

STUDIES OF PANCREATITIS AND THE PANCREATIC REACTION OF CAMMIDGE.*

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THIS work has been undertaken in order to reach a more positive conclusion regarding the claims brought forward by Mr. Cammidge of London, that he was able to obtain a specific reaction in the urine of persons who are the subjects of pancreatic involvement.

In the series of cases here reported in which pancreatitis was said to have been present, only those have been so classified which were shown at operation to present such marked enlargement that a mistake in diagnosis was improbable.

The recitation of the involved test, or of the minutiae of technic is unnecessary here, except that it has only been through the development of the latter that the data for this paper has been made apparently worthy of publication. It is possibly because other observers have not sufficiently regarded the precepts of laboratory precision that they have obtained results so at variance with those of Mr. Cammidge. In the earlier work the profusion of positive reactions was astonishing. It was only after much experience that I learned to use nothing but distilled water in every step, including the washing of the glassware, a most important point.

The results of this early inaccuracy have been discarded and the cases which have been classified in Tables I and III are the only ones considered in these statistics. They represent the results of an improved technic, and all have been checked up by a control which was not boiled with hydrochloric acid (Fig. 5). If this showed a crystalline deposit,

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and the one treated with hydrochloric acid did not, the test was regarded as negative.*

Between March and October of this year there were tests made on 62 cases, which were operated and a diagnosis of pancreatitis made from the gross appearance of the gland. The lesions in related organs were also noted (Table I).

TABLE I.

Group	Diagnosis	No. Pos. Neg		
I.	Acute pancreatitis.			
II.	Subacute pancreatitis.			
	a. With obstruction of the common duct:			
	1. By stones in C. D. + H. D. + acute cholecystitis	1	1	0
	b. Without obstruction of the common duct:			
	1. Stones in G. B.	1	1	0
	2. Stones in G. B. + cystic duct.	1	1	0
	3. Stones in G. B. + cholecystitis.	1	1	0
	c. Infective	2	2	0
III.	Chronic pancreatitis.			
	a. With obstruction of the common duct:			
	1. By gall-stones.	7	6	1
	2. By gall-stones + stones in G. B.	2	1	1
	3. By gall-stones + stones in G. B. + cystic duct.	1	1	0
	4. By gall-stones + stones in G. B. + cholecystitis.	1	1	0
	5. By growth	4	4	0
	b. Without obstruction of the common duct:			
	1. Gall-stones in G. B.	16	11	5
	2. Gall-stones in cystic duct.	1	1	0
	c. Cholecystitis	7	4	3
	1. With stones in G. B.	6	5	1
	2. With pigment in G. B.	2	2	0
	3. With stone in C. D.	2	1	1
IV.	Atrophic pancreatitis.	2	2	0
V.	Cancer of the pancreas.	5	5	0
		62	50	12

* The following notes on the technic of the pancreatic reaction (*ref. Robson and Cammidge: The Pancreas, Its Surgery and Pathology*) may be of interest. The albumin is easily precipitated out. Sugar, if present, is removed by fermentation, which may take 48 hours or more. After 24 hours, fresh yeast should be employed and a phenylhydrazin test for sugar by the v. Jaksch or Kowarski method made before the solution is carried through the pancreatic reaction. In some of the cases the elimination of all traces of sugar has been difficult, but must be accomplished if any value is to be ascribed to the results.

Of these 82 per cent. (50 cases) showed positive reactions in the urine, and the remaining 18 per cent. (12 cases) were negative. In the group of subacute cases (6) all were positive, while in the group of chronic pancreatitis (49) we had 77 per cent. of reactions. Both of the cases of atrophic conditions and all of the cancers (5) showed typical crystalline deposits.

