Alterations in the Pancreatic Resistance to Bile in the Pathogenesis of Acute Pancreatitis *

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ACUTE pancreatitis warrants further investigation because the mortality rate remains high and the cause in doubt. The pathogenesis was linked to gallstones more than 50 years ago by Opie, who proposed the "common channel" theory,[19] by which bile regurgitates into the pancreas, producing pancreatitis. However, it has been impossible to reproduce this in animals except under pressures much higher than those which exist in the biliary tree.[8, 15] Experimental evidence will be presented which suggests that following obstruction of a common channel (12 to 24 hours), a series of events occur by which bile can regurgitate into the pancreas at physiologic pressures, producing pancreatitis.

There are two major experimental observations in conflict with the idea that bile can regurgitate into the pancreas and produce varying degrees of pancreatitis. First, experiments have been devised by which bile runs through the pancreas enroute to the duodenum at normal pressure without harm.[5, 27] If bile is to produce a significant lesion, it must be injected into the gland with sufficient force to rupture the finer ducts. This requires a pressure above 100 cm. of water in the dog, which is higher than that ever observed in the biliary tree of man or animals.[2, 15] Secondly, the average pressure in the biliary tree is uniformly lower than the secretory pressure of the pancreas, both normally, and after several hours of obstruction.[20, 28] If the pancreatic and common bile ducts are connected by transparent tubing, pancreatic secretion can be seen to flow into the biliary tract for several hours.[8, 15] This same direction of flow occurs in man, according to Popper, who found high levels of pancreatic enzymes in bile from the gallbladders of 16 patients he operated upon for acute pancreatic necrosis.[21]

The experiments to be reported were concerned with what might happen following the flow of pancreatic secretions into an obstructed biliary tree. They were designed to determine whether the resulting mixture of bile and pancreatic secretions could later re-enter the pancreas under physiologic pressure and produce hemorrhagic pancreatitis.

In a first group of experiments performed in dogs, pressures within the pancreatic duct were followed through longer periods of obstruction than previously reported,[28] with observations made at intervals through a period of at least 48 hours. In a second group of dogs, the pancreatic duct was infused with mixtures of bile and pancreatic secretion in varying proportions, bile and saline, and bile with pancreatic enzymes under a physiologic pressure.

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METHODS

I. *Determination of Pancreatic Ductal Pressures Following Prolonged Obstruction (48 Hours).* Eight mongrel dogs weighing about 15 kilograms were prepared, to make their pancreatic ducts available for pressure determinations without the influence of anesthesia or surgical manipulation.[2] At an initial laparotomy the main pancreatic duct was divided near the common bile duct, and a modified and enlarged Thomas cannula [10, 25] was placed in the duodenum opposite the accessory duct, which is the larger of the two in dogs. A small indwelling cannula was sutured in the accessory pancreatic duct to make subsequent pressure determinations easy and atraumatic. This cannulated duct then provided the only outlet for pancreatic secretions into the duodenum. In three or four days, when the animals were active and eating well, initial pressure measurements were obtained from the accessory pancreatic duct, and its cannula then capped, producing complete pancreatic ductal obstruction. The methods and individual pressure readings have been prepared for a separate detailed report.

Normal initial pressures ranged about 30 cm. of water, as reported by others.[20] Following ductal obstruction there was a uniform rise in pressure over a period of six to 12 hours. The amount of this rise varied widely, but peak pressures lay between 40 and 80 cm. of water, which has also been reported.[28] However, upon continuing the observations over a longer period, it was found that within 24 hours of obstruction, pancreatic ductal pressure falls again and approaches the initial normal values, despite continued ductal obstruction. No later secondary rise in ductal pressure could then be elicited by secretory stimulation with either food or secretin during several more days of obstruction.

Common bile duct pressures were measured by a similar technic, with normal readings from 15 to 20 cm. of water, a range well below normal pancreatic secretory pressures. During the first 24 hours of obstruction there was on the average a modest steady rise to the range of 25 to 30 cm. pressure, which was sustained steadily over at least several days. Therefore, common bile duct pressures approach pancreatic duct pressures after 24 hours of obstruction.

It would appear from these observations that in an obstructed common channel, the pancreatic and hepatic secretory pressures will approach an equilibrium sometime after 12 to 24 hours of obstruction. Meantime, pancreatic secretions have entered the biliary tree, which becomes distended. The stage is then set for the mixture of bile and pancreatic secretions in the biliary tree to enter the pancreas and produce pancreatitis. However, if this occurs, bile will have to infiltrate the pancreas at much lower pressures than previously reported. The next group of experiments were done to explore this possibility.

