ACUTE CHOLECYSTITIS ASSOCIATED WITH PANCREATIC REFLUX

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IN 1901, Opie[14] reported a case of acute hemorrhagic pancreatitis in which autopsy disclosed a calculus, occluding the duodenal orifice of the ampulla of Vater, but so small that the orifices of the choledochus and pancreatic duct were unobstructed. The two ducts, therefore, were converted into a continuous channel. This made possible the retrojection of bile into the pancreatic duct which probably accounted for the acute pancreatitis present. Stimulated by Opie's observation, other instances of acute pancreatitis were reported in which the pancreatic tissues were bile stained.

Interest was then aroused as to the different anatomic arrangements of the ducts in relation to the ampulla of Vater, and in which type of variation the lodgment of a small stone would convert both ducts into one continuous channel. Investigators have reported varying results. Mann and Giordano[12] concluded that in 3.5 per cent of their dissections the termination of the ducts was such that a continuous channel could be effected if the papilla were obstructed. From roentgenologic studies of ducts injected with lipiodol, Schmieden and Sebening[17] found that this anatomic arrangement was present in 20 per cent of their cases. Subsequently, by occluding the papilla with a small stone and pouring Woods metal into the choledochus, Cameron and Noble[6] noted that the pancreatic duct was in the mold of 75 per cent of the preparations. If the biliary reflux is to be considered in the etiology of acute pancreatitis, there must be other factors causing papillary obstruction inasmuch as the incidence of a stone occluding the ampulla is small.

In a collected series of 1,278 cases of acute pancreatitis, Schmieden and Sebening found that the ampulla was obstructed by a calculus in only 4.4 per cent, and in a series of 51 cases of primary acute pancreatitis reported by one of us[8] in 1930, a papillary calculus was found in only one instance, although the common duct was definitely dilated in seven. The statement was made then that "the ampulla of Vater may be occluded either reflexly, or by the edema and spasm incident to the passage of stone in some cases, and in others by an inflammatory pancreatic enlargement."

Undoubtedly, edema of the papilla and spasm of the sphincter of Oddi not infrequently convert the choledochus and duct of Wirsung into one channel. Balo and Ballon[2] reported the necropsy findings in four cases of simple catarrhal jaundice without stone in which a retention of pancreatic juice and simultaneous jaundice was presumably due to swelling and edema of the

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duodenum and papilla. The rôle of spasm of the sphincter of Oddi was stressed and verified by Archibald[1] in his work on this sphincter in cats. This was subsequently corroborated by Westphal[18] who made a detailed study of the actions of the muscles near the orifices of the choledochus and the large pancreatic duct, and emphasized the functional importance of this muscular area in normal and pathologic processes. In addition, he demonstrated in 42 of 50 cadavers that the anatomic relationships were such that the flow within the bile and pancreatic ducts could occur in either direction.

However, there is even more conclusive clinical evidence proving that spasm or edema under certain anatomic conditions may convert the orifices of the choledochus and the duct of Wirsung into a cloaca, resulting in the appearance of pancreatic ferments in the bile. This is well recognized by the occasional occurrence of severe skin digestion about biliary fistulae. Chemical analysis of the biliary discharge in these cases invariably discloses the presence of pancreatic ferments in large amounts. These ferments can only be accounted for by pancreatic reflux in the absence of duodenal contents either from a fistula or retrojection. Nordmann[13] recorded two cases of acute pancreatitis in which pancreatic ferments were present in the drainage from a choledochostomy, and Westphal,[18] too, demonstrated large quantities of ferments in a dilated choledochus.

