FURTHER DATA CONCERNING THE EXPERIMENTAL PRODUCTION OF PANCREATITIS*

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The problem of the exact cause of pancreatitis and of the exact mode in which that cause works is still somewhat unclear. As you know, there are three principal theories: according to one the pancreatic lesion is caused by the entrance of bile into the pancreatic duct by reason of an obstruction, either stone, or shred of mucus, or spasm of the common duct sphincter, at the outlet of the common duct; according to the second, which in this country is associated particularly with the name of Deaver, the lesion is caused by an infection traveling from the inflamed gall-bladder along lymphatics to the head of the pancreas; and the third theory is that duodenal contents are forced into the common duct through the papilla, temporarily relaxed, and so into the pancreatic duct. Of these theories the first and the third may be considered as proved for a considerable proportion of the cases reported, at any rate of the acute cases; while the second is still under discussion, and in any event is hardly susceptible of absolute demonstration—it lacks as yet experimental proof, depends upon purely clinical inferences, and goes, on the whole, contrary to the rules of pathology.

It is true that the entrance of duodenal contents has also never been demonstrated by animal experimentation. Nevertheless, the conclusion that pancreatitis is sometimes brought about in this way imposes itself. I refer to cases in which postmortem dissection has shown that the pancreatic duct opened directly upon the mucous surface of the duodenum and not into the common duct, and to one or two rare cases in which there has been demonstrated localized pancreatitis of that part of the organ drained by the small duct of Santorini. These conditions, however, are fulfilled but rarely; and most of our evidence, both clinical and experimental, goes to show that the entrance of bile into the pancreatic duct is by all odds the most frequent mode of causation. This hypothesis has now got outside the bounds of mere theory and is widely accepted as being definitely proved.

I need not in this place recount the history of the clinical and experimental work which has been published in support of this proposition, but shall confine myself to recalling to your minds certain outstanding facts of the experimental work which has engaged my attention for the past few years, and which I presented before this Society two years ago. It was proved that in cats, in which animals the anatomical relationships of the common and the pancreatic ducts resemble those present in the human much more exactly

* Read before the American Surgical Association, June 15, 1921.

than they do in other laboratory animals, it was possible to run a solution from the gall-bladder under a pressure of from 300 to 600 mm. of water into the pancreas to such an extent that even the finer radicles between the acini were found filled with the solution. In later experiments it was found possible in the same way to run bile, infected or not, solutions of bile salts, and mucin-free bile, from the gall-bladder into the pancreas with consequent production of various grades of pancreatitis from the least severe up to the acute hemorrhagic form, with death inside an hour. In all these cases the only obstruction possible lay in a resistance of the common duct sphincter.

From a consideration of these experimental facts and of clinical experience it seemed justifiable to present the problem of the etiology of pancreatitis in the following way. "The conditions for actual serious damage to be done in the pancreas must pretty certainly be three: (1) a change in bile composition, increasing the proportion of bile salts; (2) undue resistance, perhaps often amounting to spasm, of the common duct sphincter; and (3) abnormal rise of pressure in the biliary system behind, either in the gall-bladder or in the common duct.[1]

"Our problem, therefore, is to discover in the facts of clinical experience circumstances fulfilling these postulates. Here we come on to uncertain ground. It is probable that hyperacidity may have a good deal to do with it. Symptoms indicating hyperacidity are frequently found in the previous history of patients with pancreatitis (Egdahl, 14). Certainly the injection of hydrochloric acid into the duodenum or even into the stomach (Oddi) will cause a spasm of the sphincter. In man we are still unacquainted, so far as I know, with the condition of the duodenal contents as regards the length of time which is necessary for neutralizing the acid chyme of the stomach. In alcoholics, anyhow, and in patients who have duodenal ulcers, it would seem probable that the duodenal contents might remain acid for some time, and in these two classes pancreatitis is rather frequent. One recalls in this connection three cases published by Dr. William J. Mayo, in which acute pancreatitis was present, without gall-stones anywhere, but with, in each instance, a duodenal ulcer situated close to the papilla, presumably causing hyperacidity.