It would be well to define some of the terms used in the summary, both of the classification of pancreatitis and of the accompanying conditions. While of course it is impossible to make an accurate classification merely from the gross appearance of the gland, the following has been adopted as a working basis. By acute, is indicated general enlargement, soft with hæmorrhagic tendencies; by subacute moderate general enlargement, firmer than the former and accompanied by fat necrosis; by atrophic very little remaining gland tissue, and that very soft; sclerotic denotes a small very dense gland with general involvement. Chronic pancreatitis is self-explanatory, and its two pathological types are the interacinar or large smooth gland with general involvement, and the

In the second step, *i.e.*, adding lead carbonate, the hot hydrochloric acid solution should be perfectly cooled, as the reaction with the carbonate is violent if the solution is hot, and a film is formed on the sides of the beaker where reaction would not be complete; also that the resultant lead chloride is moderately soluble in hot solution. This reaction must be allowed to complete itself before filtering, usually three or four minutes.

The third step of adding tribasic lead acetate is an important one, as it serves to remove the glycuronic acid, which has been formed by boiling the urine with the hydrochloric acid (a mineral acid), if the specimen so treated contained glycuronates originally, which is frequently the case. The reaction should be allowed four minutes, being well shaken at half-minute intervals, the resultant filtrate should then be markedly decolorized and absolutely transparent.

The lead is then completely removed by precipitation as a sulphate, the solution having been rendered absolutely cool before filtration. Care must be taken that the neck of the bottle is cooled also.

All filter papers used should be washed with distilled water, and a small amount allowed to drain through in order to wash out the ever-present chlorides, which will precipitate the lead and cloud up the filtrate at certain stages.

interlobular or hard nodular gland, which is more apt to be localized.*

As it seems to have been shown that it is the disturbance of the internal secretion which bears the etiological relation to the production of the crystals in the urine, you are asked to bear this in mind as the observations are developed.

Of the 23 per cent. (12 cases) which gave negative reactions in the group of chronic pancreatitis, all were old standing cases, all were grossly of the interlobular type, and all but one localized in or near the head of the gland, the other being a general involvement; thus tending not to interfere markedly with the physiological action of the islands of Langerhans, either histologically because the islands are intralobular in situation, or with the one exception mentioned, because of being confined to relatively small areas.

It is also significant that in nine of the cases there was no obstruction of the common duct, five of them having stones in the gall-bladder only, the other four being complicated by cholecystitis, thus causing the pancreas the least irritation.

Is this irritation an etiological factor? Is it necessary that the stone be in contact with the gland in order to produce irritation? On the contrary, observations point to the other extreme. This is very noticeable in Group II. Here in six cases of subacute pancreatitis there was only one where there was obstruction by a common-duct stone, and that was complicated by an acute cholecystitis, and stones in the hepatic duct; and further in Group III among 49 cases of chronic pancreatitis there was obstruction of the common duct by stone in thirteen cases, or 27 per cent., and six of these were complicated by stones in the gall-bladder, cystic duct or cholecystitis.

It must be considered that interference with the hypo-

* While of course it is impossible to make an exact diagnosis of these two histological types without a histological examination, yet the glands grossly so resemble those on which histological examinations have been made that one would appear warranted in the above deductions.

thetical internal secretion of the pancreas, due to reflex irritation, may be the forerunner of pathological changes in the gland, either from stasis of the secretion or through its devitalizing effect predisposing to the subsequent infection.

What importance can be ascribed to the "pancreatic reaction" in this relation? There have been several cases where it has been positive, yet no gross change has been noted in the gland at operation; but the irritant factor (gall-stones or cholecystitis) having been removed, within two weeks after operation it has become persistently negative. While I appreciate the possibility that it may be due to a derangement of the liver that this substance is excreted in the urine (although many negative reactions and no positive ones have been obtained, where that organ was markedly involved, which would tend to eliminate this factor), may it not be assumed equally as well, if not more probably, that it was due to the reflex inhibition of the internal secretion causing a disturbance of the internal metabolism, correlated in cause and effect to the reflex stimuli noted so frequently in the stomach from gall-bladder or duodenal involvement, evidenced as a pylorospasm, hyperacidity or anacidity.

On the other hand, when the gross changes have occurred they may be so extensive as to have permanently injured the gland, and the internal secretion will be correspondingly insufficient. A few patients have returned for examination a year or so after operation, at which chronic pancreatitis was diagnosed, and have shown a positive reaction. They complain not of the original trouble, but of symptoms relevant to pancreatic derangement.