II. *Perfusion of the Pancreatic Duct at Physiologic Pressures.* In the second group of experiments, efforts were made to introduce mixed bile and pancreatic secretions, bile and saline, and bile with enzymes into the pancreatic ducts of dogs at physiologic pressures. An arbitrary upper limit of pressure had to be chosen, so that it would be well within pressures found to occur in the biliary tree. Average common duct pressures in a quiet animal had been measured. However, if the biliary tree is obstructed and distended, it is subject to quite wide swings in pressure secondary to intra-abdominal pressure.[15] Spasm at the sphincter of Oddi can regularly support 50 to 70 cm. of water in dogs,[2, 3] and, with retching, levels of 100 cm. of water are reached [15, 17] although these are transitory. For these reasons it was thought reasonable to start a perfusion of pancreatic ducts at 40 cm. of water pressure, which is well below these upper limits for dogs, and only slightly higher than the average resistance

TABLE I. *Perfusion of Pancreatic Duct at Physiologic Pressure*

[The pancreas will accept only an incubated mixture of bile and pancreatic secretions.]

No. of Dogs	Mixture Infused into Pancreatic Duct	Incubation Period	Amount Accepted, 40 cm. Pressure, 30 min.	Severity of Pancreatitis	Mortality
7	Bile	None	1 to 2 cc.	Minimal	0
6	Bile and pancreatic juice** (one to one)	None	4 to 10 cc.	Moderate	0
4	Bile and saline (one to one)	None	2 to 6 cc.	Minimal	0
4	Bile and saline (one to one)	12 to 48 hours	2 to 7 cc.	Minimal	0
11*	Bile and pancreatic juice** (one to one)	12 to 48 hours	18 to 30 cc.	Severe	100%

* Includes 4 animals fed 2 hours before infusion, 3 animals with pancreatic ductal obstruction 24 hours before infusion.

** Proved high-enzyme content; same juice used before and after incubation.

of the pancreatic duct (30 to 35 cm. of water).

All dogs were subjected to the same type of laparotomy under sodium pentobarbital anesthesia. The duodenum was opened, the accessory pancreatic duct cannulated, and the main pancreatic duct occluded by a ligature. The infusion mixture was introduced into the accessory pancreatic duct directly from a manometer at a pressure never exceeding 40 cm. of water, and sometimes less, during an interval never exceeding 30 minutes. These remained standard conditions of pressure and time throughout the following experiments.

a. *Normal Bile.* As a preliminary control, normal bile from the dog's own gallbladder was infused in seven animals. No more than one to 2 cc. of bile would enter the pancreas at this low pressure, which is about the capacity of the distended pancreatic ducts.[1] All animals survived and were sacrificed two to four days later. No significant pancreatitis was produced, and serum amylases were not elevated after 24 hours in most animals (Table I).

b. *Diluted Bile.* Autogenous bile was then diluted in equal parts with pancreatic secretion collected directly from the accessory pancreatic duct of donor animals through Thomas cannulae. Bile was also diluted in equal parts with normal saline. In both instances the diluted bile would enter the pancreas in somewhat increased quantities under the standard conditions of pressure and time. All animals survived, and were sacrificed after survival was assured. Somewhat more pancreatic inflammation was observed, but on the whole, the resulting pancreatitis was extremely mild. There were a few transitory elevations of serum amylase (Table I).

c. *Incubation of Bile with Pancreatic Secretions.* In an obstructed common channel, there must be a period of time during which pancreatic secretions are mixing with bile, while the pancreas is continuing to secrete. Therefore, to mimic this, a mixture of fresh donor bile and donor pancreatic juice was incubated in a water bath at 37° C. for periods of from 12 to 48 hours before infusion into the pancreatic duct under the standard conditions. This mixture, when fresh, would enter the pancreas in amounts of not more than 5 cc., producing only a mild pancreatitis. However, after incubation, the pancreatic resistance seemed much less, so that the solution

