipulation of the pancreas, or inadvertent injury to its ductal system.[37] The irritation and inflammation of a penetrating duodenal ulcer must also be included in this group of factors, as it is a chronic form of physical injury to the pancreas.

Many attempts have been made to create pancreatitis experimentally in animals, by traumatizing the pancreas. These attempts have not been successful; only a locally restricted pancreatitis was created. Pseudocysts have not been created experimentally by this method.[38]

Vascular Ischemia

The relationship of vascular ischemia of the pancreas to acute pancreatitis has been assigned much importance. Many physicians believe that it is the major underlying factor responsible for pancreatic necrosis.[39] Cases of true pancreatic "apoplexy" have been described, with infarction and necrotizing pancreatitis.[40] Millbourn[41] reported a high incidence of postoperative pancreatitis after gastrectomy when the gastroduodenal artery was ligated. In these cases an anomalous situation existed: an inferior pancreaticoduodenal artery from the superior mesenteric artery did not exist, and obliteration of the superior pancreaticoduodenal artery (from the ligation of the gastroduodenal artery) devascularized the head of the pancreas.

In experimental animals interruption of the pancreatic blood supply has been shown to create necrotizing pancreatitis. Occlusion of the blood supply for a temporary period created pancreatic edema only. Popper, Necheles, and Russell[42]

showed that when the pancreatic duct was previously ligated, and an edematous pancreatitis was created, the addition of temporary occlusion of the pancreatic blood supply converted edematous pancreatitis to the hemorrhagic form. In experimental studies, in which particulate matter was injected into the pancreatic arterial system, hemorrhagic pancreatitis was created.[43] Similarly, ligating the pancreatic venous drainage resulted in a necrotizing pancreatitis.[44] Thal[45] observed that bile injected into the parenchyma of the pancreas produced localized vascular constriction with stagnation of blood flow, and theorized that pancreatitis from bile reflux may be initiated on this vascular basis. From these studies, it is apparent that adequate blood flow to the pancreas has importance in protecting it from pancreatitis. Even more important is the prevention of vascular ischemia in a gland already damaged by some other factor, such as obstruction. The development of vascular ischemia may readily convert mild edematous pancreatitis to a lethal necrotizing form.

Circulating Proteolytic Enzymes

Pancreatitis has occurred occasionally after splenectomy or prostatectomy. In the former instance it may be that the tail of the pancreas was injured at the time of operation. However, after prostatectomy it is difficult to conceive of pancreatic trauma. Both spleen and prostate, however, are known to contain proteases, which may be released during operation on these organs. Stein, Powers, and Browne[46] investigated the effect of circulating proteolytic enzymes on the pancreas. They injected trypsin systemically in dogs and created pancreatic edema. The same results were achieved by bruising or rubbing the spleens of dogs to release proteolytic enzymes. When the pancreatic duct previously had been ligated, the injection of proteolytic enzymes or splenic injury converted the edematous pancreatitis to a hemorrhagic form.

Allergy

Thal and Brackney,[47] and Thal[48] have emphasized that pancreatitis may be an allergic phenomenon in some instances. They have created pancreatitis in rabbits and in guinea pigs by means of a Shwartzman or an Arthus phenomenon. The pancreatitis observed with these phenomena may result from the diffuse vascular damage in the hypersensitivity reactions. In animals like the dog and the cat, with low susceptibility to allergic sensitization, it has not been possible so far to create pancreatitis by sensitization methods. Thal[49] has measured autoantibodies in humans, whose susceptibility to allergic stimuli lies between these two groups of animals. The role of these isoimmune autoantibodies is not clear, but present concepts favor their association as a result of the disease rather than as a cause. Further studies of these allergic mechanisms are in progress.

Direct Toxicity

Many investigators have attempted to identify direct toxins to the pancreas which could be shown to create pancreatitis. Most studies have been focused on alcohol. The association of pancreatitis with chronic alcoholism has been well known since its early description, such as that by Fitz.[50] Many experimental studies have been performed in which alcohol has been instilled into the gastrointestinal tract, and has been injected intravenously to study its effect on the pancreas.[51,52] To date, there has been no demonstration of a direct toxic effect of alcohol on the pancreas. Present concepts of the role of alcohol indicate that it acts through a mechanism of stimulation of pancreatic secretion against ductal obstruction[53] created by the irritating effect of alcohol on gastric and duodenal mucosa. This results in gastritis, duodenitis, and spasm of the mechanism of the ampullary sphincter. Alcohol stimulates gastric acid secretion, and the two substances, acid plus alcohol, in the duodenum stimulate the formation of secretin, the stimulus for pancreatic secretion.

In animals, ethionine has been utilized to create experimental pancreatitis through its interference with protein synthesis.[54] Ethionine is known to block the utilization of methionine, an essential amino acid. It has been noted that ethionine secondarily interferes with the transport of proteolytic enzymes from their intracellular position into the ductal system.[55] This, then, may be a cellular instance of obstruction to the outflow of pancreatic juice with ensuing cellular damage.

The association of pancreatitis with metabolic diseases such as hyperparathyroidism, or familial hyperlipemia has been shown.[56,57] At the present time, one factor or a combination of the basic factors already enumerated is thought to be involved in the pathogenesis of these unusual instances of pancreatitis. The occurrence of pancreatic calcification is frequent in these cases, and these calcific deposits may act to obstruct further the pancreatic ducts. More detailed studies of these rare and interesting cases should lead to a greater understanding of the basic factors involved.

Summary

This report has briefly defined those basic factors that, through the years, have been associated with the pathogenesis of acute and chronic pancreatitis. In the definition of these factors, observations have been drawn both from clinical and experimental studies. The number of etiologic factors that have been enumerated emphasizes that a combination of them probably acts in the majority of cases of pancreatitis. These basic factors are: obstruction of the pancreatic duct, bile reflux into the pancreatic ductal system, infection, trauma to the pancreas, vascular ischemia, circulating proteolytic enzymes, and an allergic response to previous sensitization. Present evidence does not confirm the theoretic direct toxic effect of alcohol or other agents on the pancreas.

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