In 35 per cent. (20 cases) of this series, cholecystitis was present, introducing the infective factor. There are only a very few cases where infection is beyond doubt the only factor, and these are found in the group of subacute cases, and also in the instances of atrophic pancreatitis. In the entire series of 57 cases, excluding those of cancer (6), stones in the gall-bladder formed 49 per cent. (28 cases), while stone in the common duct *per se* and together with other factors formed 25 per cent. (14 cases); thus together we find stones in 74 per cent. of the cases.

In computing the percentages in the total number of cases of pancreatitis operated upon by Dr. Mayo, 293, excluding 28

TABLE II.—ETIOLOGICAL FACTORS IN PANCREATITIS.

Group	Diagnosis	Total
I.	Acute pancreatitis.	
	1. Stones in G. B.	4
	2. Stones in pancreatic duct.....	1
	3. Cholecystitis	2
II.	Subacute pancreatitis.	
	a. With obstruction of common duct:	
	1. Stone in C. D.	2
	2. Stone in C. D. + H. D. + Acute cholecystitis.....	1
	3. cholecystitis	4
	b. No obstruction of common duct:	
	1. Stones in G. B.	7
	2. Stones in G. B. + cystic duct.....	1
	3. Stones in G. B. + cholecystitis.....	12
	c. Cholecystitis	1
	d. Infective	2
III.	Chronic pancreatitis.	
	a. With obstruction of common duct:	
	1. By gall-stones.....	32
	2. By gall-stones + stones in G. B.	22
	3. By gall-stones + stones in G. B. + H. D.	8
	4. By gall-stones + stones in G. B. + cholecystitis.....	4
	5. By growth	9
	6. Infective	16
	7. Infective + stones in G. B.	2
	8. Stones in pancreatic duct.....	1
	b. No obstruction of common duct:	
	1. Gall-stones in G. B.	75
	2. Gall-stones in G. B. + cystic duct.....	4
	3. Gall-stones in G. B. + cystic duct + infection.....	1
	4. Sclerosis	4
	c. Cholecystitis:	
	1. With stones in G. B.	39
	2. With pigment in G. B.	6
	3. With stone in C. D.	5
IV.	Abscess of pancreas.....	3
V.	Cancer of the pancreas.....	25
	1. Stones in G. B.	3
VI.	Cyst of pancreas.....	1
		321

cases of cancer (Table II), stones in the common duct occurred in 74 cases, or 25 per cent.; stones in the gall-bladder 151

times, or 55 per cent., stones in one situation or another therefore being present in 77 per cent. of the cases. Cholecystitis was found in 98 cases, or 33 per cent., both as an independent factor and in conjunction with stones. These percentages correspond so strikingly with those in the smaller series (Table I) on which observations were made as to the presence or absence of the pancreatic reaction, that it would seem almost possible to transfer these results to the larger series.

From an anatomical point of view it is interesting to note that in 28 per cent. of the cases persistent jaundice was caused by the involvement of the common duct by the head of the gland. If to this is added the 25 per cent. representing the incidence of jaundice with stone in the ampulla, we would have 53 per cent., corresponding fairly closely with the 62 per cent. given by Helly in which he found the duct involved in the gland tissue in his cadaveric studies; but we are hardly warranted in disregarding the presence of the stone as the causative factor of the jaundice in all of the cases, although in some the pancreatitis was certainly caused because of the direct irritation of the stone on the surrounding gland substance, which probably accounts for the discrepancy in the percentages of incidence of gland involvement where only related portions of the biliary tract were affected, and where stone was found in the common duct, which is shown in the next observation.

In a series of 3095 operations by Dr. W. J. Mayo on the gall-bladder and biliary passages, pancreatitis was found in 293 cases, or 9.5 per cent.; approximately it occurred once in every 10 cases. In this same series there was obstruction of the common duct by stone in 394 instances, and an accompanying pancreatic in 74 of the cases, or 19 per cent.: approximately it occurred once in every five cases.