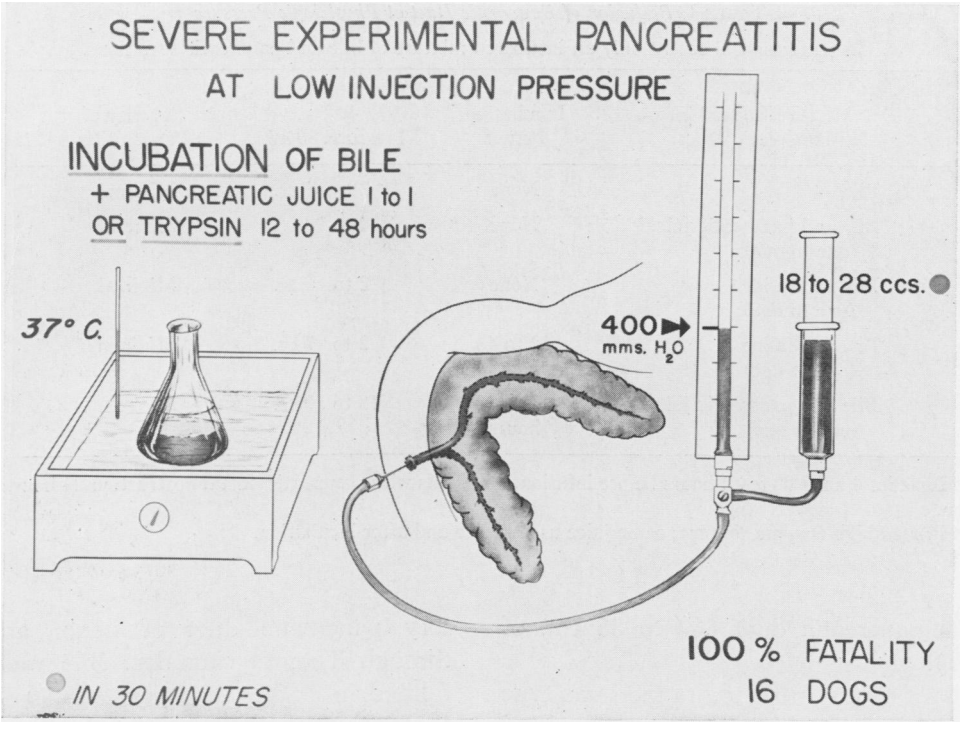

FIG. 1. Schematic representation of experiment described under IIc; after bile has been incubated with pancreatic secretion or trypsin the pancreas will accept much more of it at physiologic pressure. This results in a lethal pancreatitis.

would flow quite readily into the gland, often at a pressure as low as 35 cm. of water, and in quantities of from 18 to 30 cc. in the same 30-minute infusion period (Table I). This incubated mixture proved to be lethal (Fig. 1).

The surface of the pancreas immediately showed enormous edema, with the dark pigment of the bile appearing in the interlobular spaces before the infusion period had been completed. Before the laparotomy incisions could be closed the pancreas could be seen to weep a bloody fluid from its surface. Eleven animals had this incubated bile and pancreatic juice infused into their pancreas, and all expired 20 to 30 hours postoperatively with clinical signs of shock appearing a few hours before death. Serum amylase or ascitic fluid determinations were markedly elevated after 24 hours in all animals.

At autopsy the abdominal cavities were uniformly filled with massive quantities of a thin bloody ascitic fluid. There was a patchy fat necrosis throughout the omentum and in the mesentery of the adjacent duodenum and colon, extending into the peri-renal tissues. The pancreas showed scattered areas of hemorrhage, and often black consolidation (Fig. 2). The gross picture was that of a fulminating acute hemorrhagic pancreatitis. This was confirmed by microscopic sections which showed edema, leukocytic infiltration, interstitial hemorrhage, fat necrosis, and necrosis of the acinar cells. Some sections showed a medial necrosis of the smaller arterioles, a lesion which has previously been ascribed to the action of trypsin (Fig. 2b).[23]

The pancreas seemed remarkably willing to accept this incubated mixture at low pressure. Neither prior pancreatic ductal

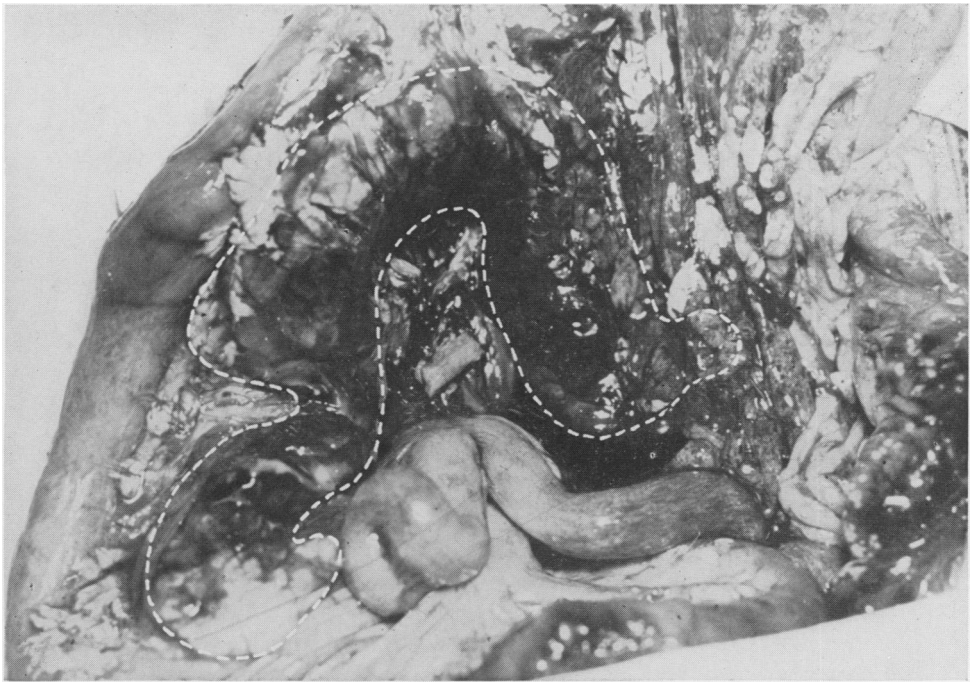

FIG. 2. Gross appearance of pancreatitis at death of dog, 24 hours after receiving 20 cc. of bile incubated 12 hours with pancreatic secretion one to one, infused into pancreatic duct under 40 cm. of water pressure for 30 min. The pancreas is outlined by the broken line. There is hemorrhage throughout gland, fat necrosis, and bloody ascites.

obstruction for 24 hours, nor feeding before infusion appeared to affect this reaction (Table I). Bile incubated with saline as a control was not different from freshly diluted bile and produced no mortalities (Table I).