But pancreatic ferments are not as infrequent in the biliary system as these few isolated instances would seem to indicate. In a recent communication, Popper[15] stated that he examined the bile (usually from the gallbladder) in 219 surgical cases for the purpose of finding pancreatic ferments. The samples examined represented cases of cholelithiasis, tumors of the pancreas, acute pancreatic disease, and cases with a healthy biliary system. Diastase was routinely sought for as a proof of the presence of pancreatic juice. Ferments were demonstrable in 17 per cent of the cases, and if those of acute pancreatic disease were excluded, 20 of 200 bile samples contained diastase. The cases in which the bile ducts contained pancreatic juice differed in no way from other cases of cholelithiasis in respect to case history, symptomatology, clinical course, operative condition, or postoperative course. Subsequent follow up examinations, months or years later, showed no indication whatsoever of any pancreatic or hepatic dysfunction. Evidently the reflux of pancreatic ferments into the bile passages is of pathologic significance only when there is prolonged blockage of the ampulla in association with other conditions.

Once a common channel has been established, the direction of flow is undoubtedly dependent upon the relative secretory pressures of the bile and pancreatic juice. Investigators are not in accord, however, as to these pressures, but the weight of evidence seems to favor the pressure as being higher in the pancreatic duct.[11] Hence the increased likelihood of ferments being found in the bile, rather than bile in the pancreatic duct. However, intraductal pancreatic pressure may be lower if the accessory duct of Santorini is present. When this communicates with the duct of Wirsung, it might

easily act as a safety valve and diminish the pressure in the main duct sufficiently to permit bile to flow into the pancreas. When this occurs, an acute pancreatitis may follow. If, however, the flow is in the opposite direction, and pancreatic juice enters the choledochus, an acute cholecystitis, or more rarely a nonperforative bile peritonitis may ensue.

Cases of nonperforative bile peritonitis bear an interesting relationship to pancreatic reflux. In 1910, Clairmont and Haberer[7] reported a case of bile peritonitis without perforation of the bile passages. They suggested that this might have been caused by alteration of the permeability of the bile duct walls, but offered no explanation for its occurrence.

Blad[3] later endeavored to explain these unusual cases from a correlation of chemical and animal experiments. He felt that the pancreatic ferments refluxly present in the biliary system in association with bacterial action digested the colloids of the bile and liberated the pigment which by some unknown process could pass through any membrane.

By injection of human pancreatic juice into the choledochus of animals, Westphal[18] was able to produce acute and chronic pathologic changes in the liver, gallbladder and extrahepatic bile ducts, many of which were comparable to those found in the human. He felt that the action of trypsin must be considered an uncommon, but nevertheless an important factor in the production of cholecystitis, in addition to infection, lithiasis, stenosis, or motor dysfunction of the biliary passages.

Wolfer[19] subsequently verified Blad's observations and some of Westphal's by a series of ingenious experiments based upon the entrance of pancreatic juice into the gallbladder. He concluded that these ferments so devitalized the gallbladder wall that bacterial invasion, especially of anaerobes, was favored. He also felt that the alkalinity of the pancreatic juice transferred the ordinarily acid medium of the gallbladder bile into an alkaline one, and that this might account for the violent reaction in the mucosa of the gallbladder.

The exact mechanism of the chemical inflammatory reaction occurring in cases of acute cholecystitis in which pancreatic ferments have been found in the gallbladder bile is doubtful. It is evident from a review of the literature, especially the work of Popper,[15] that pancreatic ferments may be present within the biliary tract and cause no damage. However, under certain conditions, the mixture of bile and pancreatic juice otherwise apparently innocuous, may be converted into a destructive tissue irritant, resulting in an alteration of the permeability, and in a chemical inflammation of the gallbladder wall. Dragstedt, Haymond, and Ellis[9] have recently thoroughly reviewed the pathogenesis of acute pancreatitis. They called attention to many facts which might explain the production of acute cholecystitis by the presence of pancreatic ferments in the bile. Nonactivated pancreatic juice as it exists in the duct system of the pancreas is nontoxic, either on intravenous or intraperitoneal injection, and even activated trypsin is not able to destroy healthy living tissue. Bile apparently produces its local toxic and cytolytic effects