In order to find out further the degree of accuracy of this test, 50 consecutive cases were chosen in which clinically diverse affections of the biliary tract were diagnosed. Group

VI (Table III) shows what was found at operation. There were seven positive reactions obtained, or 14 per cent. In

TABLE III.

Group	Diagnosis	No. Pos. Neg.		
VI.	No pancreatitis.			
	1. Gall-stones in C. D.	5	1	4
	2. Gall-stones in G. B.	17	2	15
	3. Gall-stones in G. B. + C. D.	5	2	3
	4. Gall-stones in G. B. + C. D. + H. D.	3	0	3
	5. Gall-stones in G. B. + cholecystitis.	10	1	9
		—	—	—
		50	7	43
VII.	Miscellaneous—no pancreatitis	50	3	47
VIII.	Normal	25	1	24

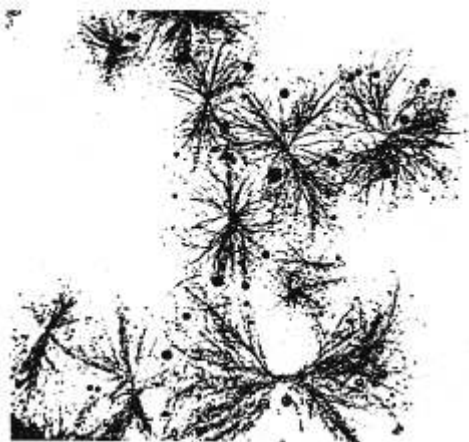
the majority of these positive cases there were many clinical signs that would lead one to believe that the pancreas might be involved, but no gross change was found at operation. It is to be noted, however, that these cases were of comparatively recent development, and it is quite possible that the hypothesis of irritation with resultant inhibition of the internal secretion indicates to us the *modus operandi*, and that this had not been in effect long enough to cause gross glandular change.

In Group VII, (Table III) there are fifty cases representing analyses on as many surgical conditions of the upper abdomen. The three positive reactions were obtained from two cases of carcinoma of the stomach, inoperable because of their extensive metastases, and from a very advanced cirrhosis of the liver in conjunction with Banti's disease.

In Group VIII (Table III) are twenty-five observations on the urine of persons apparently in normal health, only one of which was positive, and this reaction could not be obtained in a subsequent analysis.

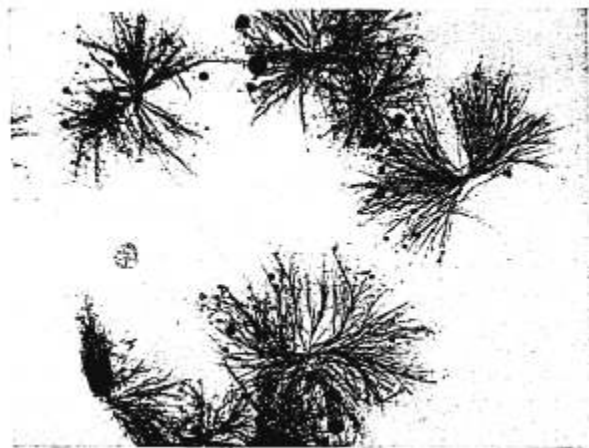
Heavy flocculent precipitates (Fig. 5) of typical crystals (Figs. 1 and 2) were noted to be rather indicative of general involvement, especially so in the group of subacute cases. While the more granular precipitates of the heavier broader crystals (Figs. 3 and 4) were found to occur more frequently in the instances of limited and moderate pancreatitis. These

FIG. 1.