"In the second place, that change in bile which results in a high concentration of bile salts and a diminution of bile mucin is probably brought about by the effect of gall-stones, especially when associated with inflammation. In infected bile, it is pretty certainly not the bacteria acting in their infecting capacity that cause the pancreatic lesion, but rather the chemical change in the bile produced by the action of bacterial growth. This at least was strongly suggested by the work of Flexner, of Carnot, Hlava, and others; and the present experiments, in which sterile bile and a solution of sodium taurocholate caused the lesion equally with infected bile, tend to confirm this view. I am unacquainted with any work upon the chemical composition of infected bile, but it may be presumed that the action of bacteria is to pre-

cipitate the mucin of bile; and indeed we see the evidence of it in the shreds observed in the bile in cases of cholecystitis and cholangitis. If this is the case, it is probable contrary to the assumption of Flexner, that the relative proportion of the bile salts is increased. I may add that Doctor Harding, Associate Professor of Chemistry in McGill University, is beginning work along this line. It must be pointed out, however, that the effect of bacteria upon the bile seems to increase very greatly the destructive effect of that bile upon the pancreas; and while this is still probably due to some chemical change in the bile it seems likely that there come into play, in addition to the bile salts, new substances possessing necrosing properties.

" It may be noted also that any obstruction in the cystic duct would probably deprive the bile of a part of its mucin content normally provided by the gall-bladder mucosa; and in such cases, theoretically at least, the occurrence of a pancreatitis may be rendered more likely.

" In the third place, the condition of increased pressure in the biliary system is presumably brought about partly by an increased resistance of the sphincter, set in motion by hyperacidity or by neighboring ulcers; partly by a sudden blocking of the cystic duct by stone or inflammation; and finally, perhaps, by any unusual increase in the amount of bile secreted by the liver. The effect of a full meal, two or three hours after which, as we see in so many case reports, the attack of pancreatitis is apt to come on, may be in the direction of increased bile production rather than in that of increased pancreatic secretion."

The present work represents a small effort to get deeper into these problems. Fourteen cats have been used. A later report will give details of the experiments performed. Briefly, we have injected ox bile, infected with various organisms, as well as human bile aspirated at operation from acutely inflamed gall-bladders, into the gall-bladder of cats, under pressure, either by running it in from a raised funnel or by squeezing of the gall-bladder. In most, the bile entered the pancreas. We have also injected by syringe direct into the pancreatic substance cat's own bile, human bile from distended inflamed gall-bladders, in one case complicated by very acute pancreatitis, the same human bile several days later running clear and normal-looking from the cholecystostomy tube. We have reopened at intervals, cut out sections of pancreas for microscopical examination, and have taken cultures from the interior of the pancreas often recovering the original organism, thus proving penetration of bile. We have injected HCl into the duodenum to stimulate the sphincter.

Microscopically we have found all grades of pancreatic necrosis of the parenchyma, with much or little stroma reaction, œdema, congestion, hemorrhage, going on after from one to four weeks to advanced replacement fibrosis, local or diffuse. We could follow the development of interstitial pancreatitis, a pancreatic cirrhosis from the original necrosis, through fibroplastic repair.

The investigation has been directed chiefly along the following lines: In the first place, what effect does infection in bile produce upon the relative proportions of the bile salts and the mucin? Secondly, what difference, if any, exists between the action of infected bile on the pancreatic parenchyma and that of normal bile? Third, is it necessary that an abnormal degree of the force which expels the bile should be present before the pancreatic duct is invaded, and if so, what is the nature of that abnormal force? Finally, under what condition is the common duct sphincter brought into resistance to the flow of bile into the duodenum?

I. *The Chemical Examination of Infected Bile.*—During the past winter Mr. Logan, working in the Chemistry Department of McGill University, under Doctor Harding and Professor MacCallum, has been analyzing, according to the methods of Foster and Hooper, samples of bile which I have brought him from the wards of the Royal Victoria Hospital, together with specimens of bile from the ox, the hog, and the cat. These biles have been variously infected. My idea was that as the result of infection the mucin of bile might be precipitated in such an amount as to leave the bile salts in a much higher proportion, and greater concentration, than in normal bile, and that such a bile being forced into the pancreas would presumably cause a more definite and more severe pancreatitis. Flexner showed that it was the bile salts that caused pancreatic necrosis, while the mucin had a protective action. Our work leaves this supposition as yet unconfirmed. Clinical experience, on the whole, seems to indicate that the more serious cases of pancreatitis are associated with conditions of serious inflammation in the gall passages. Mr. Logan's work is still very incomplete. The difficulties of the subject are much greater than the uninitiated might suppose, and I am unable to make any very definite report upon this part of the work. On the one hand, the actual amount of bile salts excreted in the bile varies very greatly according to the nature of the diet, chiefly, but varies anyhow on a mixed diet from day to day (Hooper and Foster). On the other hand, the amount of mucin in a normal fistula bile remains fairly constant. The amount of mucin, when the bile has been infected, shows in some cases a slight increase, in others a slight decrease. The analyses, so far, which have been carried out with several of the ordinary organisms, staphylo- and streptococci and B. coli, are insufficient in number to give any sure indication on this point. We expect to carry on the work during the coming year. But for the present it looks as if our hypothesis as to the greater concentration of bile salts as the result of infection remains unsubstantiated. There is probably something else in infected bile which is responsible for the more severe necrosing effect which it shows as compared with normal bile. Upon this point several of the experiments are most positive. One of these in detail is as follows:

Cat 190. Bile aspirated from gall-bladder at operation on a case of acute cholecystitis with impacted stone in cystic duct. The bile was blackish green and was obviously infected. Culture showed a scant growth of streptococcus. The gall-bladder was drained. A portion of

the original infected bile was injected with syringe into the splenic end of a cat's pancreas, and another portion of the drainage bile, which three days after operation had become clear and normal looking, was injected into the duodenal end of the same pancreas. After two days the cat was reopened, and it was found that the infected bile had caused a very marked inflammatory reaction, with fat necroses in the adjoining omentum. In marked contrast with this, the more normal drainage bile had left the duodenal end almost normal. These two areas were cut out and sectioned, and the difference in necrosing effect was confirmed. At the splenic end the necrosis of parenchyma was extensive and there was a great deal of œdema and congestion, while at the duodenal end there was very slight necrosis, little œdema, and practically no congestion.

This observation was confirmed with two other cases of acutely infected bile from cases of acute cholecystitis, and in still another one the same contrast was found between the effects of cholecystitic bile and the cat's own normal bile.

The difference is one of degree. Even normal bile entering the pancreas causes necrosis of the pancreatic parenchyma with which it may happen to come in contact. But this necrosis is aseptic, is accompanied by little, if any, surrounding reaction, whereas the infected bile causes a more massive and extensive necrosis with a great deal of œdema, congestion, even hemorrhage, and with much inflammatory response on the part of the fixed connective tissue. Fat necroses also are often more abundant.

While these results were obtained by the direct injection of bile through a needle, we were able to determine that similar results, and like differences, were found when the bile entered through the pancreatic duct from the gall-bladder. It may here be said that in the present series, as in that of two years ago, in a majority of the experiments in which any pressure was applied from behind, that is on the gall-bladder, the bile entered the pancreatic duct to some extent, as was evidenced by the finding of necrosis. In some instances the effect seemed localized to the central part of the gland nearest the entrance of the pancreatic into the common duct, while in others the bile had invaded the whole gland.

The degree of swelling of the organ was variable. One fact in particular is noteworthy, which was that there might be macroscopically very little evidence of any lesion in the pancreas in the way of swelling or congestion, and yet microscopically necrosis might be quite extensive. In all such cases the bile was practically normal. In other cases, and these the majority, the effect of bile entrance was evident in a definite œdema and swelling, with slight induration of the organ. In these, on microscopical examination, one may find all grades of necrosis, diffuse or localized, involving a few acini or whole lobules, the individual cells showing early stages of degeneration—a diffuse "cooked" appearance, or advanced stages of mass necrosis together with marked œdema and congestion. These observations are, I think, important

from the clinical standpoint. We are all of us frequently troubled at operation to decide whether the pancreas, which upon palpation we think is somewhat enlarged, a little harder than normal, and nodular, is really the seat of a mild inflammation or is normal. The pathologists tell us that in such cases, upon the opportunity of a postmortem, they can find no evidence of pancreatitis, and clinicians of prominence warn us that we should be very chary of saying that there is actual pancreatitis present. In two patients, suffering from quite definite subacute pancreatitis, one of my own and one of Doctor Garrow's, a small section has been taken from the pancreas at operation for microscopical examination. Let me repeat that the pancreas to palpation was quite certainly enlarged and hard. In both the pathologist was of the opinion that there was no clear and definite pathological change present; yet in both I felt justified in concluding that there was clear evidence of pancreatic damage. In certain areas the cells were disintegrated, cell membranes broken, nuclei swollen, cytoplasm poorly staining, and in one or two places actually necrotic. There was also marked œdema and some congestion. I felt sure that these were not artefacts or due to imperfect technic, as the pathologist was inclined to believe, because I had seen the same slight lesions in association with absolutely definite lesions so many times in animals. I would, therefore, suggest that at least in many of the cases in which, at operation, we feel that the pancreas is *probably* swollen, it really *is* swollen; and that this effect is due to the entrance of small quantities of bile not seriously infected, and constitutes a warning that the biliary system must be freed of all possible infection.

