CHRONIC PANCREATITIS AND LITHIASIS
II. PATHOLOGY AND PATHOGENESIS OF PANCREATIC LITHIASIS*

HUGH A. EDMONDSON, M.D., WELDON K. BULLOCK, M.D., and JOHN W. MEHL, Ph.D.
(From the Departments of Pathology and Biochemistry, School of Medicine of the University of Southern California, and the Laboratory of the Los Angeles County Hospital, Los Angeles, Calif.)

The pathogenesis of calculi occurring in the ducts of the pancreas and of diffuse calcification in the gland has been difficult to explain. For a long time it was thought that calcium was present in such minute quantities in the acinar secretion that it was improbable that calcium salts would be precipitated in normal juice; therefore other mechanisms, such as inflammatory factors, were considered necessary. That chronic pancreatitis is often complicated by the presence of calculi has been emphasized by Comfort, Gambill, and Baggenstoss.[1] In a previous report we presented the clinical and diagnostic features together with a brief outline of the pathologic findings in a group of 22 cases of pancreatic calculi or calcification occurring in a series of 35,000 autopsies.[2] We now have a total of 26 instances of the disease in a series of 36,000 consecutive autopsies performed between September 25, 1925, and March 16, 1948. The histologic details, their relationship to the precipitation of calcium stones, the physical chemistry involved in the formation of calculi, and other pertinent data remain to be discussed. In addition, the results of post-mortem roentgenographic examination of 200 pancreases are included.

Since July, 1946, a careful search has been made for stones in the pancreas. There have been 10 examples in 3,000 autopsies (0.33 per cent); previous to this there were 16 in 33,000 autopsies (0.05 per cent) over a period of 21 years. Because 9 of the 10 recent cases were associated with alcoholism, compared to only 5 of 16 in the preceding period, we believe there has been an actual increase in patients with calculi which parallels the increase in cirrhosis and alcoholism already noted. No doubt a careful examination of the pancreases at necropsy would have increased the total diagnosed before 1946, especially in the years following the repeal of the Volstead Act.

As stated in a previous publication,[2] not one of the first 22 patients was diagnosed correctly by the clinicians. During the past year, of the 4 additions to the list, one was so diagnosed. A study of this last group adds nothing new to the discussion of the clinical aspects and diagnosis.[2] Table I gives the complete data on all 26 patients in regard to

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TABLE I

Clinical and Pathologic Data on 26 Cases of Pancreatic Lithiasis

No.	Age	Sex	Solitary stone	Multiple stones or calcification	Alcoholism	Fatty liver	Cirrhosis	Diabetes	Abdominal pain	Weight loss	Pulmonary tuberculosis	Icterus
1	36	F		Yes	Yes	+++	+	No	Yes	Yes	No	Yes
2	86	F	Yes		No	−	−	Yes	No	Yes	No	No
3	55	F	Yes		No	−	−	No	Yes	Yes	No	No
4	22	F		Yes	No	−	−	Yes	No	Yes	Fatal	Yes
5	39	F		Yes	Yes	++++	++	No	Yes	Yes	No	Yes
6	58	M		Yes	Yes	+++	++	No	No	Yes	Yes	Yes
7	78	M	Yes		No history	++	−	No tests done	No history	?	No	No
8	55	M	Yes		No history	+	+++	No tests done	No history	Yes	Fatal	Yes
9	52	M		Yes	Yes	++	−	Yes	No	Yes	No	No
10	55	F		Yes	No	−	−	Yes	Yes	Yes	No	Yes
11	34	F		Yes	Yes	++	−	No	No	No	No	No
12	44	F		Yes	No	++	−	Yes	No	Yes	No	No
13	37	F		Yes	No	−	−	Yes	No	Yes	No	Yes
14	62	M		Yes	Yes	++	+	No	Yes	No	No	Yes
15	77	M		Yes	No	−	−	No	No	No	No	No

16	80	M		Yes	Yes	++	Biliary cirrhosis	No	Yes	Yes	No	Yes
17	46	M	Yes		?	–	–	No	Yes	No	No	Yes
18	79	M	Yes		Yes	++	+++	No	No	Yes	No	Yes
19	76	M		Yes	No	–	Biliary cirrhosis	No	No	Yes	No	Yes
20	42	M		Yes	Yes	++	+++	Yes	No	Yes	Fatal	No
21	35	F		Yes	Yes	+++	+++	No	No	Yes	No	Yes
22	52	F		Yes	Yes	++++	+	No	No	Yes	Fatal	No
23	43	F		Yes	Yes	++++	+	No	Yes	No	No	Yes
24	46	F		Yes	Yes	+	+++	Yes	No	No	No	Yes
25	60	M		Yes	No	–	–	No	Yes	Yes	No	No
26	37	F		Yes	Yes	+++	++	No	Yes	Yes	No	Yes
Totals			6	20	14	17	14	8	10	19	5	16

alcoholism, diabetes, and other clinical features. A summation of certain data of interest in this table is presented in Table II. A history of alcoholism was more prevalent (14 of 20) in those with multiple stones than in those with solitary stones (1 in 6). Diabetes mellitus was seen more often in the non-alcoholic (5 of 11) than in the alcoholic group (3 of 15). This indicates that if a person addicted to alcohol develops concretions in the pancreas, there is more than an even chance that they will be multiple. But, as noted in the group with chronic pancreatitis, the alcoholic patient does not seem to have as high an incidence of diabetes as the non-drinker with pancreatic lithiasis.

