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Etiology and pathogenesis of acute pancreatic necrosis :ba review and analysis of 9 cases

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ETIOLOGY AND PATHOGENESIS OF ACUTE PANCREATIC NECROSIS; A REVIEW AND ANALYSIS OF 9 CASES.

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Introduction

Acute pancreatic necrosis has long intrigued both the clinician and pathologist. For the clinician this disease until recently has been considered almost an autopsy diagnosis, while the pathologist is still seeking to clarify its pathogenesis.

Most investigators confirm the poor diagnostic ratio in this disease. Von Schmieden and Sebening(1927), in reviewing 1,510 cases in their collected series, found that a correct diagnosis was made in only 21.8% of the cases, and a suggested or alternative diagnosis in an additional 17.5%. McWhorter(1932), in reporting 64 cases collected from the records of members of the Chicago Surgical Society, found that a correct diagnosis was made in only 12%. In Lynch's(1940) series of 18 cases,as well as the present group of 9 cases, the clinical diagnosis was not made on any of the patients.

The history of acute pancreatic necrosis in America extends back to Matthew Baillie (1820), the first to describe the disease in this country. Clässen is credited by Archibald (1940) as being the first to present in 1842 the clinical picture as it is recognized today. Archibald presents an interesting review of the

historical development of our knowledge of the disease. He cites Rokitansky and Klebs as describing in 1861 and 1870 respectively the particular condition of pancreatic hemorrhage with severe symptoms. Friedrich was the first to present a complete picture of the disease in 1861.

It was Reginald Fitz (1889), however, whose classical paper on acute pancreatic necrosis presented both the clinical and pathological aspects of the disease, as well as establishing for the first time an acceptable classification. Fitz discussed acute pancreatitis as a process separate from acute hemorrhagic pancreatitis, and thought that inflammation came before hemorrhage. Fitz subscribed to the general theory of the time that the essential cause lay in a bacterial infection, for the influence of Pasteur and Lister still dominated scientific thought. Fitz laid the groundwork for our present day knowledge of the disease.

Because of early lack of agreement as to the pathology of acute pancreatic necrosis, there has been some confusion in the literature regarding its nomenclature. Fitz first classified acute pancreatitis according to three types:

1. Hemorrhagic
2. Gangrenous
3. Suppurative

Opie and Meakins (1909) showed, however, that the es-

sential pathological lesion is not inflammatory, but rather a necrosis of pancreatic cells or masses of cells. This is primary. They suggested that what was previously called acute hemorrhagic pancreatitis ought instead to be called acute hemorrhagic necrosis. Guleke (1912) suggested using simply the term acute pancreatic necrosis, since hemorrhage, gangrene and suppuration are merely complications. This designation has been in general use in the German medical literature for many years. The term "acute pancreatitis" is used for only those pancreatic diseases thought to have an underlying inflammatory origin. In the American and English literature "acute pancreatitis" has through usage become entrenched as the term of choice for all acute forms of the disease. Because acute pancreatic necrosis is a more accurate and descriptive term it will be used throughout this paper.

The purpose of this thesis is to review the controversial literature relating to the cause and development of acute pancreatic necrosis, to analyze all proven cases of the disease seen at the University hospital, and finally to offer several hypothesises as to its etiology and pathogenesis.

Pathology

The basic pathological picture of acute pancreatic necrosis is fairly well agreed upon by authors of present day texts. Perhaps the most concise description of the pathology of the disease is that of Foot (1940). He states that "grossly the pancreas appears 'shot to pieces'; shows many areas of hemorrhage and is crumbling and friable. Hemorrhage, necrosis, or actual suppuration may be found. Peritoneal fat in the neighborhood is flecked with small, whitish-yellow, opaque, and firm areas that look like bits of soap, and in fact are much like soap; the escape of lipases from the destroyed pancreas saponifies the neutral fats of the adipose tissue."

"Microscopic examination is not revealing, for the afflicted pancreas has become a mass of hemorrhage and necrotic pancreatic tissue, with much fibrin deposition and polymorphnuclear infiltration. The adipose cells become semi-opaque masses of slightly granular material that stains very poorly. At the margins are many lipo-phages which have engorged fat droplets and bits of necrotic fat. Varying degrees of the disease may result in pathological pictures ranging from slight focal necrosis to massive tissue destruction."

The later literature on the pathology of acute

pancreatic necrosis contains several descriptions of lesions claimed to be specific for the disease. These descriptions will be discussed later as each relates itself to the etiological concept presented.

Etiological Concepts

Perhaps the most suitable classification to use in reviewing the etiological literature of acute pancreatic necrosis is that of McWhorter (1932). This will be modified slightly for convenience of presentation.

A. Infectious Origin

1. Invasion of pancreas along lymphatics.
2. Invasion of the pancreas from the blood stream.
3. Infection by extension along the pancreatic ducts from the duodenum or bile ducts.
4. Direct infection from infected foci.
5. Infection following activation of bacteria and their toxins in the normal gland.
6. Infection by bacterial invasion from adjacent altered viscera

B. Non-infectious Origin

1. Mechanical or Obstructive
   a. Stone in the common duct or in the ampulla of Vater.
   b. Spasm of the sphincter of Oddi.
   c. Edematous occlusion of the ampulla of Vater.
2. Chemical: activated pancreatic ferments resulting from:
   a. Reflux of bile
   b. Rêflux of duodenal contents
   c. Autolysis
   d. Metaplesia of the epithelium of the

pancreatic duct.
e. Alcohol

3. Degenerative changes in the pancreas.
   a. Changes secondary to benign or malignant tumors.
   b. Changes resulting from vascular degeneration, hemorrhage or occlusion.
4. Trauma
5. Miscellaneous

C. Combination of two or more factors.

Of the many theories concerning the etiology of acute pancreatic necrosis, the first to be considered by many investigators as the answer to the problem was that of invasion of infection along the pancreatic lymphatics.

This theory was first suggested by Klippel and Lefas (1899) as a likely cause of acute pancreatic necrosis. Maugeret (1908) failed to effect an acute pancreatic necrosis by producing a chemical cholecystitis in dogs following the introduction of formaldehyde and charcoal into the gall bladder. She believed, however, that the swelling and interstitial edema of the pancreatic gland demonstrated that infection may be propagated to the pancreas from the biliary passages by the lymphatic route.

The work of earlier investigators such as Sappey (1885), Hoggan (1880), Cuneo (1903) and others had demonstrated the free lymphatic communication be-

tween the biliary tract and the pancreas. Franke (1911), by injecting the lymphatics of the gall bladder with dyes, was able to trace their course to the celiac lymph glands and the lymph channels about the head of the pancreas. He did not, however, demonstrate that the injected material entered the substance of the gland.

The concept of lymphatic invasion was given support by Deaver (1921), Judd (1921), Arnsperger (1911) and Graham (1922). After Kodama (1926), in an authoritative study, failed to demonstrate direct lymphatic connections between the gall bladder and pancreas, Graham and his coworkers(1928) retracted their original conclusions as being erroneous.

Archibald (1919) entered the controversy by stating that spread of infection by this route would be blocked by intervening nodes and would demand retrograde flow of lymph. Moynihan (1925), on the other hand, countered with the postulate that chronic infection may well have blocked the nodes draining the gall bladder and that this would cause a retrograde flow of lymph to the pancreas.

Kaufmann (1927) demonstrated that after an acute infection of the gall bladder produced in animals it was not uncommon to find bacteria present in the pancreas, but bacteria could also be found as a result of

this bacteremia in the tissues of most of the organs of the body. No pathologic evidence to suggest the presence of acute pancreatic necrosis was found in the animals.

Wangensteen, Leven and Manson (1931) disposed of the lymphatic theory of spread in a definitive manner. After their experiments on dogs they concluded that necrosis of the pancreas in no case followed the establishment of acute cholecystitis. Direct injection of bacteria into the substance of the pancreas failed to produce necrosis. They reasoned that "If lymphogenous infection were the chief etiologic factor in hemorrhagic pancreatitis, we would certainly expect to see it more commonly with the acute forms of cholecystitis, for it is well known that lymphangitis is common with acute infections and rare in chronic infections. Were this 'lymphatic theory' true it would be difficult to explain the safety of conservative treatment of acute cholecystitis." With these arguments in mind, and considering that cultures from the gland and peritoneal exudate are commonly sterile in acute pancreatic necrosis (Archibald 1919), they concluded that "lymphogenous spread of infection very rarely may be held responsible for acute hemorrhagic pancreatitis."