The second part of the problem concerns the question of the *vis a tergo*. It is probable that before pancreatitis of any severity can be caused, there must be an increase of pressure in the expelling forces of bile. A number of investigators (Doyon, Freese, Mann, Bainbridge and Dale) have investigated the contractile force of the gall-bladder in animals and give figures approximating 150 to 225 mm. of water. An exact estimation is difficult, and they were concerned only with the normal animal. It is probable that in the human, and under pathological conditions, the contracting force of the gall-bladder may be much increased. Dr. F. N. G. Starr reports the following very remarkable observation. During operation on a patient suffering from cholecystitis with stones, under very light anæsthesia, he inserted his finger into the neck of the gall-bladder and immediately found it grasped apparently by a very strong muscular contraction, so strong that, as he puts it, he would have pulled the whole liver out if he had exerted his strength to pull his finger out. It was apparently a severe reflex spasm in the semiconscious patient. It may be that, if we were not accustomed to operating under full ether anæsthesia, we might encounter the same experience upon occasion. In any case this observation seems to me to have a direct bearing on the question. If, as the result of the stimulus of stone and inflammation, the gall-bladder is able to contract violently, we are immediately provided with the driving force needed to push bile into the pancreas. In my experiments

it has been, as a rule, necessary to fill the gall-bladder more or less rapidly under pressure, or to give it a few squeezes, in order to stimulate the sphincter to contract and offer the requisite resistance. The normal contraction of the gall-bladder is undoubtedly feeble, and, according to Meltzer's law, the sphincter presumably relaxes at the same moment, so that ordinarily bile is not forced into the pancreas.

Another observation, which I owe to Doctor Mann, is that upon any sudden descent of the diaphragm with fixation of the abdominal walls, as in sneezing or vomiting, the pressure in the gall-bladder is driven up to a great height. This also might have some bearing on the question.

In three animals I have tried the effect of eserin hypodermically, and of barium chloride painted on the surface of the gall-bladder. In no case did I observe any peristaltic movement in the gall-bladder wall, although with a very high dose of eserin there seemed to be a slight tonic contraction of the gall-bladder as a whole.

With regard to the third factor, the abnormal resistance of the common duct sphincter, I have nothing new to add. One thing seems definite, that acid in the first and second portions of the duodenum will cause a temporary spasm of the sphincter. The contents of the duodenum have in the last few years been frequently examined since the use of Einhorn's tube has become general, and I understand from Doctor Einhorn (verbal communication) that sometimes he has found the duodenal contents to remain acid for a certain time. Whether one should, in cases of duodenal ulcer, or of the gastroduodenitis of the alcoholic, expect such a condition to be frequently present I do not know, but at least such an assumption is not unlikely, and in that case one might expect a recurring spasm of the sphincter; and this might serve to explain the frequency of pancreatitis in association with ulcer and alcoholism. This must still remain a matter of speculation. In any case, so far as my experiments go, it would seem that the more important factor in stimulating the sphincter to resistance lies in a sudden rise of pressure from the gall-bladder side, rather than in irritation from the duodenal side; and in this connection I am inclined to believe that the reason why a cholecystectomy is apt to cure coincident pancreatitis, lies partly in the fact that the only serious muscular contractile force in the biliary system has been cut out, and partly, also, in the fact that with the removal of the gall-bladder there is also removed the source of infected bile, at least in most cases.

SUMMARY

1. Infected bile, aspirated from the inflamed gall-bladder, exercises a much more severe necrosing and inflammatory effect upon the pancreas than does normal bile.

2. Chemical investigation of infected bile has not yet proved that this difference of effect is due to an increase in concentration of the bile salts as the result of bacterial action on the bile.

3. Mild grades of pancreatic swelling, as estimated clinically, are certainly possible, and are represented by œdema with early necrosis of the parenchyma, presumably the result of bile invasion. The clinical statement in operation records as to the presence of "a somewhat thickened and indurated pancreas" is probably a correct interpretation of fact in most instances.

4. The gall-bladder, under conditions of irritation from stone or inflammation, is probably able to go into strong muscular contraction, and the hypothesis is set up that such contractions may provide sufficient driving force to cause invasion of the pancreas with bile.

5. The common duct sphincter is provoked to resistance not only by an acidity of the duodenal contents, but also by a sudden distention of the common duct through abnormal and unexpected rises of pressure in the gall-bladder.

[1] Archibald: Experimental Pancreatitis, etc., Surgery, Gynecology and Obstetrics, June, 1919.