TABLE II

The Occurrence of Solitary and of Multiple Calculi in Patients With and Without Diabetes and Alcoholism

	History of alcoholism	Alcoholism and diabetes	No history of alcoholism	Diabetes in non-alcoholics
Multiple stones, 20	14	3	6	4
Solitary stones, 6	1	0	5	1
Totals	15	3	11	5

PATHOLOGY

Gross Observations. Because there are other excellent descriptions, only a few aspects of the gross changes need be discussed. The location of the calculi in the ducts is of interest. Sixteen were located definitely enough to chart on an outline of the duct system (Fig. 1). The remainder were widespread or indefinitely described by the prosector. The favored site for calculi is in the duct of Wirsung within 2 to 4 cm. of the ampulla of Vater. It is possible that they become impacted at this point after being carried down from the body or tail, rather than being formed at this site. Their location in the first 4 cm. of the duct of Wirsung is significant for two reasons. First, biliary obstruction may supervene because of proximity to the common duct. Secondly, a stone here allows the escape of pancreatic juice via the duct of Santorini if that duct opens into the duodenum. This in turn might prevent marked atrophy of the body and tail with resultant steatorrhea.

Two different patterns of calculous involvement were observed: first, that in which the main ducts were involved, and secondly, that in which only small ducts and acini were concerned. In the first group are the cases with solitary stones in one of the ducts with a variable degree of dilatation of the ducts and atrophy of the parenchyma distal to the calculus. The main duct may contain a large stone near the

duodenum and, back of it, great numbers of smaller calculi may be present in the ducts and/or acini. For some pancreases many calculi were described in the large ducts without mention of the size of the stone nearest the duodenum.

In the second group the large ducts were free of calculi. In the material studied since 1946, we have always been able to dissect the minute calculi from small spaces which microscopically were lined with epithelium. These spaces are evidently ductal. In the material collected previously, several pancreases were described as having only multiple areas of calcification in the parenchyma, with freedom of the large ducts from involvement. Although we shall describe microcalculi in the acini, we have not observed such involvement except in the presence of grossly detectable calculi in the small ducts.

In one patient there was a ductal carcinoma containing tiny calculi in the tail of the pancreas. Distal to the tumor the duct of Wirsung was dilated to a cystic cavity, and connected with this were smaller dilated ducts containing calculi. Calcification of fibrous tissue did occur in the walls of old cysts where the connective tissue had undergone hyalinization. Diffuse calcification of the interstitial tissue was not proved in this series. Apparently the calcium salts were always precipitated in the outflow tract of the pancreatic juice.

Microscopic Observations. The abnormalities observed microscopically were similar to those described for chronic pancreatitis. The differences were in degree of severity. Fibrosis, dilatation of ducts, and atrophy of the parenchyma were more outstanding. In some, fibrosis exceeded that seen in chronic pancreatitis alone. The wide areas of proliferation of edematous connective tissue formed a pattern peculiar to this disease (Fig. 2). A similar change was illustrated in a report by Baggenstoss.[3] Comparatively, the widely dilated ducts with great atrophy of the parenchyma were different also from those ordinarily seen in chronic pancreatitis. In part of the pancreases, however, no differences could be observed between chronic pancreatitis with and without stones. Fibrosis of the perilobular type followed the usual pattern.

Islet destruction, as well as acinar atrophy, was noticeable. The destruction of islets may parallel that of the acini. Pseudocyst formation occurred in a greater percentage (26.9 per cent) than in chronic pancreatitis (9.6 per cent). The relationship of the pseudocysts to the ducts and parenchyma was notable (Fig. 3). Even after pseudocysts had formed, repeated insults might change their character. Necrosis

of their walls with hemorrhage was common; even clots formed in some. No connection with ducts or acini could be seen for some of the pseudocysts.

Of most interest was the appearance of small concretions in the ducts. Two types were seen. The larger aggregates often were laid down in masses of inspissated débris (Fig. 4) or even in the epithelium lining the ducts (Fig. 5). Sometimes intra-epithelial calcification involved areas of squamous metaplasia. That much of the débris was desquamated epithelium was shown by ghost-like remnants exhibiting a columnar arrangement (Figs. 6 and 7). Included in the mixture there was probably protein from the acinar secretion and mucoprotein from the epithelium of the ducts. A second type of precipitate was seen once. It consisted of tiny crystals of calcium widely dispersed in débris (Fig. 8).