It was evident that the bile had undergone a fundamental change during its incubation with pancreatic secretion. However, not all specimens of donor pancreatic juice proved capable of effecting this change. It became evident that the handling of pancreatic secretions must be done in a carefully standardized manner with sterile containers and every precaution to avoid bacterial contamination. The secretions were collected by a catheter placed directly in the accessory pancreatic duct through a Thomas cannula, and dripped into an iced container, pooled and frozen immediately until they were used. If the donor pancreas was stimulated by secretin, which produces a thin watery juice, low in enzymes, the resulting juices would not produce the essential change in bile. However, if the donor animal was first fed and then stimulated by Urecholine®, potent secretions were obtained. This suggested that the change in the bile depended upon the enzymatic content of the collected pancreatic secretions. Upon quantitative testing of each pool of juice for amylase and trypsin activity, only those pools containing high levels of enzymatic activity were found to be potent in changing the bile upon incubation, so that the mixture was received readily by the pancreas. The animals reported here include every one which received a mixture containing pancreatic juice with a minimum potency, as measured in our laboratory, of 1,000 trypsin (Tryptar®) units per cc.

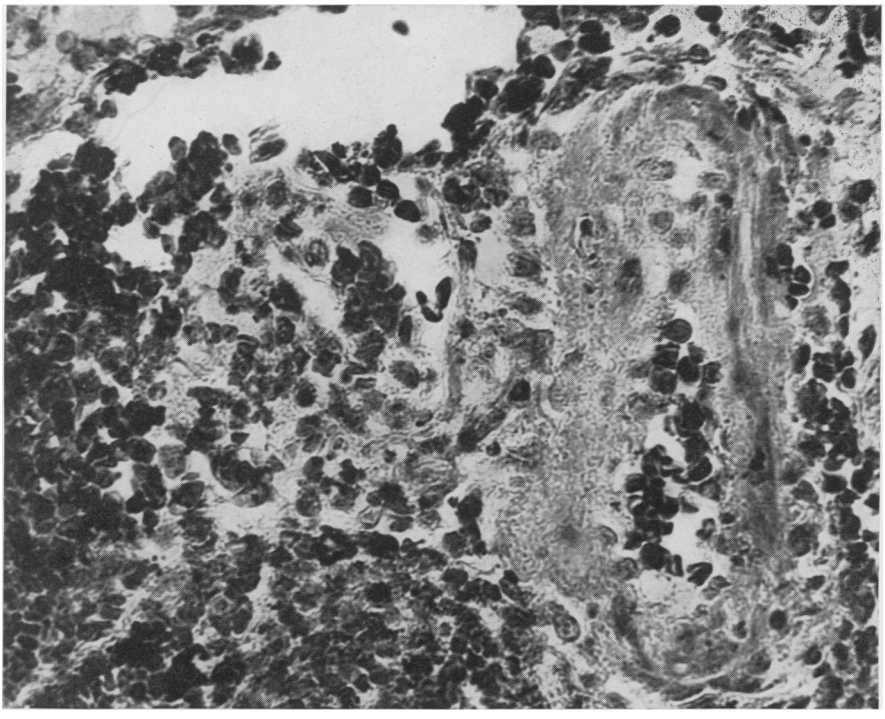

FIGURE 2B. Photomicrograph through hemorrhagic area of pancreas shown in Fig. 2. At the right an arteriolar wall shows necrosis, a lesion that has been attributed to the action of trypsin. To the left of the artery is a venule with disrupted wall.

d. *Incubation of Bile with Individual Pancreatic Enzymes.* In order to test the thesis that the essential reaction in bile was due to pancreatic enzyme activity, individual solutions were made up of trypsin and lipase with activity levels on testing similar to those of pancreatic secretions. These were incubated with donor bile. Trypsin proved as capable of producing the essential change in bile and fatal pancreatitis as did potent pancreatic secretions; the lipase employed did not (Table II). An amylase of pancreatic origin free from tryptic activity has not yet been available for testing.

e. *Infection Interferes with Pancreatic Acceptance of Incubated Mixtures.* Since Dragstedt has pointed out that pancreatic secretions can be extremely toxic if infected and re-introduced into the pancreas,[7] it seemed necessary to be certain that the potency of the incubated mixtures is not due to bacterial growth. However, despite all precautions, it is practically impossible to gather pancreatic secretions from donor animals without bacterial contamination, and there is no satisfactory way to eliminate these bacteria without destroying the enzymatic activities of the pancreatic juice. Passing it through filters reduced the enzymes below the level of potency, and this has been the experience of others.[18] However, thimerosal (Merthiolate®) has been used by enzyme chemists for years to control bacterial growth during periods of enzyme activity. It does not appreciably affect the activity of trypsin when used in very small quantities. Therefore, thimerosal, one part in 30,000, was added to most of the incubation mixtures reported. These then proved to contain very small quantities of bacteria on colony-counts even after

TABLE II. *Perfusion of Pancreatic Duct at Physiologic Pressure*

[Pancreas will accept trypsin incubated with bile as readily as pancreatic juice.]