through the bile salts, which have been shown to constitute the toxic element in bile. Gallbladder bile, because of its greater concentration of bile salts, should be and undoubtedly is more effective in its destructive activity than hepatic duct bile. There is, however, an important element which tends to neutralize the destructive effect of an increased concentration of bile salts in the gallbladder. Bile as it is secreted by the liver is invariably alkaline, whereas under normal conditions the bile in the gallbladder tends to be kept acid through the selective concentrating activity of that organ. Bile salts are far more soluble, and, therefore, much more toxic under alkaline than under acid conditions. If a large quantity of pancreatic juice is retrojected into the gallbladder, the alkalinization of the normally acid gallbladder bile, together with the presence of pancreatic ferments probably activated by infected bile, produce conditions favorable for tissue destruction. Trypsin, now activated, may act in several ways. It may digest the proteins which have a definite protective action against the destructive effects of the bile salts. It may remove the taurine and glycine from the conjugated bile salts, liberating the more toxic free bile acids. Finally, it may be regarded as an active catalyst and, as such, accelerate a reaction which otherwise would take place slowly, thereby increasing and enhancing the toxic effect of the bile.

Active pancreatic ferments have been found in the bile of acutely inflamed gallbladders, and their presence appears definitely related to the acute inflammatory process present. Such instances have been reported by Bundschuh,[5] Ruppanner,[16] Dziembowski,[10] and Brackertz.[4] Three similar cases of acute cholecystitis associated with the presence of pancreatic enzymes in the gallbladder bile have been observed on the Surgical Services of the Mount Sinai Hospital during the past year.

Case Reports

Case I.—History No. 357862, M. McG., a well-developed and stout Irish laborer of 65, was admitted to the Surgical Service of Dr. Harold Neuhof on October 7, 1933, for acute urinary retention due to prostatism. On October 13, 1933, a suprapubic cystostomy was performed. Two days later, without ever having had any previous symptoms of a similar nature, while lying in bed, he developed sudden acute persistent pain in the right upper quadrant. On examination, the gallbladder was found to be palpable, markedly tender and distended. Temperature 103°. The symptoms disappeared within two days. Ten weeks later, while convalescing from a second-stage prostatectomy, the same symptoms suddenly recurred and after three days of conservative treatment, it was felt that operation was indicated. On opening the peritoneal cavity, the gallbladder was found to be distended. The wall was thickened, edematous and gangrenous in several areas, and covered with recent omental adhesions. It contained 60 cc. of thick dark bile and several small cholesterol stones in the cystic duct. Free, bile-stained fluid was found in the peritoneal cavity, although no visible perforation was apparent in the gallbladder wall. After its removal, the gallbladder was distended with formalin and no perforation was found. The liver was normal in appearance. Convalescence was uneventful. On analysis the gallbladder bile was found to be markedly alkaline with a pH of 7.75 (normal 6.8 to 7.1). By qualitative tests, large amounts of both amylase and trypsin were found to be present. Cultures of both the bile and gallbladder wall were found to be sterile.

Microscopic Findings.—Sections were taken from the fundus, neck and ampulla of

the gallbladder. These showed essentially identical changes. The mucosa and lamina propria were necrotic. There was a marked polymorphonuclear leukocytic infiltration immediately below the epithelium which extended down through the muscular and fibrous coats and subserous tissues to the serosal wall (Fig. 1). The entire wall was edematous and a pronounced fibrinous exudation was present. The vessels were dilated and engorged, and frequently surrounded by polymorphonuclear leukocytes, which, at times, extended into the wall of the vessels. The lymphatics were likewise dilated and filled with nuclear débris. No fat necrosis was observed microscopically. The entire gallbladder was then stained with Benda's solution and carefully sectioned for evidences of fat necrosis. None were found. Bacteria were not found in the microscopic sections.

CASE II.—History No. 363431, R. M., a well-developed, rather thin 25-year-old Porto Rican woman, was admitted to the Surgical Service of Dr. Harold Neuhof on March 7,

FIG. 1.—(CASE I.) Photomicrograph of gallbladder wall showing acute diffuse inflammation. Diffuse polymorphonuclear leukocytic infiltration of wall with marked edema (hematoxylin and eosin).