Frequently the acini contained microcalculi (Fig. 9). In most of these the epithelium was not discernible; in some, portions at least still remained. It is possible that necrotic epithelium may have formed the basis for calcium precipitation. On the contrary, early post-mortem change may have destroyed the epithelium around the calculi. We are attempting to collect enough fresh material to settle this point.

The duct carcinoma with calculi noted grossly failed to reveal minute calculi on microscopic examination. We have no way of knowing which came first, the carcinoma or the stones. Areas of calculous formation may be limited to the tail. It would not be surprising to find carcinoma arising in ducts which are the site of such remarkable epithelial hyperplasia as is seen in chronic pancreatitis. In several instances it was necessary to study such areas carefully before being certain that malignant change had not occurred.

Chronic inflammation, exemplified especially by round cell infiltration, was present in all cases except those with extreme atrophy and in two with solitary calculi. The perineural round cell infiltration emphasized by Comfort *et al.*[1] was quite striking in several examples.

Acute pancreatic necrosis was noted in 5 cases and was severe enough to contribute to the cause of death in 3.

Lüdin[4] in Basel made post-mortem roentgenograms of 542 pancreases. They were then dissected. He demonstrated calculi in 28, or 5 per cent. We examined 200 unselected pancreases of adults, first by dissection of the duct system and then by roentgenograms. We failed to find any calculi. Tiny areas of increased density noted on some of the plates proved to be calcium in small arteries, the seat of sclerosis.

Thorough dissection of the pancreas revealed calculi in all cases diagnosed roentgenographically during the past 2 years. Undoubtedly, in time we would have found some stones by x-ray examination that we had missed by dissection, but the project did not seem worth pursuing further.

Pathogenesis

We wish to present a possible explanation for the precipitation of calcium salts in the ducts of the pancreas. The normal pancreatic juice is formed at the rate of 2000 to 3000 cc. daily and the rate of its production is more constant than originally thought.[5] The quantity, pH, and enzyme content vary with the stimulating agent. Secretin stimulation following meals produces a free flow of highly alkaline juice poor in enzymes. Vagal or pilocarpine-stimulated juice is smaller in quantity, less alkaline but rich in enzymes. In some animals, the latter type of stimulation can exhaust the secretory granules of the acinar cells without forming enough juice to enter the duodenum. Secretin stimulation occurs chiefly after meals when the acid stomach contents enter the small intestine. This type of stimulation results in flushing out the pancreatic duct system, carrying the needed enzymes into the intestine.

The problem of predicting the nature or extent of precipitation of an insoluble salt in a complex solution such as pancreatic juice presents obvious difficulties. It is, however, possible to calculate whether solubility products of insoluble salts are exceeded, and whether precipitation may be expected to occur.

There is general agreement[6-9] that the total ionic concentration of pancreatic juice is about the same as that of serum, and that the relative proportion of chloride and bicarbonate varies with the secretory activity of the gland. In general, the concentration of bicarbonate is considerably higher than that of serum, and increases with the amount of pancreatic juice formed. In dogs, at least, the bicarbonate may increase at the expense of almost all of the chloride ion,[8] and in man the bicarbonate may reach values of at least 130 mM/l.[9] With the increase in bicarbonate there is, of course, an increase in pH. In the dog, values are commonly from 8.0 to 8.3.[7,8] Except under the influence of mecholyl or secretin, the pH in man usually does not appear to be consistently above 7.5.[9] In measurements on man, of course, some opportunity for neutralization of pancreatic juice by mucoproteins and by contact with the intestinal mucosa is afforded. We may assume, at any rate, that a pH of 8.0 and a bicarbonate concentration

of 100 mM/l are not uncommonly reached. From the second ionization constant of carbonic acid, determined at the ionic strength of pancreatic juice,[10] there would be 1.57 mM/l of carbonate present for each 100 mM/l of bicarbonate at pH 8.0 (0.99 at pH 7.8, and 2.48 at pH 8.2).

The calcium ion concentration found by Ball[11] in the pancreatic juice of dogs was generally 1.0 to 1.5 mM/l. This would correspond roughly to the diffusible calcium of serum and would appear to be a reasonable value. The concentration of phosphate also was found to be somewhat variable, but generally between 0.3 and 0.6 mM/l.[11] Although reliable values for human pancreatic juice under a variety of conditions would be desirable, we will assume that at least 1.0 mM/l of calcium and 0.3 mM/l of phosphate will be found in human pancreatic juice.