A corollary of the "lymphatic theory" is that of blood stream invasion of the pancreas. In rare cases bacterial invasion of the pancreas from the blood stream may produce acute pancreatic necrosis, either by metastatic foci in the presence of pyemia or by extension of infectious thrombophlebitis. Rosenow (1921) found that streptococci isolated from the tonsillar crypts of patients who were suffering from disease of the biliary tract had an elective affinity for the gallbladder and pancreas when injected intravenously into animals. Streptococci of unrelated strains showed no such localization. Kaufmann (1927), however, injected bacteria directly into the portal vein and found that a generalized bacteremia was the result. The organisms were then not only isolated from the pancreas but from almost all of the other body tissues as well. Microscopic sections of the pancreas revealed low grade perivascular round cell infiltration.

Blood borne metastatic lesions complicating mumps have been observed by investigators for many years. Brahdy and Scheffer (1931) reported 156 cases of clinically suggestive acute pancreatic necrosis in 8306 cases of epidemic parotitis. They reported two autopsies which confirmed the diagnosis, but in both cases the pancreas was edematous, congested and enlarged, not the typical

picture of acute pancreatic necrosis. Farnam (1922) reported a case of acute pancreatic necrosis following mumps. Streptococcus viridans was isolated from the peritoneal exudate.

Acute pancreatic necrosis secondary to an acute infectious disease such as typhoid fever, scarlet fever or diphtheria is a rare complication and usually results in suppurative pancreatitis. Acute pancreatic necrosis resulting from bacterial invasion by an infective thrombus or embolus is most infrequent, but when it is recognized the pancreas is found to be the site of either single or multiple abscesses.

In a series of 35 cases presented by Lewison (1940), only three patients were found to have had an infection of the upper respiratory tract immediately prior to the onset of acute pancreatic necrosis. No further evidence to incriminate the more obvious foci of infection could be uncovered from his records or from the protocols of other investigators.

The theory that bacterial invasion along the pancreatic ducts from either the duodenum or the bile ducts is one of the causes of acute pancreatic necrosis has been proven true experimentally. Egdahl (1907) noted clinically that in 32 of 105 cases of acute pancreatic necrosis there were associated GI disturbances

which could be directly invoked in a causal relationship. It has been suggested that these lesions occur by direct extension of bacteria through an altered intestinal wall, although the mechanism of this process is vague.

Von Schmieden and Sebening (1927) reported 50 cases of invasion of the duct of Wirsung by ascarides with resultant pancreatic necrosis. This demonstration of the ability of motile organisms present in the duodenum to enter the pancreatic duct is virtual proof that infection and irritation may be secondarily responsible for the production of some cases of acute pancreatic necrosis. Polya (1912) made injections of bacteria into the pancreatic ducts of 12 dogs and only once succeeded in causing acute pancreatic necrosis.

Direct extension from infected foci as an etiological factor is mentioned only for completeness. There have been many cases of so-called acute pancreatic necrosis reported as resulting from penetration of a duodenal ulcer into the pancreatic parenchyma, but the pathologic mechanism of this process remains obscure.

In summarizing the theories of the infectious origin of acute pancreatic necrosis it becomes evident that this concept lacks universality. Although perhaps a factor in a very small number of cases, the fact remains

that it has never been substantiated clinically. This concept is interesting as it relates itself to the development of our knowledge of the subject, but should now be discarded in light of our newer understanding of the disease.

The activation of bacteria present in the normal gland as a cause of acute pancreatic necrosis has been given only slight consideration by most authors on the subject. Andrews, Rewbridge and Hrdina (1931) offered some support of the idea by investigating the role of Cl. welchii in the production of peritonitis. Using dogs, they concluded that the action of bile supposedly aids in permitting local tissue permeability by these organisms. There is no evidence, however, that the powerful hemolysin produced by Cl. welchii is related to the hemorrhage and necrosis associated with acute pancreatic necrosis.

The question of bacterial activation of normal gland contents as the cause of the toxemia and death seen in the disease has, on the contrary, been the subject of some controversy. Sweet (1915) reported a series of experiments in which he compared the toxicity of non-proteolytic and proteolytic pancreatic juice, He found that non-proteolytic pancreatic juice was harmless on intraperitoneal injection into animals, but that the injection

of a like amount of pancreatic juice activated by intestinal juice produced severe toxemia and death. This same procedure was repeated by the intravenous route and the same results were obtained. He then concluded that much of the toxemia of acute pancreatic necrosis was the result of systemic absorption of activated trypsinogen. Dragstedt et al. (1934) were critical of these and earlier experiments on the basis of inability to rule out bacterial contamination. They, in turn, injected 50cc. of contaminated active pancreatic juice intraperitoneally into one dog which died of toxemia in 24 hours. The animal showed no evidence of fat necrosis. Active pancreatic juice was sterilized by passage through a Berkefeld filter. This solution was then injected intraperitoneally into three dogs in amounts varying from 110 to 170 cc. No toxemia or pancreatic necrosis occurred, and all of the animals lived. This experiment was then repeated on a large series of mice, and the same results were obtained. They concluded from these studies that some other factor than absorption of pancreatic enzymes from the peritoneal cavity was responsible for the toxemia of acute pancreatic necrosis.

The belief that autodigestion of pancreatic tissue and subsequent absorption was the toxic factor in the disease was also emphasized by Sweet (1915). The

evidence consisted in the transplanting of the pancreas of one animal into the peritoneal cavity of another under strictly aseptic conditions. The recipient animal died in toxemia. Dragstedt and his coworkers again challenged these results on the same basis of inability to rule out bacterial contamination. Tower (1926) had reported that she successfully cultured bacteria from the normal pancreas in 15 of 16 dogs. Dragstedt et al. confirmed these results with the finding of positive cultures in 76% of 17 normal glands. They then repeated the transplantation experiments of Sweet and found that 12 of 18 animals died. In 11 of the 12 animals they were able to culture an anaerobe "resembling, if not identical with Cl. welchii" from the peritoneal exudate. This experiment would indicate that death resulting from such transplantation procedures can be ascribed to the absorption of bacterially activated pancreatic contents and not to the absorption of pancreatic contents alone.

Dragstedt and his colleagues continued their experiments by transplanting five autoclaved pancreases into the peritoneal cavity of dogs. No ill effects were observed. Muscle, liver, and pancreatic tissue were then digested in vitro by sterile pancreatic juice. The toxicity of the sterile digestant mixture was compared with a similar contaminated digestant mixture by intraperitoneal

injection of mice. It was found that the sterile digestant mixture uniformly produced no toxic effects, while in the majority of cases the contaminated mixture was fatal.

They then conducted what they considered an almost critical experiment by implanting a sterile mixture of ground autoclaved pancreas(containing inactivated enzymes) and sterile activated pancreatic juice into the peritoneal cavity. No toxemia resulted. They felt that they had "proved conclusively that neither activated pancreatic juice nor the products resulting from digestion of dead pancreas within the abdomen by pancreatic juice are sufficiently toxic to produce the picture(of acute pancreatic necrosis) when bacteria commonly found in the intact pancreas are first removed".

In evaluating Dragstedt's transplantation experiments involving sterile pancreases it must be remembered that the trypsin within the pancreas has been destroyed. The fact that acute pancreatic necrosis does not occur when implanting sterile pancreases does not rule out the possibility that trypsin may still be the main etiological factor in the production of the disease. Although Dragstedt recognizes this criticism of his work, he has conducted no experiments to clarify this point.

Dragstedt and his co-workers could find little in the literature to support their contention that bact-

erial contamination was the responsible factor in toxemia of acute pancreatic necrosis. They cite three cases where Cl. welchii were isolated, and one case in which aerogenes capsulatis was held responsible. They attribute the lack of literature on this subject to the fact that surprisingly few attempts to culture the necrotic pancreas have been made. By inference the opinion has grown that the majority of cases of acute pancreatic necrosis are sterile.

Von Schmieden and Sebening (1927) reported that of 184 cases studied by culture, 103 were positive and 81 were negative. The results are difficult to evaluate because of the nature of their study. In ten of their own cases, only one was positive, and that might have been a contaminant. Rich and Duff (1936) and Smyth (1940) both state that they were unable to find evidence of bacteria often enough in microscopic sections to consider this as a factor in the disease.