No. of Dogs	Mixture Infused into Pancreatic Duct	Incubation Period	Amount Accepted, 40 cm. Pressure, 30 min.	Severity of Pancreatitis	Mortality
4	Bile and trypsin*	None	2 to 7 cc.	Moderate	0
5	Bile and trypsin*	12 to 48 hours	15 to 25 cc.	Severe	100%
3	Bile and lipase*	12 to 48 hours	2 to 5 cc.	Minimal	0

* Enzymes were placed in solution at an activity level equal to potent pancreatic juice, as measured in our laboratory; the solution was mixed one to one with bile.

48 hours' incubation, while the enzyme activity remained good. The mixtures which were sterile on culture were as potent in producing pancreatitis as those incubated without thimerosal (Table III). In control animals receiving bile and saline mixtures, the addition of such minute quantities of thimerosal did not alter the pathologic picture of the pancreas.

Early in these observations, incubated mixtures of bile and pancreatic juice without thimerosal were encountered which would readily enter the pancreas and produce pancreatitis after 12 hours of incubation, but which, after 24 or 48 hours' incubation, would no longer enter the pancreas under low pressures. These were invariably found to be heavily contaminated. Therefore, it seems clear that infection interferes with rather than supports the reaction taking place in the bile upon incubation with pancreatic secretion. Generally, the pancreas seems to resist infiltration by infected solutions.

f. *Incubation of Pancreatic Juice with Bile in the Living Animal.* The studies reported above dealt with donor mixtures of bile and pancreatic juice incubated in glassware. It was not clear whether the same changes could occur when pancreatic secretion was incubated in the biliary tree. Therefore, a preparatory laparotomy was performed on a group of dogs, in which the common bile duct was ligated, and the bile in the gallbladder was replaced with potent pancreatic secretions. From 10 to 25 cc. were placed in the gallbladder, depending on its capacity. Antibiotics were adminis-

TABLE III. *Infection of Incubation Mixtures Interferes with Perfusion of Pancreas at Physiologic Pressure*

Mixture Incubated	Period of Incubation	Culture	Colony Count	Amount Accepted, 40 cm. Pressure, 30 min.	No. of Dogs	Mortality
Bile + pancreatic juice 1 to 1	12 hrs.	+	—	18 to 30 cc.	3	100%
Same mixture	24 to 48 hrs.	+	Heavy growth	2 to 9 cc.	3*	33%
Bile + pancreatic juice 1 to 1 + thiomerazole 1 to 30,000	12 to 48 hrs.	—	1 to 2 per cc.	18 to 30 cc.	8	100%

* These animals eliminated from series, Tables I and IV.

TABLE IV. *Incubation of Bile with Pancreatic Juice or Trypsin in Obstructed Biliary Tree*

[When infection is prevented, incubated mixture produces variable pancreatitis.]

No. of Dogs	Substance Placed in Obstructed Biliary Tree	Bile Infected at Second Operation	Amount Accepted in Pancreas at 40 cm. Pressure, 30 min.	Mortality
11	Pancreatic juice 15 to 25 cc.	0	12 to 20 cc.	45%
6	Pancreatic juice 15 to 25 cc.	+	4 to 9 cc.	33%
4	Trypsin 10 to 20 cc.*	0	12 to 24 cc.	75%

* Tryptar® in solution at same activity as pancreatic juice, by laboratory assay, equivalent to about 2 mgm. per cc.

tered to prevent infection in the obstructed biliary tree. The animals tolerated this well, and were usually willing to eat the next day. Either 24 or 48 hours after the initial laparotomy, the second operation was performed in which the incubated mixture was removed from the gallbladder, and infused into the pancreas under the standard conditions of pressure and time. In 11 animals in which the gallbladder content was not grossly purulent, the mixture incubated in the animals entered the pancreas equally as well as did the mixtures incubated in glass. However, the resulting pancreatitis varied widely in severity, from only mild edema to true hemorrhagic necrosis, and the mortality rate was only 45 per cent (Table IV). All animals showed amylase elevations, and some degree of pancreatitis at sacrifice or necropsy. In six animals in which the gallbladder content was grossly infected (proved by cultures) the infected material would not enter the pancreas in amounts sufficient to produce a severe pancreatitis or mortality. Trypsin in amounts equivalent to that in pancreatic secretion, when incubated with bile in the gallbladder of four dogs, was as effective as pancreatic secretions in changing the bile so that it would enter the pancreas and produce fatal pancreatitis (Table IV). It was thought that the wide variation in mortality might be due to difficulty in determining the relative amounts of bile and pancreatic secretions present together in the gallbladder after the preliminary operation.