At pH 8.0, then, the product of the ionic concentrations of calcium and carbonate may be taken to be $(1 \times 10^{-3})\ (1.6 \times 10^{-3}) = 1.6 \times 10^{-6}$. The solubility product of $CaCO_3$ at 38° C. and an ionic strength of 0.156 has been found to be between 4 and 5×10^{-8}.[10] Thus, under the above conditions, the solubility product is exceeded in pancreatic juice. If it can be assumed that the pH is determined by the carbon dioxide tension and the bicarbonate concentration, or by some entirely different buffer system, precipitated carbonate would be continually replaced from bicarbonate without any significant change in the bicarbonate concentration or the pH. Precipitation of calcium carbonate could then continue until the solubility product was no longer exceeded. This would correspond to a situation in which $(Ca^{++})\ (CO_3^{--}) = 5 \times 10^{-8}$, and since (CO_3^{--}) is assumed to be fixed at 1.6×10^{-3}, $(Ca^{++}) = \frac{5 \times 10^{-8}}{1.6 \times 10^{-3}} = 3 \times 10^{-5}$. If precipitation took place until equilibrium was reached, $1 - 0.03$ mM/l or 0.97 mM/l of Ca^{++} would be precipitated as calcium carbonate. Essentially all of the calcium could be removed in this way, and about 0.1 gm. of $CaCO_3$ could be precipitated from each liter of pancreatic juice. It may be pointed out that, according to this view, increasing the bicarbonate concentration above 100 mM/l, or the pH above 8 would not materially increase the maximum amount of calcium carbonate which could be precipitated, but would increase the initial degree of supersaturation and might promote the initiation of precipitation.

The problem with respect to the probability of precipitation of calcium phosphate from pancreatic juice must be much the same as that of precipitation from serum. If we consider, first, the case of $CaHPO_4$,

the HPO_4^{--} concentration can be calculated from the total phosphate concentration and the second ionization constant of phosphoric acid. At pH 8.0, over 90 per cent of the phosphate will be in the form of HPO_4^{--}, and (Ca^{++}) (HPO_4^{--}) will be in the neighborhood of 3×10^{-7}. This is less than the solubility product of 2.5×10^{-6},[12] and precipitation could not take place. For Ca_3 $(PO_4)_2$, however, the solubility product is exceeded. The calculations would be essentially the same as those for serum,[13] except that at pH 8 an even larger proportion of the total phosphate is in the form of PO_4^{---}. If precipitation were to depend, as postulated in the case of bone formation,[13] upon the initial precipitation of $CaHPO_4$ and subsequent modification of the composition of the precipitate to give Ca_3 $(PO_4)_2$, precipitation of calcium phosphate in pancreatic juice would be less likely than precipitation of calcium carbonate. It is well known that calcium carbonate is actually the principal component of pancreatic calculi. This we have found true of the stones we have subjected to analysis.

With these basic factors in mind, what further can be postulated in regard to the formation of calculi? In a normal duct system any small amounts of precipitate formed would flow freely into the duodenum. Occasionally though, as seen in this series, a solitary stone is observed near the ampulla of Vater. Such stones may have started to form farther back in the duct system and lodged near the ampulla, to continue to grow. In symptomless patients without microscopic evidence of chronic pancreatitis some local disturbance in one of the lobules may have started precipitation, or it may be of spontaneous occurrence in the larger ducts. This must be an unusual type, however, for most of the calculi are multiple and often occur following attacks of pancreatitis. In these circumstances, there are the added effects of stasis and inflammation. Dilated ducts filled with stagnant juice would give more opportunity for precipitation. The protein débris in the ducts sometimes seems to act as a nidus for calculous formation. Inflammatory exudate did not seem to be a factor in the precipitation of calcium in the tissues we have studied. The evidence that stasis is important is seen in those patients who have a solitary stone diagnosed by the roentgenogram and in whom, a few months later, many stones are noted back of the first one. This gross pattern was noted twice at necropsy.

The examples of extreme calcification of the pancreas are more difficult to explain. As acinar atrophy becomes advanced the total volume of secretions must fall considerably. Whether enough Ca^{++} and

CO_3^{--} would be secreted to account for the amount of calcification we are not prepared to say. One must consider the possibility of calcium salts being laid down in necrotic acinar epithelium. As noted in Figure 9, acinar calcification occurs, but the fate of the epithelium is difficult to determine.

Since phosphatase has not been observed in acinar cells,[14,15] it need not be considered in the pathogenesis of calculi.

Discussion

From the etiologic standpoint it is difficult to relate either clinically or pathologically all of the pancreatic stones in this series to previous attacks of pancreatitis. This is especially true of the symptomless solitary calculi. Back of the point of obstruction, only dilatation of the ducts and atrophy of the parenchyma were noted. No evidence of chronic inflammation was seen. It must be considered, though, that a subclinical attack of pancreatitis or one forgotten by the patient may have occurred. Opie[16] and Friedreich[17] have commented upon the fact that pancreatic calculi were often symptomless. In a majority of the patients under consideration, a history of excessive use of alcohol and attacks of upper abdominal pain point toward pancreatitis as an etiologic factor. The evidence is not so strong as when the patients have had repeated x-rays and calculi are known to have appeared after bouts of pancreatitis, as described by Comfort *et al.*[1]

The relationship of alcohol to repeated attacks of pancreatitis and the formation of calculi is most striking, It is strange that no attempts have been made to elucidate this connection by animal experimentation. Some of the possibilities worth consideration include: action of alcohol on secretin formation; stimulating effect of blood alcohol on the pancreatic secretion; and the possibility of excretion of alcohol in the pancreatic juice.