1934. For the past 18 months she had suffered from six acute attacks of sharp pain in the right upper quadrant, radiating to the epigastrium and occasionally to the back. The pain was accompanied by nausea, vomiting and slight jaundice. Each attack persisted about two weeks during which time there would be only intermittent amelioration of the symptoms. In the intervals between attacks, belching and distention were marked; fatty foods could not be tolerated. The last attack, which began two days before admission, was the most severe and persisted up to the time of operation. On admission, unusually acute tenderness was noted in the right upper quadrant. Temperature 101°. At operation, five days after the onset of the last attack, the liver was found enlarged, extending about five cm. below the costal margin. It was deep red and congested. The gallbladder was closely surrounded by edematous omentum containing several areas of fat necrosis. Upon careful separation of the omentum from the gallbladder, a thin layer of definitely bile-tinged fluid was found. The gallbladder itself was enormously distended. The edematous thickened walls showed many areas of gangrene and fat necrosis. One hundred cm. of blackish bile were aspirated and several buckshot-sized cholesterol

stones were found in the cystic duct. Because of the acute inflammatory process, cholecystectomy was performed without further exploration. The patient was discharged on the 13th day, after a smooth convalescence.

The gallbladder bile was found to be alkaline with a pH of 7.78 and contained 450 Elman units of amylase per cc. Trypsin could not be detected. Cultures of both the gallbladder wall and the bile were found to be sterile.

Microscopic Findings.—Numerous sections from various areas of the gallbladder revealed identical changes. There was a marked necrosis of the mucosa extending into the subepithelial tissues, and in many places into the muscularis and subserous tissues. A diffuse polymorphonuclear leukocytic infiltration was present throughout. These cells were often collected in masses about necrotic foci. The vessels were dilated, the walls often infiltrated by leukocytes, and the lymphatics were filled with pyknotic débris.

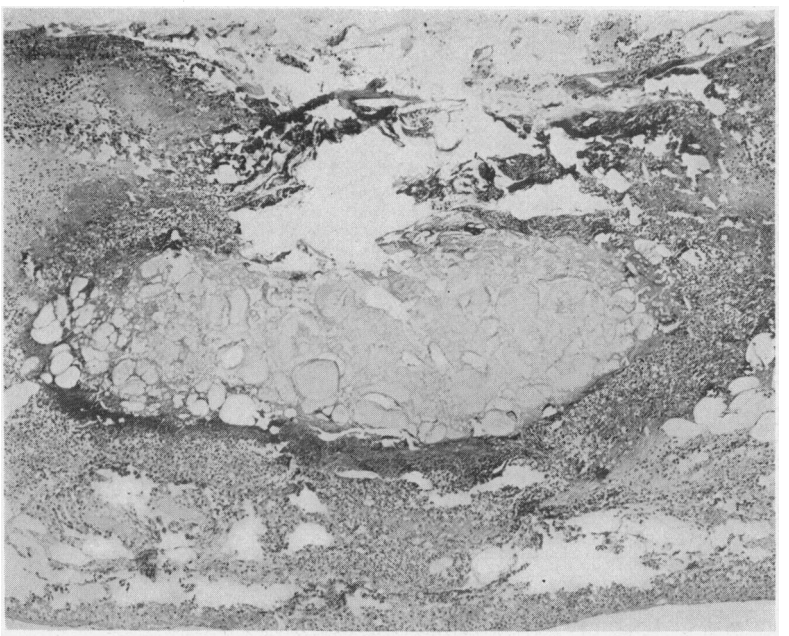

FIG. 2.—(CASE II.) Photomicrograph of gallbladder wall showing large subserous area of fat necrosis. Calcium deposit surrounds necrotic fat cells. Entire area surrounded by a wide zone of inflammation (hematoxylin and eosin).

The entire subserosa, in many sections, contained extensive areas of fat necrosis (Fig. 2), the necrotic fat cells taking a deep blue color with the hematoxylin and eosin stain. The necroses frequently involved the serosa, although microscopically it was not possible to determine whether actual perforation had occurred. The entire gallbladder was stained with Benda's solution. This revealed many scattered subserosal areas of fat necrosis (staining a deep green color) chiefly present on the free surface of the gallbladder. Bacteria were not found in the microscopic sections.