In summing up the theory that bacterial activation of the normal pancreas is responsible for the toxemia of acute pancreatic necrosis we must conclude that there is only scanty evidence favoring this hypothesis. Experimental proof is incomplete because of inability to rule out the factor of intrapancreatic trypsin, while clinical confirmation has not been forthcoming. Further study of this problem is indicated.

The theory which has attracted the most support to date is that of bile retrojection into the pancreatic duct. This concept began with the classic autopsy finding of Opie (1901) in which a gallstone impacted in the diverticulum of Vater acted to occlude the common orifice of the bile and pancreatic duct. This obstruction had the effect of creating a continuous closed channel. Opie (1901) admitted that anatomical peculiarities of the ampulla of Vater do not permit this sequence to take place in all individuals.

Opie (1903) measured the diverticulum of Vater in 100 specimens and found 89 instances in which the two ducts joined to form a common opening. The diameter of the ampulla was greater than the length in 21% of the cases, thus making partial occlusion of the orifice by a spherical stone obviously impossible.

Opie and Meakins (1909) analyzed 100 autopsy specimens and found that a common opening into the duodenum existed in 89% of the cases. In only 30% of the cases was the distance from the ostium to the apex of the ampulla great enough to allow formation of a common channel by an impacted biliary stone.

Thus it can be seen that although Opie first suggested the common channel theory he was well aware of its limitations. Much has been contributed to the lit-

erature regarding the relation of common channel formation to acute pancreatic necrosis.

Mann and Giordano (1923) found that in only 3.5% of 200 routine autopsies was it anatomically possible for obstruction of the ampullary exit to convert the ducts into a continuous channel. They ligated the bile duct below the entrance of the pancreatic duct in a series of adult goats. Bile was not forced into the pancreas except after a considerable time, and then only when under maximum pressure. Acute pancreatic necrosis did not result from this procedure

Bisgard and Baker (1940) working on goats, confirmed the work of Mann and Giordano (1923). They observed that acute pancreatic necrosis did not occur in adult goats upon ligation at the level of the ampulla. This procedure, however, resulted in very young goats getting the disease.

Cameron and Noble (1924) approached the problem of the emptying of the ducts into a common ampulla by studying fresh material. They examined 100 fresh specimens by placing a small biliary stone into the ampulla and injecting colored fluid into the common duct. They found that regurgitation occurred into the pancreatic duct in 66% of routine autopsy prodeedings. In 74% of the cases an ampullary communication was present.

Hozapfel (1930) reported that in 20% of 50 bodies studied the biliary and pancreatic ducts were united and presented a common opening into the same papilla, wheras in 60% they opened separately into the same papilla. It is unfortunate that similar studies of the incidence of a common channel formation in patients with acute pancreatic necrosis were not also made.

Wolfer (1931) produced a common channel in dogs by connecting the two ducts with a cannula and found that pancreatic juice readily flowed into the biliary tree. Wangensteen et al. (1931) found that retrojection of bile into the pancreatic duct under the influence of contraction of the gall bladder caused pancreatic necrosis in the cat with a fair degree of regularity (60%). This regurgitation was caused by ligaturing the ampulla. Fatty foods were fed through a gastrostomy tube, no substances being introduced into the duct system. The rarity with which any evidence of pancreatic necrosis was observed following simple establishment of a common channel (once in seven cases) as compared to 15 of 31 cases when fatty meals were added bespeaks of the significance, according to the authors, of easier activation of pancreatic ferment at the height of digestion. That contraction of the gall bladder may have been a factor in the production of acute pancreatic necrosis is indicated by the decreasing incidence of pancreatic necrosis(three of eleven cats) after

excision of the gall bladder.

Elman (1940) quotes the work of Bottin who anastamosed the bile and pancreatic ducts in dogs and failed to produce acute pancreatic necrosis. Popper (1942) states that the presence of a common channel was noted in 16 of 18 cases of acute pancreatic necrosis. In the majority of these cases pancreatic juice had entered the bile passages, but only in a few of them had bile entered the pancreas. He assumes that an extension of the process of activation from the bile ducts to the congested pancreatic ducts takes place, although he does not explain the mechanism.

Dragstedt et al. (1934) stated that the direction of flow of bile and pancreatic juice depends upon an anastamosis between the minor and major pancreatic ducts and if the duct of Santorini is opened or closed. Bile can flow into the pancreatic ducts if patency and anastamoses are present because the pressure of the pancreatic secretion is bypassed. The reverse process can, of course, also occur.

Colp and Doubilet (1938) have gathered the statistical evidence relating to common channel formation. This is presented in table 1. (see page 21). Although some of the authors are in marked disagreement as to the percentage of cases in which a stone in the ampulla

Author	Number of Cases	% of Cases with common ampulla.	% of Cases in which stone of ampulla might form common channel.	% of Cases in which ducts emptied separately.
Ruge	43	75	-	-
Opie	100	89	30	11
Baldwin	90	78	-	32
Oser	100	-	32	-
Von Schmieden & Sebening	35	-	32	-
Judd	170	-	4.5	-
Mann & Giordano	200	-	3.5	--
Cameron & Noble	100	74	66	-
Belou	50	-	54	30

TABLE I (Colp & Doubilet 1938)

might form a common channel, there seems to be a fairly general acceptance of 30 to 60% as the correct figure.

Several isolated cases of acute pancreatic necrosis caused by rare types of common channel formation are reported in the literature. Robins (1926) describes a case of the disease in which there was bile and gallstones present in a dilated pancreatic duct. McGowan (1945) presents a case of stricture of the ampulla of Vater causing a reflux of bile, which in turn caused a pancreatic necrosis.

The data relating to the presence of cholelithiasis in association with acute pancreatic necrosis is presented in table 2(see page 23). Most writers report this figure as varying from 40 to 75%.

Archibald (1913) introduced a provocative concept by contending that spasm of the sphincter of Oddi could convert the common bile duct and main pancreatic duct into a common channel. He observed that the sphincter of Oddi in cats was rarely overcome by a hydrostatic pressure of less than 600 mm. of bile. He then introduced solutions of iron and water into the gall bladder at pressures of 300 to 800 mm. and demonstrated by special stains that this solution had been driven into the pancreas due to resistance of the sphincter.

Continuing this work, Archibald and Brow (1919)

Data on Association of Cholelithiasis with Acute Pancreatic Necrosis.

1. Egdahl (1907). Reported gallstones in 42% of a series of 105 cases.

2. Guleke (1912). Inquiry of 437 cases showed calculous obstruction at the ampulla present in only 1.4% of cases. Stones present in common bile duct in 5%.

3. Jones, (1922). Found gallstones in 50% of 42 cases.

4. Von Schmieden and Sebening (1927). In a series of 1278 cases collected from German clinics, a gall stone at the ampulla recorded in only 4.4% of cases. A stone was present in common duct in 13.6% of cases.

5. Eliason and North (1930). Reported gallstones in 71% of cases of acute pancreatic necrosis.

6. Fallis and Plain (1939). In 26 cases found that stones present in 68%, ampullary stones in 4%, with a normal gall bladder present in 27% of cases.

7. Molander (1946). In a series of 158 cases found that 36% of males and 68% of the females had associated gallstones.

8. Present Series (1947). Stones present in 3 of 9 cases (30%). Common duct stone present in 1 case (11%).

Table 2

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substituted bile for the iron solution and found that they could produce the typical picture of hemorrhagic necrosis of the pancreas. They concluded that the disease was due to reflux of bile against the resistance of the sphincter. Spasm of the sphincter was caused by instilling hydrochloric acid into the duodenum.

Boyden (1937) showed that closure of the pancreatic duct is accomplished primarily through the layer of circular muscle which is common to both bile and pancreatic ducts. The production of a common channel by spasm of the sphincter of Oddi would thus appear to be anatomically improbable although physiologically possible.

Mann and Giordano (1923) argued against Archibald's theory of spasm by showing that the usual position of the muscle fibers ofthe sphincter is proximal to the termination of the common bile duct. Some of the fibers pass around the pancreatic duct as well as the common bile duct. Although there is a great variation in the location of these muscle fibers it appears that there are only a few possibilities where Archibald's theory might apply.