The excessive deposit of fat in the liver in patients with pancreatic stones has been noted by Comfort *et al.*[1] Its presence has been explained by lack of lipocaic.[18] We found excess liver fat in 17 (or 65.4 per cent). It was associated with alcoholism and/or cirrhosis in 15, with diabetes in one, and no history was obtainable in the 16th patient. The frequent association of a fatty liver with alcoholism and diabetes is universally recognized. It might be pointed out that failure of the external pancreatic secretion in patients with lithiasis leading to creatorrhea and lack of sufficient absorption of such amino acids as methionine could contribute to the formation of fatty livers.

The association of pancreatic stones with pulmonary tuberculosis has been mentioned repeatedly in the literature. It occurred five times in this group. In three patients, tuberculosis was the primary cause of death. Two patients were diabetic and two gave a history of chronic alcoholism. Both conditions often leave their victims more susceptible to tuberculosis.

From the clinical standpoint, the presence of pancreatic stones should be suspected in patients with diabetes mellitus, chronic alcoholism and cirrhosis, repeated attacks of upper abdominal pain (especially if pancreatitis is suspected), steatorrhea, and unexplained weight loss.

The occurrence of calculi of various sizes along the outflow tract of the pancreatic juice is in accord with the theory that precipitation is due primarily to the supersaturation of pancreatic juice with calcium carbonate. Some factors must operate to prevent the formation of stones, else they would occur more frequently, especially in patients with chronic pancreatitis and dilated ducts in which much protein débris indicative of stasis is often seen. It may be that small calculi are formed in the ducts more frequently than we realize, but pass into the duodenum.

In addition to supersaturation of the pancreatic juice with calcium carbonate, the major rôle of pancreatitis is recognized. Whether these have any direct influence on the formation of calculi is hard to determine. Inflammatory débris and cyst-like dilatation of ducts presumably may initiate the precipitation of calcium carbonate during an acute attack. But it is more plausible to consider that stasis secondary to chronic inflammation is the more important. There is no reason to assume that there would be a change in the pancreatic juice toward the alkaline side in chronic disease. If alcohol acts on the pancreas through a secretin mechanism, excessive stimulation of the formation of alkaline juice may be important.

That calcification of the interstitial tissue may occur we do not deny, but we could find no appreciable evidence of it either in the 62 patients with chronic pancreatitis or in the 26 with stones.

We have never seen calcification of the adipose tissue in and around the pancreas. Even in patients known to have had acute pancreatitis, such lesions have not been seen at necropsy or in surgical material. The fate of the calcium soaps precipitated in the areas of fat necrosis which are seen in acute pancreatitis has been a subject of controversy. Klotz[19] postulated that precipitation of calcium soaps precedes pathologic calcification. The evidence has been discussed by Barr.[20] The experiments

of Wells and Mitchell[21] demonstrating that injected calcium soaps are absorbed, and not converted to inorganic calcium salts, are most convincing. Our studies give no indication that the calcium soaps found around the pancreas in areas of fat necrosis are sites of subsequent calcification. The formation of inorganic calcium deposits where calcium soaps have been deposited would require some mechanism for the rapid removal of fatty acids, leaving a high local concentration of calcium ions. Such a mechanism is not known outside the cell, in which oxidation might occur. It would seem more reasonable to assume that calcium soaps are removed by a gradual process of solution without a local increase in calcium concentration.

It is difficult to explain the difference in incidence of calculi found in post-mortem roentgenograms in Basel[4] and in Los Angeles. This work should be repeated in other parts of the globe. In a series comparable to ours, Simmonds[22] noted in Germany an incidence of 19 in 36,004 necropsies.

SUMMARY

Twenty-six cases of pancreatic lithiasis were found in a series of 36,000 autopsies. Ten of these were discovered in the last 3,000 autopsies.

A history of alcoholism was obtained in 14 (53.8 per cent) and diabetes was a complication in 8 (30.7 per cent).

The deposition of calcium salts was noted only in the outflow tract of the pancreatic juice.

Under normal conditions the pancreatic juice is supersaturated with $CaCO_3$, for the ion concentration product will reach values of at least 1×10^{-6}, whereas the solubility product is about 5×10^{-8}. The precipitation of $CaCO_3$ to form calculi in the ducts of the pancreas can thus be explained.

Other factors affecting the ducts, such as stasis, inflammation and accumulation of protein débris, must be considered in the pathogenesis of calculi.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 7

FIG. 1. Diagramatic representation of location of stones in main pancreatic ducts. Pancreas approximately one-half normal size.