g. *Severity of Pancreatitis Varies with Ratio: Bile to Pancreatic Secretions.* In an effort to explain the widely varying differences in the pancreatitis produced following incubation of pancreatic secretion in the obstructed biliary tree, a group of experiments were performed in which the proportion of bile to pooled pancreatic juice was varied widely in the incubation mixtures. The results are shown in Table V and Figure 3. When the proportion of active pancreatic secretions to bile is quite small, no appreciable change has taken place in the bile during incubation, and this mixture will not enter the pancreas at low pressure, so that no mortality is produced. If large quantities of pancreatic secretion are added to less bile, the resulting solution will enter the pancreas with ease, but the pancreatitis is much less severe. It seems evident that the pancreas rejects normal bile, but accepts its own activated secretions. A critical quantity of each, near equal parts, is necessary for both entry of the mixture into the pancreas at low pressure and for true hemorrhagic pancreatitis to

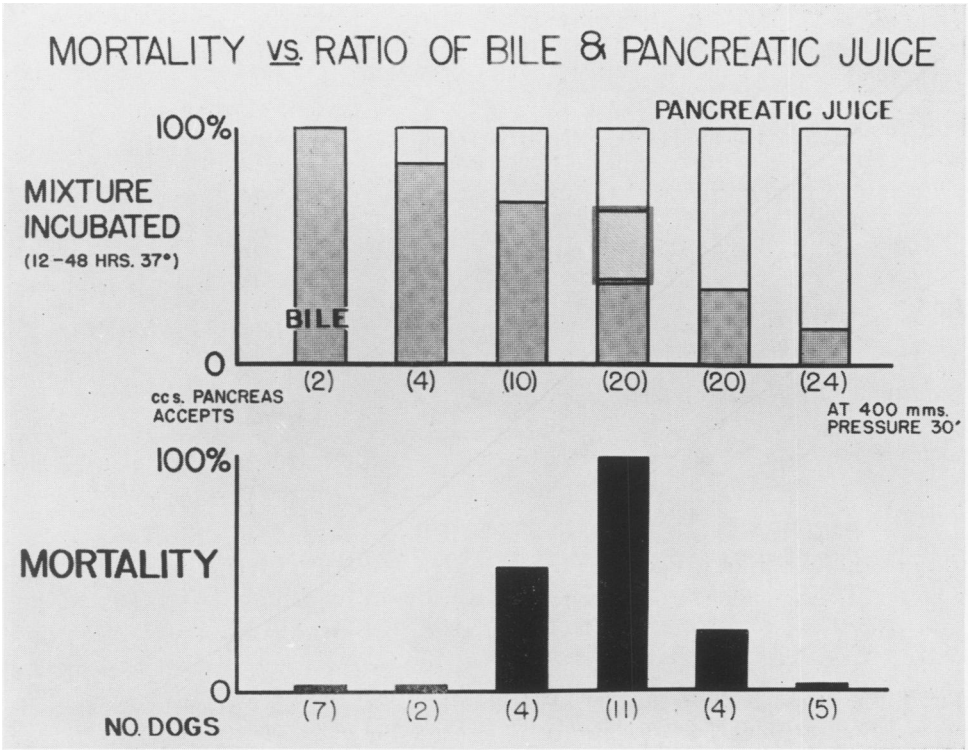

FIG. 3. Experiment IIg, highest mortality from pancreatitis is produced by an incubated mixture of bile and pancreatic secretion in about equal proportions when this is infused into the pancreas under physiologic pressures. See Table V.

result. It appears that bile pancreatitis can vary widely in severity, from mild edema to overwhelming necrosis, depending upon the constituents of the solution infiltrating the pancreas.

DISCUSSION

The experiments reported above were designed to examine events occurring through a longer period of time following obstruction of a common channel than is possible in single acute experiments. The findings suggest that the role of bile in the etiology of pancreatitis still needs further exploration. Dogs, which have no common channel, were selected for this study, not only because the literature contains a wealth of experimental data for comparison, but also because the biliary tree and the pancreas can be examined separately. This has permitted a step-by-step dissection of events following obstruction of a common channel.

The experiments reported fall into two separate groups: 1) those dealing with the course of pancreatic ductal pressure following obstruction, and 2) those measuring the capacity of the pancreas to resist infiltration by potentially dangerous mixtures at a physiologic pressure.