Wangensteen et al. (1931) agree as to the possibility of Archibald's theory being true, but state that regurgitation of bile by such a means remains to be dem-

onstrated in man. He was unable to effect regurgitation of bile in cats without mechanical blockage. Wangensteen and his co-workers found that single factors such as obstruction of pancreatic ducts, chemical stimulation of the vagus nerve with pilocarpine and the presence of bile in the substance of the pancreatic gland were all ineffective in causing acute pancreatic necrosis. When any of these factors acted jointly with another factor, they were, however, capable of producing the disease.

Another etiological factor in theproduction of a common channel was suggested by Weiner (1903). He offered the hypothesis that edema of the ampulla of Vater might so deform its normal structure so as to produce a common channel with retrojection of bile into the pancreas. Balo and Ballon (1929) supported this idea. They suggested that it might exist in association with acute or chronic diseases of the biliary tract. In their examination of autopsy material they noted evidence of pancreatic retention due to obstruction at the ampulla of Vater. This obstruction was the result of traumatic passage of a stone associated with an edematous occlusion or a late stricture, or was possibly the result of a localized inflammation. Lewison (1940) presents evidence of edematous occlusion of the ampulla seen in an operative case of acute pancreatic necrosis.

Williams and Busch (1907) described an autopsy in a case of fatal pancreatic necrosis in which they found the papilla of Vater dilated and gaping with a small stone a little further down in the bowel. They offered the theory that duodenal contents might be forced back into the common duct by arrhythmic duodenal contractions and so possibly into the pancreatic duct. Such a patulous papilla as found by Williams and Busch will explain very few cases of the disease.

Hess(1905) suggested that antiperistaltic movements of the intestine, frequently associated with enteritis, may aid in forcing gastric or duodenal contents into the pancreatic duct. Anatomic evidence fails to support this view. Regurgitation of duodenal contents is prevented by the oblique, valvelike entrance of the ampulla of Vater, which under increased intraduodenal pressure serves to close the ampulla more effectively and prevent reflux.

Archibald (1940) questions the effectiveness of this mechanism in causing the disease. He states that when the papilla of Vater is incised, as in a transduodenal choledochotomy for the removal of stones impacted at the papilla, an operation always followed by a permanent gaping of the ampulla, there is no record of resulting pancreatic necrosis. He tried to force the sphincter

by use of high pressure and creating a closed sac from the pylorus to the duodenum. He was able to force the sphincter in only one case and concluded that although this mode ofcausation was clinically possible it still would account for only a small majority of cases.

Seidel (1910) experimentally caused low duodenal obstruction and noted that it was followed by stasis, regurgitation and so-called acute pancreatic necrosis, but Dragstedt (1934) has challenged the evidence obtained from this experiment as being incorrectly interpreted.

Best and Hicken (1935) were able to visualize the pancreatic duct cholangiographically because of reflux of lipiodol into the pancreatic duct in four of nine cases of biliary disease. Using this same method Leven (1938) studied 91 patients with gall bladder disease. He demonstrated reflux of bile into the pancreatic duct in the absence of organic obstruction in 16 cases, with only five cases of obstruction showing this reflux.

Colp and Doubilet (1938) compared the incidence of biliary reflux into the pancreatic duct by use of cholangiography with that of finding amylase in the biliary tract drainage in cases of chronic cholecystitis. They demonstrated by cholangiography that filling of the

pancreatic duct occurred in the absence of organic obstruction in 20% of 37 cases studied. This reflux into the pancreatic duct occurred in seven of ten cases in which amylase was present in the biliary drainage and in none of the 25 cases in which it was absent.

Mirizzi (1942) studied the functional disturbances of the biliary duct system by cholangiography and concluded that reflux of lipiodol into the pancreatic duct seen on cholangiography is not a mechanical or passive process, but rather due to an active biliary flow in the opposite direction. He concluded that a reflux of lipiodol into the pancreatic duct is a characteristic x-ray finding of a biliary "dystonia" of the sphincter of Oddi. He considered this to be a functional disturbance. Mirizzi (1942) further reports that in "dystonia" of the sphincter the pancreatic duct is dilated and tortuous and has the "morphologic aspect" which indicates repeated increased tension in the duct, both because of stagnation of pancreatic secretions and reflux of bile. This would indicate that reflux of bile into the pancreatic duct occurs in patients showing no signs of acute pancreatic necrosis.

In summarizing the bile retrojection theory it is apparent that there is an anatomical possibility for either a gall stone, spasm of the sphincter of Oddi, or

edema of the sphincter to cause the formation of a common channel. Even the supporters of this theory, however, admit that there are many cases in which the above factors cannot possibly be responsible for the formation of such a common channel.

Although Wangensteen et al. (1931) states that "biliary disease is the common denominator of acute pancreatic necrosis", Weiner and Tennant (1938) prefer a different baseline of comparison. They emphasize the fact that although the incidence of gall bladder disease is 50-75% higher in patients with acute pancreatic necrosis, the incidence of acute pancreatic necrosis in patients with gall bladder disease is only slightly, if at all, higher than in general autopsy series.

The method of clinical investigation which seems to be the most helpful in the clarification of the problem of pathogenesis is that of cholangiography. As described above, present studies reveal that biliary reflux into the pancreatic duct in the absence of organic obstruction is not an uncommon occurence in cholecystitis. Yet these cases show no acute pancreatic necrosis.

It is apparent that biliary backflow into the pancreatic duct occurs many more times (as evidenced by

cholangiography) than does acute panereatic necrosis. It would seem, then, that the formation of a common channel should be considered merely as another one of the "trigger mechanisms" acting upon a susceptible pancreas, and that the cause of this susceptiblity should be the factor occupying our attention.

It was the master French physiologist, Claude Bernard (1856), who first recognized the fact that irritating substances introduced within the pancreatic ducts could cause acute pancreatic necrosis. He produced the disease by injecting olive oil and bile into the pancreatic duct.

Opie (1901) and Flexner and Pearce (1901) demonstrated that the injection of 5 cc. or more of bile into the pancreatic duct and subsequent ligation will produce a fatal pancreatic necrosis in a majority of cases. Flexner and Pearce (1901) also demonstrated that the injection of 16 cc. of blood into the duct was without effect.

Flexner (1906) demonstrated that the power of bile to cause pancreatic lesions is attributable to the cytolytic properties of sodium taurocholate and other bile salts. Sellards (1908) observed that local necrosis followed the injection of bile into the parotid

gland. Tatum (1916) was able to demonstrate a marked cytolytic activity for bile on tissue by immersing small blocks of various tissues in bile at body temperatures. Archibald (1929) showed that bile diverted into the pancreatic duct is not only capable of producing glandular necrosis, but can produce intense edema of the gland.

Polya (1908) found that the injection of active trypsin into the pancreatic duct precipitated acute pancreatic necrosis in practically every experimental attempt. After inactivation of the trypsin by heat the injection of the same amount gave no results. The amounts used were under 5 cc., tending to rule out acinar rupture due to excess fluid. His conclusions related the results to the proteolytic activity of the trypsin. Mann and Giordano(1923) and McCaughan (1934) were critical of these conclusions, believing instead that moderate amounts of any highly irritating fluid injected into the duct under pressure would distend and rupture the ductal-acinar system, thus favoring the development of acute pancreatic necrosis. Sailer and Speese (1908) suggested that the great variety of substances that cause pancreatic necrosis on injection into the ducts is proof that mechanical distention of the pancreatic tissue is the destructive agent. Dragstedt

et al. do not feel that this objection is valid in view of the many reports that the injection of equal amounts of bland substances does not produce necrosis.

The prevailing opinion of these early investigators that bile caused the disease by activation of intraglandular trypsinogen with subsequent autodigestion and spillage of pancreatic contents into the peritoneal cavity was to go virtually unchallenged until Dragstedt and his co-workers presented their ingenious experiments.

They believed that pancreatic necrosis was mainly theresult ofthe destructive action of the bile salts, trypsin merely acting as a scavenger of the surrounding dead proteins. They first demonstrated that living tissue was not affected by immersion into highly proteolytic pancreatic juice but became necrotic after being placed in bile. Demonstrating excellent research technique, they conducted a series of window implant experiments in which the living pancreas was exposed to the digestant action of gall bladder bile in one group of animals and to the action of duodenal contents in another. Only the former group regularly developed acute pancreatic necrosis.