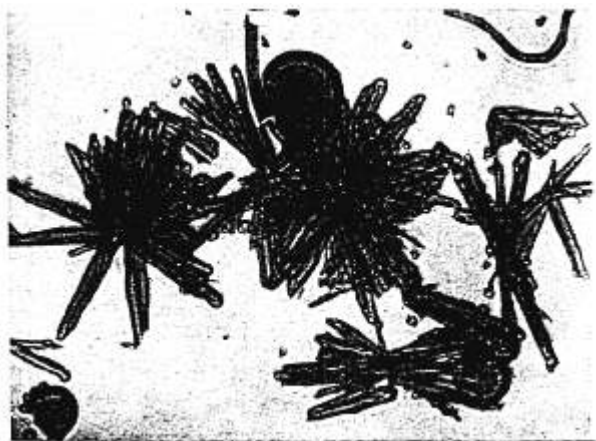
Typical crystalline deposits in case of general pancreatic involvement of interacinar type.

FIG. 2.



Typical hair-like or filiform crystals, showing sheaf formation in case of chronic pancreatitis with general involvement, of interlobular type.

FIG. 3.



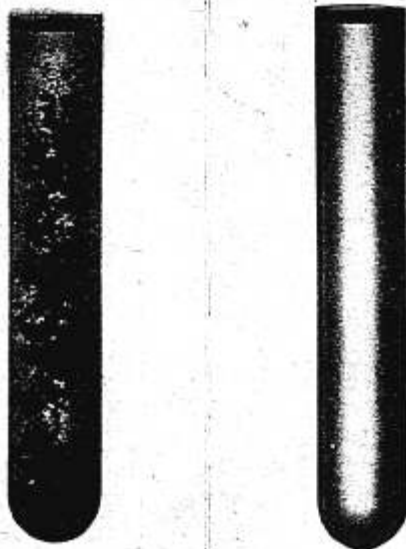
Acicular or saber type of crystals found in case of chronic pancreatitis with moderate involvement, of interlobular type.

FIG. 4.



Acicular crystal found in the heavy granular precipitates in cases of chronic pancreatitis with localized involvement.

FIG. 5.



Gross appearance of typical pancreatic reaction; heavy flocculent precipitate with a negative control.

observations are not by any means to be considered pathognomonic, and are suggestive only. Many hypotheses might be formed regarding the nature of the osazones forming these two types of crystals. Any statement of their structure must, owing to our present incomplete knowledge of the subject, be merely tentative. However, it seems that if investigations were pursued along the lines of the disturbance of the internal metabolism rather than attempting to account for the phenomenon through absorption of some substance from the gland itself, more progress could be made. The rapid disappearance of the reaction post-operative would seem to be fairly presumptive evidence that we have not to deal with simple absorption, as in that short period of time it is difficult to conceive of an entire regeneration of the pancreas, but rather with an incomplete catabolism in the blood.

EXPERIMENTAL DATA.

In order to determine whether the conclusions regarding the etiological factor played by the lack of internal pancreatic secretion both temporarily and permanently have more than a hypothetical basis for the production of these crystals in the urine, Dr. George Eusterman and myself undertook some dog experiments.

The dogs chosen were adult males, and in each instance were treated in one of the following four ways: (1) Segmental ligation, in which the gland substance was tightly constricted for its entire length at intervals of one and a half to two inches, the head and excretory ducts being left intact and patent; with the idea that there would be a temporary interference with the internal secretion and a permanent occlusion of the external secretion except that which could be obtained from the two inch segment containing the head and excretory ducts; and that the internal secretion would be renewed after the temporary sectional œdema had subsided. (2) Peripheral ligation; or the complete stoppage of all efferent and afferent vessels permanently, which was accomplished by throwing contiguous ligatures around the entire periphery of the gland, by which procedure the fact was expected to be established that it was not from any absorption of the gland

substance but because of a lack of its internal secretion that the pancreatic reaction was obtained in the urine. (3) Partial extirpation; usually of the right half of the gland. (4) Total extirpation, by which it was desired to control the reactions obtained from peripheral ligation and eliminate the factor of fat splitting in the necrosed areas.

In Group I (Table IV) we find the reaction appearing between 24 and 48 hours and ceasing about the 96th hour, at which time we may assume the resumption of the internal secretion, after the subsidence of the local reaction. These dogs recover completely their normal health.

TABLE IV.—SYNOPSIS OF DOG EXPERIMENTS.