The pancreatic ductal pressure measurements are not new, and confirm the findings of others in the early period following ductal obstruction.[28] These measurements indicate that pancreatic secretions can and do enter the biliary tree.[6, 21] However, these pressure determinations were carried through a more prolonged period, and demonstrated a fall to the range of normal within a 24-hour period. This fall is con-

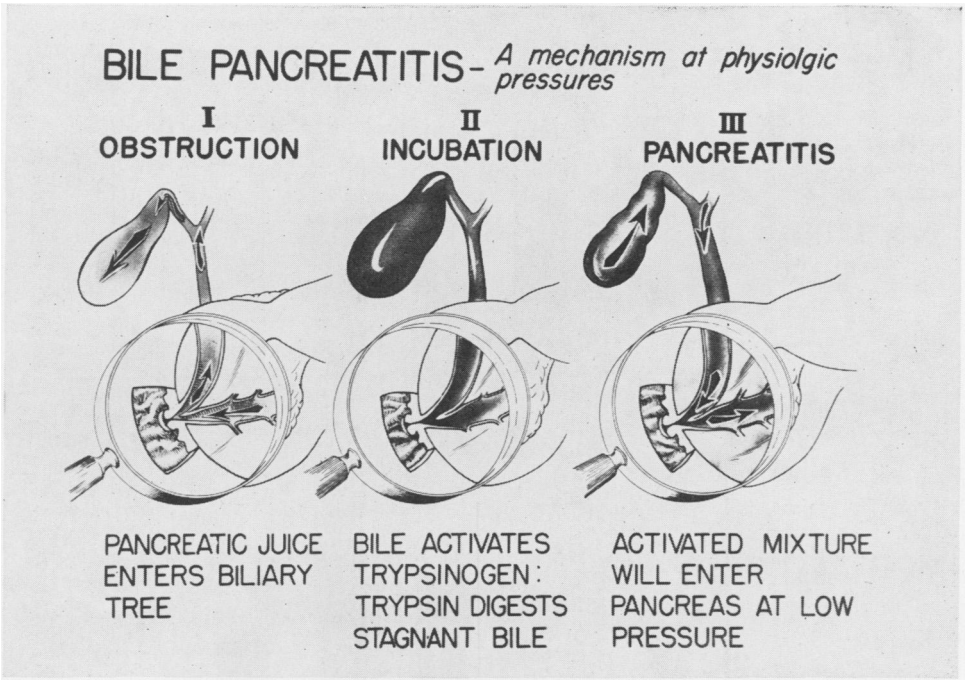

FIG. 4. The mechanism suggested by which obstruction of a common channel can induce the regurgitation of bile into the pancreas and acute pancreatitis.

sistent with what is known to occur in other glands of external secretion, such as the kidney and the salivary glands, and is consistent too with the early appearance of pancreatic atrophy following obstruction.[14] The return of pancreatic ductal pressures to near normal and sometimes to below normal levels, during a time when the obstructed biliary tree pressures are showing a modest rise, seems to make possible the entrance of substances from the common duct into the pancreas. This is particularly so when the very wide variations are considered that occur in common bile duct pressure secondary to intra-abdominal pressure changes, particularly when the biliary tree is obstructed and distended.[13]

The remainder of the experiments deal with the possibility that bile, when mixed with the pancreatic juice in the biliary tree, can infiltrate the pancreas within the physiologic pressure variations that have been observed in the common bile duct. Results indicate that this retrograde movement of bile into the pancreas can occur, but two things are necessary: 1) incubation for 12 hours or longer, and 2) the presence of enzyme-rich pancreatic secretions in the bile; the active agent probably is trypsin.

The nature of the change which occurs in bile during incubation is not yet completely clear. Grossly, the bile is changed in appearance after incubation with either trypsin or pancreatic juice. The bile loses its natural opalescence, becomes darker in color, and seems much less viscous. However, the change in viscosity is not the factor determining whether or not the mixture will enter the pancreas at low pressure, according to data available. The specimens of pancreatic juice which are most effective in producing the essential change in bile have good concentrations of trypsinogen when collected. The bile converts this to trypsin. Trypsin will attack the normal

TABLE V. *Mortality of Pancreatitis Depends upon Ratio of Bile to Pancreatic Juice in Incubated Mixture*

No. of Dogs	Proportions of Mixture, Incubated 12 to 48 Hours: Bile	Proportions of Mixture, Incubated 12 to 48 Hours: Pancreatic Juice*	Amount Accepted, 40 cm. Pressure, 30 min.	Mortality
7	100%	0	2 to 4 cc.	0
2	83%	16%	4 to 5 cc.	0
4	75%	25%	10 to 12 cc.	50%
11	33% to 67%	33% to 67%	18 to 30 cc.	100%
4	25%	75%	20 to 26 cc.	25%
5	16%	83%	20 to 30 cc.	0

* High enzyme content on testing.

mucin of the bile during incubation. Years ago Flexner [9] showed that in the production of bile pancreatitis, the mucin content of the bile protects the pancreas, while the bile salts are particularly damaging when freed of mucin.[9] The mixture which enters the pancreas also contains active trypsin, and there has been much evidence that some of the damage in the pancreas must be due to its activity.[12, 18, 22, 23]

To produce a significant pancreatitis in experimental animals, the mixture introduced in the pancreatic duct at low pressure must be both accepted by the pancreas, and contain a lethal agent. It appears from the results shown in Table V that the presence of active pancreatic enzymes, incubated with bile, accounts for the acceptance of the mixture by the gland. The enzymes alone are not sufficient to produce a severe lesion or a mortality, and this is in agreement with others.[7] Bile seems to be the lethal factor.