Rich and Duff (1936) are critical of these re-

sults. They suggest that the surface of the pancreas in contact with the duodenal juice was destroyed and replaced by scar tissue. They claim that the same result was noted by Rosenbach (1911) in similar experiments. They further remark that Dragstedt and his co-workers apparently overlooked the fact that since the pancreas remained unharmed after implantation in the duodenum below the ampulla, their experiment argues equally well against the view that the pancreas can be injured by bile.

Another criticism of their work may be mentioned at this point. They do not adequately rule out the possibility of pancreatic juice acting intracellularly rather t han showing any destructive action on the outside of the pancreas. It is known that certain parasitic organsi sms have anti-trypsin substances in their cell walls and it may be that acinar as well as other cells have similar anti-trypsin substances. This point awaits clarification by the biochemist.

Dragstedt et al. offered the alternate hypothesis that after the initial attack of bile has been repulsed by the exudation of serum or even frank hemorrhage the protective colloids die. As a result proteins are then promptly digested by the tryptic pro-

teinase and polypeptidase of the pancreatic juice, with bile salts being freed for further destructive action.

In spite of their interesting experimental work Dragstedt et al. are unable to account for the many cases in which there can be no regurgitation of bile into the pancreas, nor does their hypothesis allow for the later findings of cholangiography in cases of biliary disease that regurgitation of bile into the pancreas occurs more often than does acute pancreatic necrosis.

Rich and Duff (1936) have approached the problem of pathogenesis in a thoughtful and well executed piece of experimental work. They believe that most cases of the disease are the result of partial obstruction to the outflow of secretion. Pancreatic juice escapes into the surrounding tissues as a result of distention and rupture of acini and ductules behind the obstruction. If the escaping juice happens to be rich in tryptic ferments it will destroy any arteries or veins which come in contact with the juice. Extensive or localized hemorrhage will result. They have described a vascular lesion which they claim to be specific for this disease. "The adventitia of the affected artery or vein may ap-

pear condensed and pink-staining and may contain leucocytes or necrotic cells; but the striking changes are in the media. Muscle fibers of the media swell and are sometimes separated by pink staining fluid or by spaces in which nothing stains. Their nuclei become shrunken, pyknotic and often karyorrhectic, and PMN's may be seen early. The internal elastic lamina loses its undulations and takes on a swollen appearence. Individual fibrils split off so that the elastic membrane appears frayed. Breaks appear in the membrane or it ceases to take the stain as though it were completely dissolved. Finally all nuclear staining is lost and the necrotic tissue of the wall stains homogeneously pink with eosin-hematoxylin. The first alterations in the media are always found in the outer layer, the muscle fibers of which may be necrotic, while those near the intima remain intact; but the damage in most cases proceeds rapidly to involve the entire thickness of the vessel wall with final destruction of the intima."

A precisely similar lesion can be produced elsewhere in the body, according to the authors, by the local injection of purified trypsin or even by inactivated pancreatic juice. The activation of trypsinogen by enterokinase is not necessary for the production of

the vascular necrosis. Bayliss (1927), Babkin (1906) and Savitsch (1909) have shown that pancreatic secretion induced by vagus stimulation contains active trypsin. Rich and Duff speculate that if the juice that escapes into the tissues happens to be juice that was secreted under the influence of vagus activity it would be able to exert its digestive powers without the benefit of extrapancreatic activation.

Popper and Necheles (1940) reported some provocative findings which help to strengthen the observations of Rich and Duff. These authors injected bile and olive oil into the pancreatic ducts of animals in amounts under 3 cc. They found that in all cases a marked interstitial edema of the gland occurred very rapidly and that a bloody exudate appeared within the abdomen within an hour. They could demonstrate a high concentration of amylase and lipase in the subcapsular edema fluid and exudate. Acute pancreatic necrosis was not produced in any of these animals but they did show that amylase and lipase had diffused out from the pancreatic ducts into the interstitial tissue and into the peritoneal cavity. Were this also true for trypsin, one would expect that in diffusing outward it would come in contact with vessel walls and thus cause the picture described by

Rich and Duff. Their series is too small and their studies as yet not complete enough for one to draw any definite conclusions substantiating Rich and Duff's work.

Rich and Duff further reason that rupture of dilated thinned out acini behind an obstruction is particularly liable to occur during periods of increased pressure within the system which result from secretory stimuli(e.g. a large meal or the ingestion of alcohol). In most cases the obstruction in the pancreas is situated in the branches of the duct within the pancreas and not in the main duct. The nature of this obstruction in many cases, according to the authors, is a proliferative metaplesia of the epithelium of the branches of the pancreatic duct which leads to partial obstruction and dilatation of the acini and ductules behind the site of the obstruction. They found such a condition in 18.6% of 150 consecutive autopsies on individuals over 25 years of age. They found it in routine sections of 13 out of 24 cases of acute pancreatic necrosis. This percentage does not seem impressive enough to warrant drawing any positive conclusions, although it may be that destruction of pancreatic tissue has obscured many of these metaplastic lesions.

Priesel (1922) and Balo and Ballon (1929)

were the first to describe metaplesia of the ductal epithelium in routine autopsies, but they made no mention of its relation to acute pancreatic necrosis. This change consists in a localized proliferation of the ductal epithelium which, in the affected area, loses its cuboidal or columnar character and assumes that of transitional or basal epithelium. This epithelial proliferation leads to the formation of masses of cells which project into the duct and partly or completely obstruct its lumen. Rich and Duff are unable to offer any suggestions as to the etiology of the metaplesia, but feel that it is not due to a vitamin A deficiency. The authors offer the interesting hypothesis that the thinning and flattening of the ductal epithelium offers a point of lowered resistance to the increased pressure of the pancreatic ferments. They point out, however, that this concept is purely speculative and has yet to be supported by any experimental evidence.

Yotuyanagi (1937), in an exhaustive study of pancreatic ductal metaplesia, found that it occurred normally in the the human in at least 64% of the specimens which he examined. The metaplesia was a genuine epithelial proliferation as described by Rich and Duff. Yotuyanagi suggested a causal relation to vitamin A deficiency or, perhaps, local ductal stasis and irrita-

tion.

Weiner and Tennant (1938) examined 261 slides of pancreatic tissue, 84 of which were from normal tissue. A total of 32 cases with metaplesia were found. Three occurred in the group of acute pancreatic necrosis, five were in normal pancreases, and 24 appeared in pancreases showing fibrosis or chronic pancreatitis. Lynch (1940) found that in his series of 18 cases, metaplesia of the ductal epithelium was seen only once. He raised the interesting question of the metaplesia perhaps representing an attempt at islet cell formation. He also considers the possibility of the metaplesia being a response to a chronic disease process. Smyth (1940) found epithelial metaplesia of the pancreatic ducts in 13 of the 40 cases of acute pancreatic necrosis in his series (33%), while Clark (1942) reported that metaplesia of the ductal epithelium was seen on only four occasions in his series of 36 cases (11%).

The evidence indicting ductal metaplesia as an etiological factor in the production of acute pancreatic necrosis is not impressive. It would seem, instead, that ductal metaplesia may be considered along with gall stones, spasm of the sphincter, edema of the ampulla and perhaps biliary "dystonia" as one of the many exciting factors in the disease process.

Archibald (1940), in a rather acrimonious paper, disagrees that either epithelial metaplesia or tryptic activity has any role in the etiology of the disease. He considers Rich and Duff's observations of epithelial metaplesia as imperfectly supported. In addition he calls attention to the number of observations showing stones, strictures, and cysts in pancreatic tissue at autopsy and in which acute pancreatic necrosis had not developed. It would seem that Archibald has overlooked the fact that his own theory of sphincter spasm and subsequent biliary reflux is also open to the same type of criticism, for as mentioned earlier, biliary regurgitation occurs many more times than does acute pancreatic necrosis. Archibald concludes his attack upon Rich and Duff by stating that all of their observations relate only to cases of pancreatic necrosis with hemorrhage, wheras in many cases of pancreatic necrosis hemorrhage is absent. He concedes that trypsin may perhaps play a secondary role by digesting cells already killed. Rich and Duff had attempted to circumvent part of such future criticism of their theory by stating that if the pancreatic secretion were low in trypsin and rich in lipase that necrosis without hemorrhage would result.

It will be enlightening at this point in the discussion to briefly explore the late biochemical lit-

erature relating to trypsin. Schmidt (1937) has obtained active trypsin from blood plasma by precipitation with trichloracetic acid. This enzyme in the plasma appears to be combined with an inhibitor substance in a way similar to the trypsin-inhibitor compound found in pancreatic extracts.