FIG. 2. Extensive replacement fibrosis of pancreatic lobules, with chronic inflammation and edema. Hematoxylin and eosin stain. × 70.

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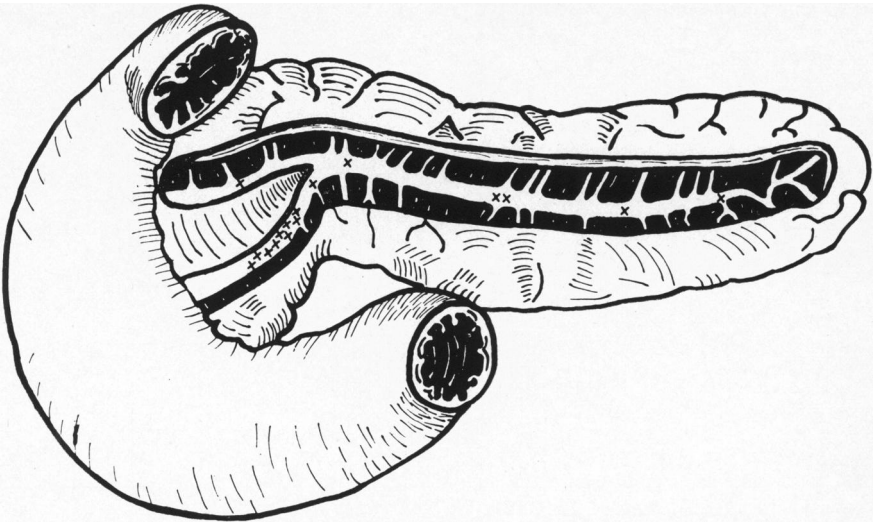

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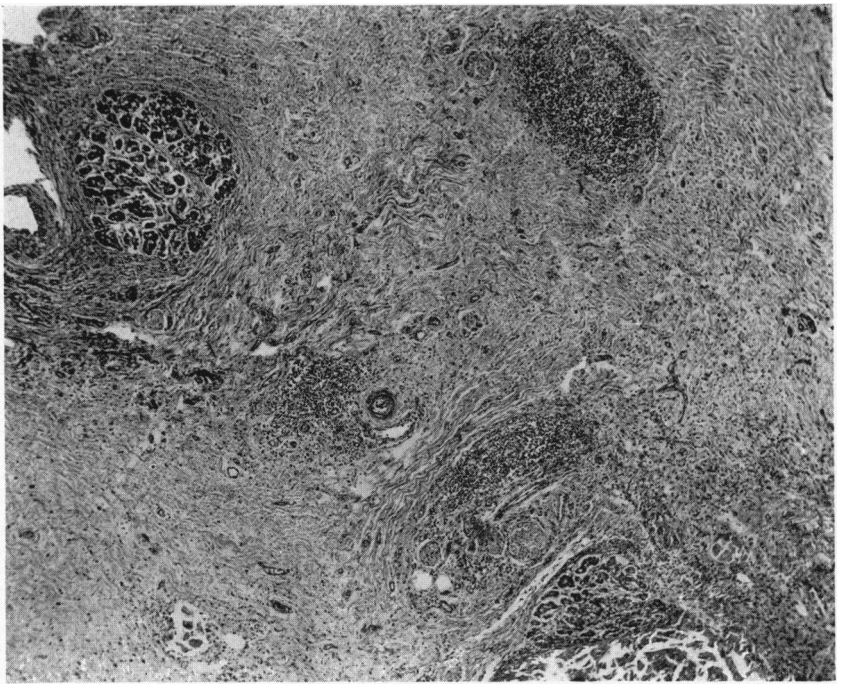