For the development of pancreatitis as a result of these changes, there must be 1) an open common channel obstructed at the sphincter of Oddi, and 2) a pancreas stimulated to produce an enzyme-rich secretion. Wangensteen [26] produced pancreatic necrosis 25 years ago by obstruction of the common channel present normally in cats. However, pancreatitis occurred only when the animals were stimulated by force-feeding. Others have recognized the importance of these two factors of obstruction and stimulation in the pathogenesis of pancreatitis.[14]

SUMMARY AND CONCLUSIONS

A series of experimental observations have been presented which appear to substantiate a mechanism by which obstruction of a common channel at the sphincter of Oddi can lead to acute pancreatitis. This mechanism consists of three successive events: 1) the entry of pancreatic secretion into the biliary tree; 2) incubation of pancreatic secretions with stagnant bile; and 3) infiltration of the pancreas at low pressure by this incubated mixture, to which it has little resistance. Pancreatitis results, which may range in severity from mild edema to fulminating hemorrhagic necrosis.

Evidence supporting this mechanism has been obtained in dogs through a series of experimental observations:

1) Pancreatic secretory pressure is higher than average common bile duct pressure, so that pancreatic secretions enter the biliary tree following common channel obstruction. This has been confirmed.

2) During prolonged periods of obstruction (12 to 24 hours), pancreatic ductal pressures first rise but then fall again; common bile duct pressures rise moderately, so that after 24 hours of obstruction, pan-

creatic and biliary tree pressures approach one another.

3) Under pressures known to occur in the distended biliary tree (in these observations, less than 40 cm. of water), the pancreas resists infiltration by normal bile. If bile is mixed in equal parts with enzyme-rich pancreatic secretion, more will enter, but little damage is done. If this same mixture is incubated at body temperature for 12 to 48 hours, the pancreas accepts it in large quantities at low pressures. Hemorrhagic pancreatitis results which is 100 per cent fatal.

4) Bile incubated with trypsin also will enter the pancreas at low pressure and produce fatal pancreatitis. Bile incubated with lipase or saline will not. Infection of the incubated mixtures interferes with infiltration of the pancreas.

5) Bile incubated with pancreatic secretions or trypsin in the dog's obstructed biliary tree is as effective in entering the pancreas as bile incubated *in vitro;* the mortality varied widely.

6) The ratio of bile to pancreatic secretion in the incubated mixture determines the mortality of the pancreatitis. Both must be present in about equal parts to produce a lethal lesion.

These observations appear to meet the previous objections to bile as a cause of pancreatitis, which have been based on experimental pressure measurements. The experimental evidence obtained supports Opie's "common channel theory" in the pathogenesis of acute pancreatitis, at least for the 60 per cent [4, 24] to 90 per cent [6, 16] of patients with a common channel.

The pancreas normally rejects bile at physiologic pressure. It will accept an incubated mixture of bile and its own secretions. These observations have suggested a mechanism by which bile can enter the pancreas as a result of common channel obstruction and produce acute pancreatitis.

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Discussion

DR. MCKENZIE: Mr. President, members and guests, I enjoyed the presentation of Dr. Elliott and his colleagues very much, indeed. Having had the opportunity of reading the manuscript last night, I would like to commend them on the well conducted and nicely conceived experiment. I believe this is a significant addition to those contributions aimed at correlating the possible role of bile reflux in the etiology of pancreatitis. Most of us would agree that the elimination of gallbladder disease is our first objective in the treatment of pancreatitis. Some of us feel that decompression of the extrahepatic biliary tract and pancreatic duct system is necessary, but sphincterotomy has a more definite place in the treatment of these patients with pancreatitis who have had gallbladder disease than those who have not.

A study of our limited experience supports this observation. In our laboratory, about a year ago, we attempted unsuccessfully to extend the work of Allen that was carried out in Dr. Wangensteen's laboratory. As you will remember, that related the Schwartzman reaction to the etiology of pancreatitis by sensitizing the pancreatic ductal system to toxoid, and then producing equal pancreatitis by use of a provocative intravenous dose of the same toxoid.

Our attempt to use bile in a similar manner was not possible because, like Dr. Elliott, we were unable to persuade bile to enter the ductal tree without using non-physiologic pressures. I would like to ask Dr. Elliott two questions: (1) Does he have an explanation for the increased capacity of the ductal system with the use of the bile-pancreatic mixture? And, (2) has he observed widespread thrombosis of small veins in the early stages of pancreatitis produced in this manner?

Dr. Elliott has stimulated us to visualize the possibilities in these alterations in pancreatic resistance to bile. (Applause)

DR. MULHOLLAND: Like Dr. McKenzie, I would like to commend Dr. Elliott and his coworkers for an imaginative and direct experimental approach to a puzzle. The evidence seems