Schmitz (1938) was able to isolate a water soluble inhibitor of crystalline pancreatic trypsin from the blood. Sufficient quantity is present in blood to completely inhibit the trypsin isolated from blood fibrin.

Kunitz (1939) found that a solution of crystalline trypsinogen containing a trace of active trypsin gradually, but incompletely, turned to trypsin when standing at a pH of 5-9. The proportion of trypsin formed was larger in the acid range of pH. Kunitz (1940) also found this observation to hold true for chymotrypsinogen and chymotrypsin. He concluded that both processes were essentially autocatalytic.

Grossman, Greengard and Ivy (1943) studied the relation of diet to the amount of trypsin in the pancreas. Diets of various composition were fed to rats for three weeks, after which the enzyme content of the pancreatic tissue was determined. A high protein diet

resulted in greatly increased trypsin levels in the pancreas as well as a definite but smaller increase in lipase. A diet rich in fat and decreased in protein caused a repression of all pancreatic function.

Risley, Buffington and Arnow (1944) found that dried bovine serum is resistant to the action of trypsin, but that this resistance can be overcome by the use of digestion mixtures containing 10-30% solutions of ethyl alcohol. They suggest that the effect of the alcohol may be caused by the inhibition of the anti-proteinases normally present in serum.

The significance of these findings will be discussed later, but even a cursory examination of the evidence will show that Rich and Duff's concept of intrapancreatic release of trypsin is the most applicable to date, for it is not outdated by results of biochemical investigations into the problem. Although Dragstedt's concept of bacterial activation and bile digestion have not been disproven, it would appear that the most fruitful avenue of investigation lies in gaining a more complete understanding of trypsin metabolism.

The relation between alcohol and acute pancreatic necrosis has long been recognized by investigators on the subject. Egdahl (1907) reported that in 105

cases of the disease, 17 (16%) were related to an alcoholic duodenitis. He suggested that the frequent bouts of vomiting associated with enteritis might act to force duodenal contents through the sphincter of Oddi and up into the pancreatic duct. This idea has been discarded by most authors as being anatomically unsound.

Meyers and Keefer (1934) found that of 29 cases of acute pancreatic necrosis, 6 (20%) were associated with acute and chronic alcoholism, 4 with fatty liver, and 2 with cirrhosis of the liver. A mechanism of action of alcohol in the production of the disease was postulated: 1. Direct action upon the pancreas as alcohol is carried there by the blood stream, 2. Obstruction of the pancreatic ducts due to duodenal congestion following acute alcoholism, 3. Forcing of duodenal contents or bile into the pancreatic duct as a result of persistent vomiting. Rich and Duff (1936) also reported on the incidence of alcoholism in the disease, stating that it occurred in 7 out of 24 cases (29%). They were unable to offer any etiological explanation.

Weiner and Tennant (1938) reported that in 38 cases of acute pancreatic necrosis (cases related to trauma, malignancy, etc. were excluded) alcohol was a probable factor in 25(66%). Only 6 (15.8%) had gall

bladder disease. They concluded that alcohol alone is not enough to produce the disease, for it may attack an individual who has had little or no previous indulgence, while the chronic and severe alcoholic may be completely spared.

To help clarify this problem, Clark (1942) studied 36 cases of pancreatic disease in alcoholics. He found that disease of the gall bladder or biliary passages was completely absent. In 15 cases (42%) death was attributable to acute pancreatic necrosis. In 11 cases (31%) death was due to alcoholic cirrhosis. In 14 of the 15 cases of death due to pancreatic necrosis symptoms appeared or death occurred during or shortly following an alcoholic bout. The most striking pathological finding was the presence of deeply eosiniphilic inspissated or coagulated secretion within the pancreatic ducts. This condition was encountered 30 times (83%). Clark was unable to determine if this were the cause or the result of the disease. Rich and Duff also observed this lesion, although its incidence was not stated. They suggested that this coagulated secretion is associated with the production of the more viscid type of secretion which has a higher trypsin concentration than the more fluid type of secretion. This viscid type of secretion was seen in all of their ex-

periments, including those of pilocarpine stimulation.

Duct obstruction due to a coagulated secretion was the most common finding in Smyth's (1940) study of 18 cases of the disease. He found this condition in 8 cases (44%). In the present series this inspissated secretion with dilated ducts was found in 4 of the 7 specimens examined (57%).

Pancreatic cysts or neoplasms, by their slow growth and compression of the pancreatic ducts, usually cause atrophy and fibrosis of the secretory acini rather than acute pancreatic necrosis, although this is not always so. The above factors may be included under the rare causes of the disease.

The vascular theory as a factor in the causation of acute pancreatic necrosis has received recent support from Smyth (1940). He has comprehensively reviewed the experimental literature relating to vascular changes associated with the disease. In his study of 40 cases of acute pancreatic necrosis seen at autopsy, thrombosis was the most frequently observed vascular lesion; it was present in 26 of the 40 cases. Many of these lesions were recent ones, and Smyth admits that it could not be determined from the material available whether the fresh thromboses occurred before or after the establishment of necrosis. In 11 of the 40 cases

small lesions were found which corresponded to the "specific vascular lesion" of Rich and Duff (1936). Smyth concludes that this lesion is a result or concomitant factor in the disease but is of no etiological significance.

In an attempt to experimentally produce the disease, Smyth(1940) injected mercury into the pancreatic arteries of 21 dogs. Although localized area of acute pancreatic necrosis were uniformly produced, none of these animals died of a spreading type of acute pancreatic necrosis.

Lynch (1940) reports 3 cases of vascular occlusion causing acute pancreatic necrosis. This represented a series of 18 cases of the disease. Of these 3 cases, 2 were associated with malignant hypertension.

Tower (1926), investigating the vascular factors in the production of the disease, reported that she was able to produce the typical picture of acute pancreatic necrosis with toxemia and death by tying off a sufficient portion of the pancreatic blood supply. She questioned her results, however, because cultures of the peritoneal exudate were positive in every case. Dragstedt et al. (1934) believe, on the contrary, that the disease is not readily produced by ligation of pancreatic arteries.

The vascular factor in the production of acute pancreatic necrosis is undoubtedly important in a small percentage of cases. Although this factor cannot be seriously entertained as explaining the disease process, it must be recognized that it may be one of the many exciting agents in the production of acute pancreatic necrosis.

Trauma to the abdomen may result in a typical case of acute pancreatic necrosis (Lewison 1940). This factor deserves no more than passing mention as one of the exciting causes of the disease.

To complete the list of possible etiological factors there must be included, under the grouping of miscellaneous, a few isolated case reports.

Brodie and Ficarra (1944) present a case of acute pancreatic necrosis precipitated by sodium morruhate injections in the treatment of varicosities of the leg. They considered it an anaphylactic reaction. They review the literature concerning pancreatic allergy in the etiology of the disease.

Cracovaner (1933) describes 3 cases of acute pancreatic necrosis which occurred during general anesthesia. In only 1 case were there preceding upper GI symptoms. The author concluded that acute pancreatic necrosis was the primary result of the anesthesia.

Ackerman (1942) describes what he states to be

the only case reported in the literature of acute pancreatic necrosis following the transfusion of incompatible blood. He suggests that pancreatic changes were secondary to thrombosis.

Several of these minor factors may, of course, act together to initiate or intensify the disease. They deserve no further study, however, until the underlying mechanism of the disease becomes clarified.

Analysis of University Hospital Case Records.

MATERIAL

In an attempt to evaluate the etiological factors present in acute pancreatic necrosis, the case records of the University hospital dating back to 1919 were studied. Cases included in this series were selected on the basis of autopsy verification, those cases with accompanying carcinoma of the stomach and pancreas also being included. Although some authors exclude cases associated with carcinoma from their series, it was felt that such a procedure was unwise, for until proven otherwise carcinoma plays no more of a part in the production of acute pancreatic necrosis than does any of the other many etiological factors associated with the disease.

INCIDENCE

There have been 9 proven cases of the disease in 92,700 hospital admissions, giving an incidence of .01%. There have been 25 cases recorded in which the diagnosis was only made clinically, which, when included with the 9 proven cases, gives an incidence of .04%.

In none of the 9 patients autopsied was the clinical diagnosis made.