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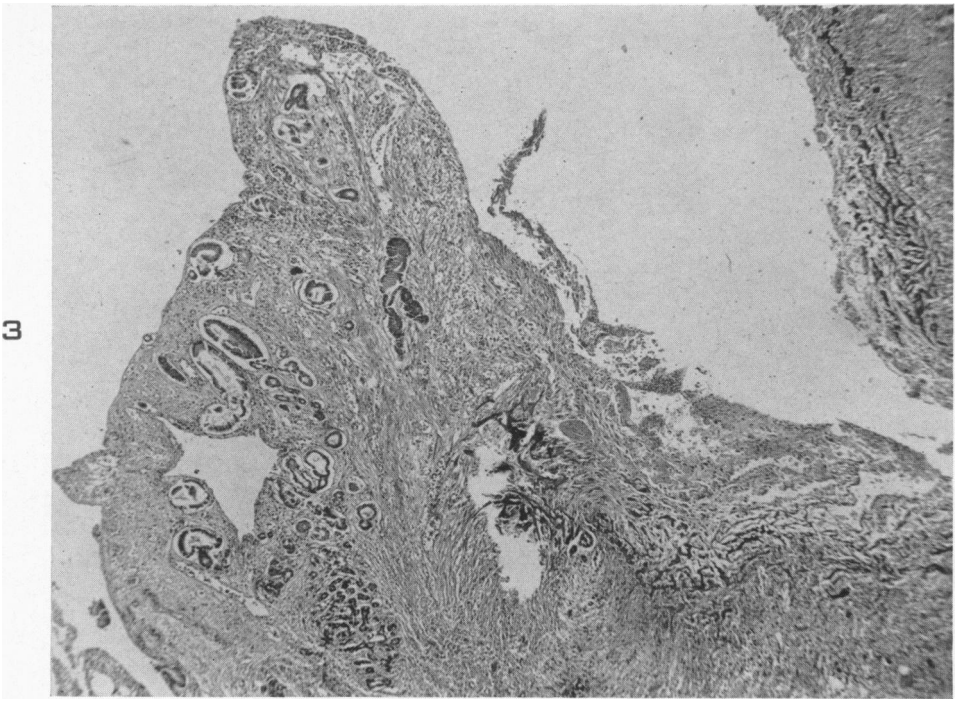
Plate 8

Fig. 3. Lining of pseudo-cyst with connecting ducts. Some necrotic tissue tags are still attached to lining. Hematoxylin and eosin stain. × 70.

Fig. 4. Microcalculi precipitated in masses of protein débris. Hematoxylin and eosin stain. × 175.

Fig. 5. Multiple calcific masses in ducts and also within the epithelial lining cells. Hematoxylin and eosin stain. × 150.



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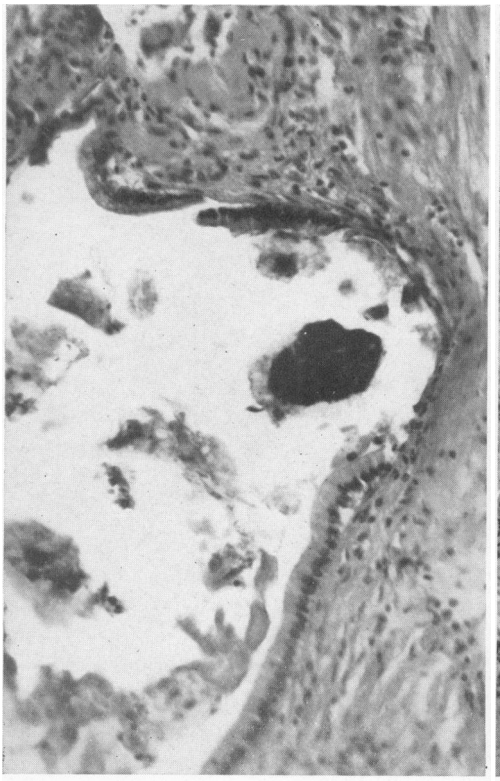

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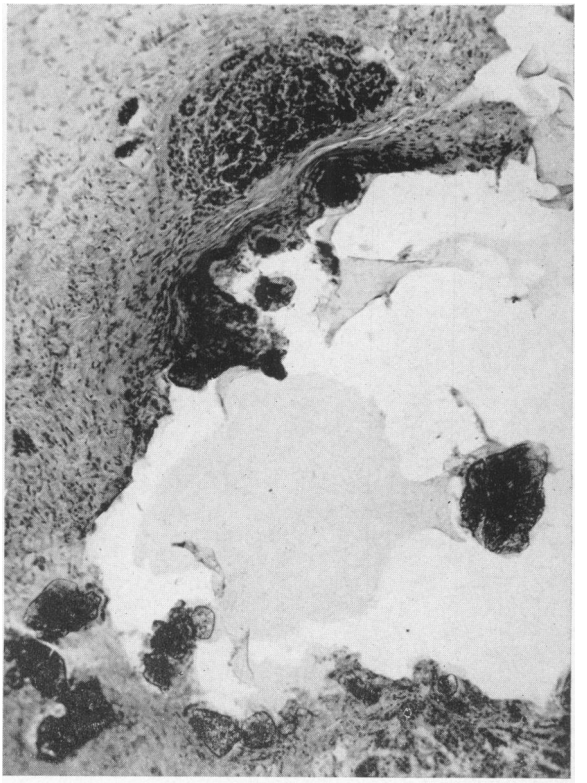