CASE III.—History No. 371810, A. L., a well-nourished Italian woman of 41, was admitted to the Surgical Service of Dr. Ralph Colp on October 6, 1934. The patient had been perfectly well up to 15 hours before admission when she suddenly developed epigastric pain which spread to the periumbilical region and to the right lower quadrant. After two hours, the pain suddenly became very severe and was accompanied by chilly sensations and vomiting. On admission, the patient appeared to be acutely ill and in

great pain. Tenderness and rigidity were marked on the right side of the abdomen; the right upper quadrant being excruciatingly tender. Temperature 101.4°.

Nineteen hours after the onset of symptoms operation was performed. Grayish pus was found free in the upper abdomen and over the superior surface of the liver. The gallbladder was greatly distended, acutely inflamed, and the wall thickened and edematous. One small point of gangrene was noted but the gallbladder was found subsequently not to be perforated. Cholecystectomy was performed. Fever persisted for two weeks rising to 102° at times. On the ninth day postoperatively, bile began to flow through the site of drainage. This persisted until the 20th day when five very small mulberry-shaped cholesterol stones were discharged through the sinus, following which the sinus closed rapidly. The patient was discharged on the 35th day, symptom free.

The gallbladder bile was found to be very alkaline, the pH being 8.85. Both

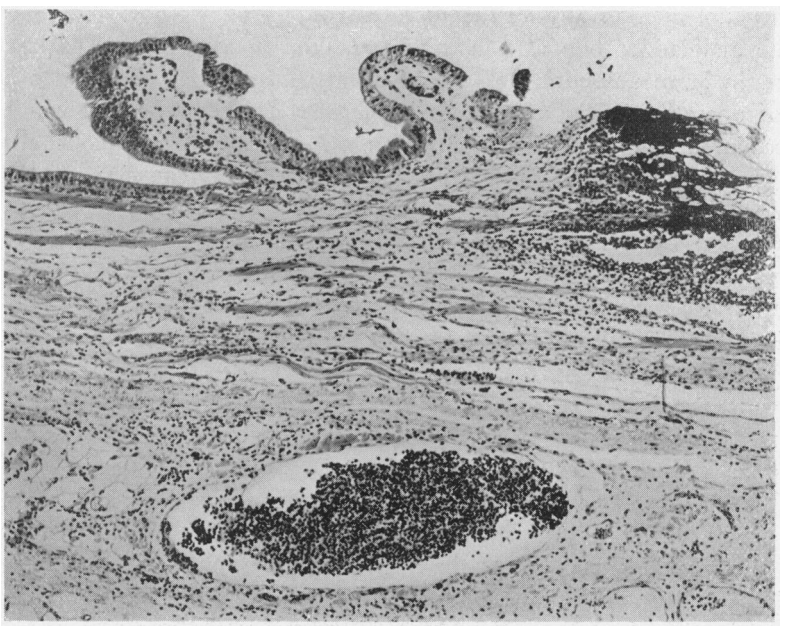

FIG. 3.—(CASE III.) Photomicrograph of gallbladder wall showing focal necrosis of mucosa and diffuse submucosal infiltration of polymorphonuclear leukocytes with marked edema. A dilated lymphatic vessel is filled by leukocytic exudate (hematoxylin and eosin).

trypsin and amylase were present in large quantities; the amylase being 200 Elman units per cc. The blood amylase taken at the time of operation was 2.6 units. Culture of the gallbladder wall and gallbladder bile showed the presence of both *Bacillus Friedländer* and *Bacillus coli*. Culture of the peritoneal pus was sterile.