AGE

All of the patients studied were past middle age. The average age was 62 years, with a range of 45 to 83 years. Lewison (1940) states that acute pancreatic necrosis may occur at any age, authentic cases being reported in which the patients were between 2 and 77 years old. In Lewison's series 60% of the patients were between 30 and 50 years of age, death being distributed uniformly through the middle-aged group.

SEX

The sex distribution was slightly in favor of females, with a ratio of 5 to 4. Acute pancreatic necrosis is supposed to be more common in women because of their higher incidence of obesity and gall bladder disease. Von Schmieden and Sebening (1927) report a ratio of 9 females to 5 males in this disease, while Mc Whor-

ter finds that the disease affects both sexes equally.

RACE

Of the 9 cases studied, 8 were white and 1 was colored. The disease is usually considered to be more common in the white race.

OBESITY

In the 5 cases in which the weight was recorded in the history, the average weight was 174 pounds, with a range of 150 to 235 pounds. If these figures are broken down according to sex, the results are striking.

Number of Cases -	Sex	Av. Weight
2	M	151
3	F	199

Obesity was a striking characteristic of those women who had their weight recorded in the history. It did not seem to be a factor in the 2 male patients whose weight was recorded.

GASTROINTESTINAL HISTORY

Previous attacks of a similar although milder abdominal pain were described by 6 of the patients(67%), while the other 3 patients (33%) gave no previous abdominal history of any type. Of this latter group 2 rep-

resented the cases of carcinoma of the stomach and pancreas which was present with the acute pancreatic necrosis.

The duration of the last attack was considered as the time elapsing from the onset of abdominal pain to death. The average duration was 43 days, with a range of 5 to 110 days. Using pain as a criterion of the onset of the disease renders any conclusion suspect, for the accompanying factors of biliary stones and carcinoma in themselves cause pain. Correlation of the clinical picture with the microscopic appearence of the pancreas shows that patients revealing the typically acute pathological appearence of the disease have a similarly brief duration of their attack.

This histological picture of acute fairly widespread necrosis was seen in 3 slides. An examination of the corresponding clinical records showed an average duration of the final attack of 8 days. This would fit in with the clinical concept of a disease which is characterized by a sudden, fulminating and usually fatal attack. The pancreases of the rest of the cases were characterized microscopically by fibrosis and necrosis, the latter appearing in small and

isolated areas.

ALCOHOLISM

Alcoholic habits were mentioned in only one history. The patient was a bartender and stated that he was a "moderate drinker".

ASSOCIATED BILIARY DISEASE

In accordance with reports of most investigators, biliary disease was a concomitant finding in 3 cases (30%). All of these cases were characterized by biliary stones. There was cholelithiasis of the gall bladder in 2 cases, with only 1 case showing a common duct stone. It is of interest to note that of the 3 cases which showed the most extensive pancreatic destruction, only 1 had associated biliary disease. The remaining 2 cases were those accompanied by carcinoma of the stomach and pancreas.

AMPULLA OF VATER

Because many writers have stressed the role of obstruction of the ampulla of Vater in the formation of a common channel, this factor was investigated. Changes in the ampulla were noted only in those cases which were associated with biliary disease. In 2 cases the ampulla was dilated but not obstructed, while

in only 1 case was there reflux of bile into the pancreatic duct due to the apparent formation of a common channel.

MICROSCOPIC EXAMINATION

Only 7 preparations were available for microscopic study. An attempt was made to confirm the findings of Rich and Duff (1936) concerning proliferative ductal metaplesia in acute pancreatic necrosis. In none of the slides reviewed, however, was there any evidence of this proliferative metaplesia as described by them, although flattening of the columnar epithelium of the pancreatic ducts was seen in a few cases. This, of course, is not sufficient evidence against the presence of this type of metaplesia, for only 2 slides of each pancreas were available and it was not known in any case from what portion of the pancreas these sections were taken.

Of the 7 slides reviewed, 4 (57%) showed the presence of an eosiniphilic coagulated secretion inthe pancreatic ducts. In 3 of these 4 cases there was an associated dilatation of the ducts, but there seemed to be no correlation between the presence of this coagulum and the severity of the pathological picture.

Discussion

The work of Wangensteen (1931) and Dragstedt (1934), although classic, has become outdated in the light of the later biochemical literature. Most clinicians, surgeons, and pathologists, however, still base their etiological concepts on the fact that "biliary disease is the common denominator of acute pancreatic necrosis". (Wangensteen et al. 1931)

Present day investigators are tending to break away from this concept. Warren Cole (1947) states that "the answer to acute pancreatic necrosis must be sought within the pancreas itself, for fully 25% of the cases have no relation to biliary disease". Many authors have shown that 40% is more like the proper figure.

In an attempt to explain our latest knowledge of the metabolism of trypsin and its relation to acute pancreatic necrosis, this section of my paper will be devoted to developing two general hypothesises as to the etiology and pathogenesis of the disease, and finally to offer indications for further experimental work.

One mechanism in the production of acute pancreatic necrosis which may be postulated is that of pri-

mary breakdown of a trypsin-inhibitor substance within the plasma. Alcohol has been reported as being able to inactivate this inhibitor substance(Risley et al.1944). Several factors, unknown as yet, may act to cause this breakdown. At any rate, this freeing of trypsin within the plasma may be considered the initiating factor of the disease. As this trypsin rich blood bathes the acinar cells of the pancreas an autocatalytic reaction between trypsinogen and trypsin takes place. Conditions leading to local lowering of pH in the acinar cell such as stagnation of secretion, biliary regurgitation, ductal metaplesia, circulatory stasis, edema, pancreatic stones and carcinema would facilitate this autocatalytic reaction. The high concentration of trypsin resulting from this reaction acts to destroy the acinar cell and escape into the pancreatic interstitium. Whether or not hemorrhage results may depend upon the concentration of trypsin, although this point needs further clarification. The findings in rats that the trypsin and lipase level of the pancreas is markedly increased after a diet rich in protein and fat would help to explain the clinical observation that the disease often occurs following a heavy meal. The high incidence of obesity in the disease might also be ex-

plained by these findings.

It is interesting to consider the possibility that acute pancreatic necrosis is essentially an autonomic nervous system disease. The presence of coagulated secretion in dilated ducts as reported by several investigators may indicate that excess vagal stimulation with its known production of a more viscid secretion is the key factor in the pathogenesis of the disease. The observations cited by Rich and Duff (1936) that excess vagal stimulation causes the production of a pancreatic juice rich in trypsin would fit well into this concept. This plugging of the ducts with a resulting stagnation and anoxemia may lead to inactivation of the anti-proteinases in the acinar cell wall as well as speeding up the autocatalysis of trypsinogen. The cholangiographic findings of dilated and tortuous pancreatic ducts(Mirizzi 1942) in cases of biliary "dystonia" suggests that biliary malfunction may be related to pancreatic necrosis because of a chronic stagnation of pancreatic duct contents. That this cholangiographic finding is seen more often than the disease indicates, however, that it represents a secondary mechanism.

If this theory is to be considered, however,

the relationship of cystic-fibrosis of the pancreas to acute pancreatic necrosis must be clarified. It will be instructive at this stage to quickly scan the literature of cystic-fibrosis.

The clinical and pathological aspects of the disease have been comprehensively reviewed by Andersen (1938) and Rauch, Litvak and Steiner (1939). Perhaps the most challenging paper on the subject is that of Farber (1943,1944). He describes the characteristic lesion of the disease as a dilatation of the ducts, inspissation of secretion, atrophy of acinar structure and replacement by connective tissue leading to pancreatic fibrosis. The islets of Langerhans are not involved. From this histologic picture, interference with the production, liberation or passage of pancreatic enzymes leading to pancreatic achylia may be expected.

In considering the relationship between acute pancreatic necrosis and cystic-fibrosis, it is of interest to note that in Farber's (1944) report of 87 post-mortem examinations of children with cystic-fibrosis, not one showed any associated acute pancreatic necrosis. Andersen (1938) found no evidence of a coexisting pancreatic necrosis in 49 cases of cystic-fibrosis of the pancreas which came to autopsy. The

fact that cystic-fibrosis represents the most extreme form of pancreatic enzyme stagnation and yet causes no necrosis leads one to inquire further into the essential differences in the mechanism of the two diseases.