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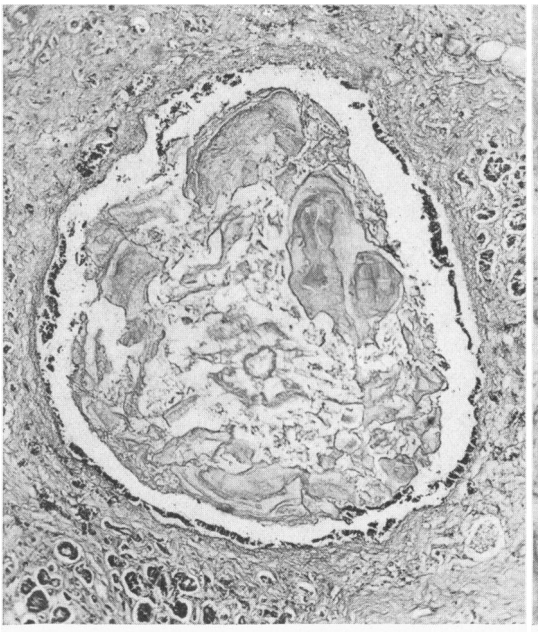
PLATE 9

FIG. 6. Dilated duct filled with conglomerate mass of protein. Hematoxylin and eosin stain. × 55.

FIG. 7. Higher magnification of protein débris shown in Figure 6. Of note are the remnants of columnar epithelium. Hematoxylin and eosin stain. × 145.

FIG. 8. Fine crystalline calcium precipitate widely dispersed in protein débris in small duct. Severe chronic pancreatitis and atrophy. Hematoxylin and eosin stain. × 55. Polarized light photomicrograph.

FIG. 9. Spherical intra-acinar masses of calcium salts. These appear to be precipitated in necrotic acinar epithelium. Hematoxylin and eosin stain. × 205.



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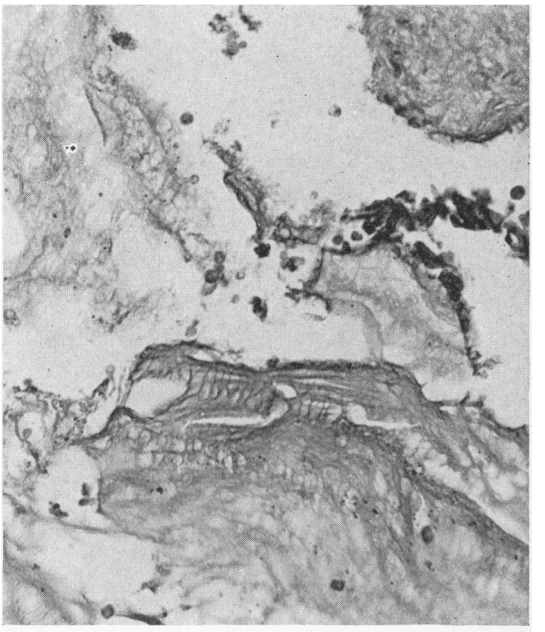

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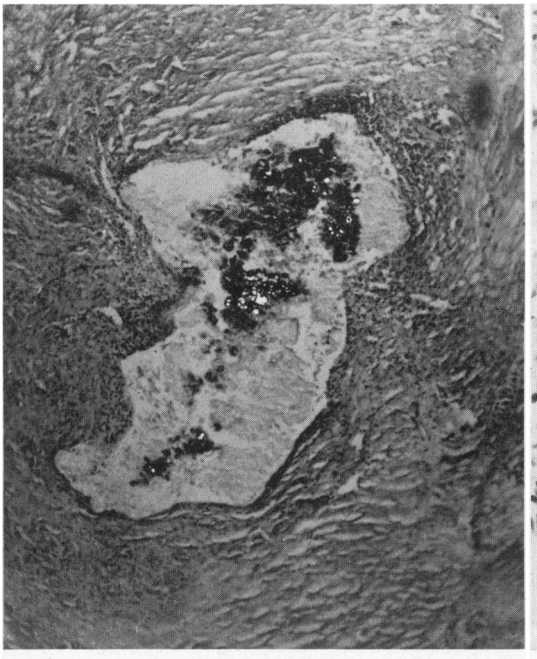

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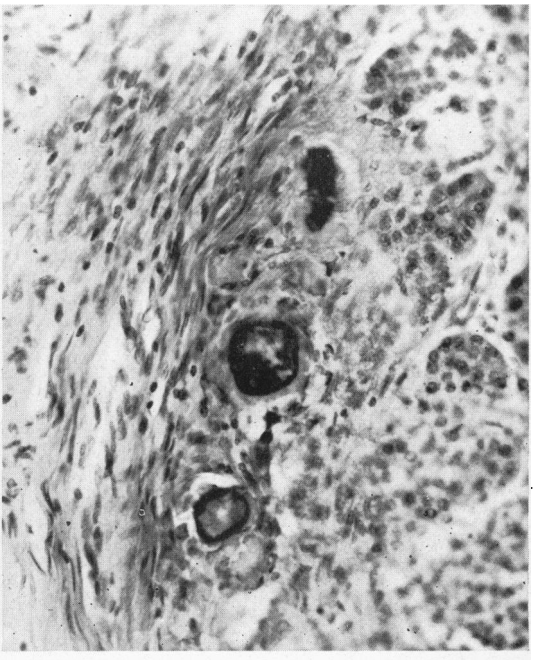

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