Microscopic Findings.—There was a widespread necrosis of the mucosa of the gallbladder. The necrotic areas were surrounded by dense infiltrations of polymorphonuclear leukocytes. The entire wall showed a most striking edema, together with a diffuse polymorphonuclear leukocytic infiltration, which extended to the serosal wall (Fig. 3). The latter was covered in areas by fibrinous exudate. In addition to the edema, there was an exudation of fibrin which was present in the form of wide bands, chiefly in the subserous and fibromuscular layers. The lymphatic and blood vessels were dilated and engorged. The entire gallbladder was stained with Benda's solution but no areas of fat necrosis were found upon careful sectioning. No bacteria were found in the microscopic sections.

The history and physical findings in these three cases are typical of acute gallbladder disease. While the inflamed gallbladders, presented the characteristic pathologic changes noted in the various stages of acute cholecystitis without perforation, there were other features present which were unique or unusual and not found in a control series of 70 cases of acute and chronic gallbladder disease.

In Cases I and II, free bile was present in the peritoneal cavity, and in Case II, fat necrosis was seen not only throughout the gallbladder wall, but also in the omentum adherent to the inflamed gallbladder. The cultures were sterile in the first two cases, and *Bacillus coli* and *Bacillus Friedländer* were present in the third. No bacteria were found in the microscopic sections of the gallbladder in any of the three cases.

The gallbladder bile was definitely alkaline in all cases. Diastase was present in large amounts in the bile aspirated from the gallbladder at the time of operation. The amounts of pancreatic ferments present could only be accounted for by pancreatic reflux. Retrojection of duodenal juice charged with pancreatic ferments into the bile ducts can be excluded together with the assumption that pancreatic ferments entered the bile by way of excretion by the gallbladder mucosa, or through the blood or lymph streams.

Pancreatic reflux as an initiating or precipitating cause of acute cholecystitis is probably more common than the paucity of cases reported would seem to indicate. If pancreatic ferments are found as frequently as Popper reports, their rôle, under certain conditions, not only in acute cholecystitis but also as a possible causative agent in the production of chronic gallbladder disease as Westphal has shown experimentally, cannot be denied.

Methods.—In the first case presented, the determination of both amylase and trypsin was done by qualitative methods, made roughly quantitative by using varying dilutions. Thus the amylase determination was estimated by the disappearance of the blue color produced by iodine in a 1 per cent starch solution incubated with varying dilutions of the bile. It was noted that a fourfold dilution produced splitting of the starch. Similarly a Mett tube showed digestion of the albumen in this sample diluted six times, evidence of a fairly high concentration of trypsin.

In Cases II and III, the amylase was determined quantitatively by means of the viscosimeter method of Elman, in which the equivalent of one unit of amylase, acting for one hour on five cc. of a 3 per cent starch solution, reduced the viscosity by 20 per cent. The starch solution was standardized so that various samples of normal human serum gave an amylase content of two to five units.

Amylase determinations of bile obtained from other cases of both acute and chronic cholecystitis were attempted. In such cases only unmeasurable traces of amylase could be detected. The presence of trypsin was assayed by incubating the bile with Mett tubes. The pH was determined in all cases potentiometrically by means of the hydrogen electrode.

CONCLUSIONS

It has been shown that if certain anatomic relationships exist between the choledochus, duct of Wirsung and the papilla of Vater, both ducts may be converted into a single continuous channel by obstruction of the papilla. This papillary obstruction might be caused either by a calculus, or by edema of the duodenum and papilla, or by spasm of the sphincter of Oddi muscle.

Once a single channel has been established, bile may flow into the duct of Wirsung or pancreatic juice may flow into the choledochus. The varying intraductal pressure is probably the factor which determines the direction of the flow.

If pancreatic juice refluxly enters in the biliary system, no clinically recognized sequelae may result. On the other hand, if the pancreatic ferments are present in the gallbladder bile in sufficient concentration and amounts to change its usual acid reaction to alkaline, the bile salts may act destructively on the gallbladder wall together with the activated pancreatic ferments. As a result of the chemical inflammation caused by these various factors, either an acute cholecystitis or nonperforative biliary peritonitis may result.

Three cases of acute cholecystitis associated with the presence of pancreatic ferments in the gallbladder bile are reported.

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