Andersen (1938) states that a decreased or absent trypsin activity of the duodenal contents is pathognomonic of cystic-fibrosis. Lipase and amylase secretion, although usually reduced, may remain normal. Farber (1943) and other authors concur with this idea.

It can be seen, then, that cystic-fibrosis differs in its functional effect from acute pancreatic necrosis in that the trypsin activity of the duodenal contents is markedly diminished or absent in the former, while normal in the latter. This fact in itself is not helpful in our study, for it does not indicate the character ofthe intrapancreatic trypsin in cystic fibrosis, but only that extra-pancreatic trypsin activity is diminished. If the trypsin within the gland isof normal activity in cystic-fibrosis, the idea that pancreatic stagnation is the mechanism responsible for acute pancreatic necrosis then becomes untenable. Further studies of pancreatic activity in children with and without cystic-fibrosis are indicated.

Blackfan and Wolbach (1933) are impressed

with the diffuse keratinizing metaplesia seen in cystic-fibrosis. This metaplesia was present in one half of their 12 cases, and manifested itself in the trachea, bronchi, renal pelvises, salivary glands and pancreas. Other authors do not mention metaplesia of the pancreatic duct epithelium in cystic-fibrosis. Rich and Duff (1936) state that this keratinizing metaplesia described by Blackfan and Wolbach is not the same as the metaplesia observed by them in acute pancreatic necrosis. Metaplesia of the ductal epithelium in the latter shows no keratin granules and much less of the squamous type of epithelium described in cystic-fibrosis.

Farber (1944) suggests that the character of the duodenal drainage and the appearence of the inspissated secretions in the acini and small ducts are reminiscent of the results of vagal stimulation. If this is true, the secretion within the pancreas would have a higher concentration of trypsin than normal (Rich and Duff 1936). Farber(1944) concludes from his studies that cystic-fibrosis is really a systemic disease, with manifestations present in the upper respiratory tract, lungs, liver, gall bladder, upper alimentary tract, and pancreas. This systemic disease appears to depend upon a primary alteration in the character of secretions of mucous glands leading to

obstruction and loss of function. This stimulating concept and its relation to acute pancreatic necrosis deserves careful consideration and investigation.

In any discussion considering new etiological concepts, suggestions as to how the laboratory worker may bridge the gap between speculation and reality are always in order. Perhaps the most important task is that of gaining further knowledge of the biochemistry of trypsin and its precursors. What substances normally present in plasma and pancreatic cells act to prevent destruction by trypsin?; What is the trypsin-inhibitor substance?; What substances beside alcohol can act within the plasma or cell to destroy this substance and thus permit trypsin to become destructive?; All of these questions must be answered by the biochemist before the pathogenesis of the disease can be clarified.

The physiologist will be of invaluable aid in the solution of the problem as he gains a fuller understanding of the factors operating to regulate pancreatic secretion. The relationship of the autonomic nervous system through the vagus nerve to viscosity of secretion, amount of secretion, proteolytic activity, and finally general health of the pancreas should all be thoroughly reviewed and re-investigated. The role of secretin in the disease must be considered as well,

in that a reduced output of this hormone may lead to sluggishness of pancreatic secretion.

Perhaps the most difficult part in the experimental attack on acute pancreatic necrosis must be taken by the pathologist, for in addition to his knowledge of pathology he must be in full command of the latest biochemical and physiological techniques.

The pattern of approach to the problem as established by Wangensteen (1931) and Dragstedt (1934) seems to be the one of choice. Several methods of those described earlier should be employed in causing the disease. As the animal develops acute pancreatic necrosis the pathologist must be able to correlate pancreatic tissue changes with trypsinogen and trypsin levels in plasma and pancreatic cells, pH and local blood supply to the acinar cells, as well as changes in the quantity and quality of pancreatic secretion. The effects of a high protein and high fat diet and excess alcohol in the blood stream must both be considered in his study of factors related to change of the normal cell pattern. Only by this dynamic method of investigation can we hope to gain a true concept of the disease.

In taking the history and observing the course of the disease, the clinician can contribute much to our knowledge of the disease. This of course implies

an improvement in his diagnostic acumen of the disease. A complete and detailed history, especially as related to the gastrointestinal tract, food habits, alcoholism, obesity and associated diseases is invaluable in any attempt to determine pertinent etiological factors. If the diagnosis is made early, frequent study of blood trypsin levels and their relation to the course of the disease would be of extreme value.

Thus it can be seen that each branch of medicine has an important part to contribute in the study of this challenging disease, and that only with the aid of the newer biochemical and physiological methods of investigation can we hope to bridge the gap between theory and fact in the problem of acute pancreatic necrosis.

Summary

The many theories relating to the etiology and pathogenesis of acute pancreatic necrosis can be divided into two groups; infectious and non-infectious. The theories of infectious origin include invasion of the pancreas from the lymphatics, blood stream, nearby viscera, biliary system and infected foci. All of these concepts have been discarded by most writers on the subject, for they explain only a few cases of the disease. The theory that bacterial activation of the normal gland contents is responsible for the toxemia and death in the disease cannot be overruled, for the importance of the trypsin factor in the process has not been satisfactorily determined.

The non-infectious theory which is most popular at present is that of a common channel formation, implying biliary disease and retrojection of bile into the pancreatic duct. Although this theory has some anatomical and clinical support, 25-40% of the cases have no associated biliary disease and thus cannot be explained by this concept. The common channel theory makes no allowance for the later findings of cholangiography, which shows that regurgitation of bile into the

pancreatic duct occurs in patients showing no evidence of acute pancreatic necrosis. This theory is particularly inadequate in the light of the newest knowledge of the metabolism of trypsin.

Rich and Duff (1936) introduced the concept that stagnation of secretion due to obstruction results in intraglandular activation of trypsinogen followed by destruction of surrounding tissue. They attribute this obstruction to metaplesia of the ductal epithelium, while other authors consider that coagulated secretion plays a similar role. The evidence supporting either of these forms of obstruction as playing a role in the disease is scanty. The theory of intraglandular activation of trypsinogen is still a plausible one, however, and is strengthened by later reports on the metabolism of trypsin in the biochemical literature.

Nine cases of acute pancreatic necrosis seen in the last 28 years at the University hospital were analyzed. The average age of the patients studied was 62 years, the number of white females and males being equal. Although the males with the disease were of normal weight, the average weight of the females was 199 pounds.

About 67% of the patients gave a history of

previous though milder attacks. In the more acute cases the average duration of attack was 8 days, while the average duration of all the cases was 43 days.

Biliary disease was present in one third of the cases, with a common duct stone and a common channel formation recorded in only one case. There was no correlation between the severity of the disease and the presence of lithiasis.

Microscopic examination failed to reveal the proliferative ductal metaplesia described by Rich and Duff (1936). Eosiniphilic coagulated secretion with associated dilated ducts was seen in 4 of 7 slides, no correlation being present between this finding and the severity of the disease.

Hypothesises relating to the etiology and pathogenesis of acute pancreatic necrosis were suggested. Incorporating the later biochemical literature on trypsin, the theory was advanced that a breakdown of the trypsin-inhibitor substance in the plasma leads to an autocatalytic reaction between trypsinogen and trypsin, liberating free trypsin within the pancreas. Tissue destruction and hemorrhage result.

The alternate concept that acute pancreatic necrosis represents an autonomic nervous system disease

was also developed. The more viscid and proteolytic secretion characteristic of vagal stimulation may cause obstruction and rupture of ducts, thus leading to intraglandular release of trypsin.

Several suggestions for future experimental work were made. The necessity of close cooperation between all branches of medicine in solving the problem of acute pancreatic necrosis was stressed.

Conclusions

1. The popular common channel theory is inadequate in explaining acute pancreatic necrosis. The cause of the disease must be sought within the pancreas itself.

2. The most plausible theory to date is that of intraglandular release of trypsin suggested by Rich and Duff(1936). Further work is needed before this theory can be fully accepted.

3. The etiological factors present in 9 cases studied at the University hospital were discussed. Fully 67% of the cases showed no biliary disease and thus could not be explained by the common channel theory.

4. The task of the pathologist in solving the mystery of acute pancreatic necrosis is the most difficult of all, for he must have a command of biochemical

and physiological techniques in addition to his mastery of pathology.

5. Greater diagnostic acumen by the clinician is necessary if complete etiological studies as well as concurrent laboratory work are to be done on the patient.

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