Group	Reaction ante operation	Reaction 24 hours post operation	Reaction 48 hours post operation	Reaction 72 hours post operation	Reaction 96 hours post operation	Reaction 120 hours post operation
I. Segmental ligation	—	—	+	—	—	—
II. Peripheral ligation	—	+	+	+	+	—
III. Partial extirpation	—	+	+	+	+	+
IV. Total extirpation	—	+	+	+	+	+

In Group II (Table IV) the reaction is exceedingly prompt, especially if the operation is done during the period of active absorption from the bowel, as is evidenced by the lymphatics being full of chyle, and it remains permanent to death, which occurs usually between the twenty-fourth and forty-eighth hour. Glycosuria intervenes in the interim, immediately, if the above-mentioned absorption is going on. Postmortem extensive and active fat necrosis is always found, being more marked the longer the dog lives, a few hours making a great difference. Careful examination has failed to reveal any rupture of the enveloping serous membrane by the gland, although it is very tense and swollen, which would tend to the deduction that the ferments escape into the free peritoneal cavity by transudation.

In Group III (Table IV) the reaction is liable to be

delayed somewhat because of the secretion obtained from the uninjured one-half of the gland; but when once established is persistent until death, which occurs in from two to four weeks or longer from malnutrition. Toward the last, however, the dogs in this series refused to eat, and then only did the reaction fail. At postmortem the bowels were completely empty and the remaining portion of the gland enormously hypertrophied.

The results in Group IV (Table IV) are exactly comparable to those of Group II, except that the dogs lived a day or so longer, perhaps accounted for by the elimination of the toxic tryptic ferment. Proof that the fat necrosis was not the etiological factor is also hereby demonstrated.

Previous to each operation negative pancreatic reactions were obtained in every dog. The urines were all obtained uncontaminated, either by catheter or by being caught. The controls in every instance were negative. The typical stools and the rapid development of emaciation and languor have formed perfect clinical pictures when the animal lived long enough to develop this condition, as in Group III.

It would seem from these experiments outside of their value as corroborative evidence, that there is some abnormal substance excreted in the urine in cases of deranged internal secretion of the pancreas, that the gland proper is not absolutely essential to the well being of the dog, if its destruction is accomplished gradually, but that the internal secretion which seems to originate from the islands of Langerhans is most vital. It is not difficult to draw similar conclusions from an analogous condition in the human, namely in cases of atrophic pancreatitis; here the gland tissue is practically nil, but the islands of Langerhans seem to be intact if one might judge clinically, for the excretion of the substance giving the pancreatic reaction is certainly stopped after elimination of the irritant factor by operation, the patients recovering in a very short time a condition of health which they had not enjoyed for many months.

The most plausible explanation why these bodies which secrete their as yet hypothetical product internally are not destroyed at the same time as the remainder of the gland, is

that they receive an entirely different nerve supply from the sympathetic, and for the same reason it might be inferred that their secretion would be more liable to be disturbed by either direct or reflex irritation.

These observations certainly seem to illustrate rather aptly the remarks of Dr. W. J. Mayo to the effect that "the surgeon cannot intelligently operate upon organs of double function without a full knowledge of their internal as well as their external secretions, for therein may lie the cause of the failure of a mechanically well executed operation to cure the patient."

Conclusions.—While the above experiments and observations are of course too few to be considered final, the following conclusions may be tentatively made. Briefly the appended data indicates the premises and the deductions.

1. There is some substance excreted in the urine in cases of pancreatic irritation, as shown by the pancreatic reaction (dog and man).

2. The external secretion is not responsible for it (dog).

3. Therefore there must be an internal secretion (dog).

4. Interference with its production causing therefore a disturbance of the internal metabolism (dog).

5. The catabolism in the blood not being complete the substances are excreted as foreign bodies in the urine (dog).

6. In atrophic pancreatitis the pancreatic reaction is positive before operation (man).

7. At operation the irritant or etiological factor of the condition is removed (man).

8. After operation the pancreatic reaction disappears within a few days (man).

9. In a few days the pancreas is incapable of completely regenerating itself (man).

10. Therefore the same conclusions seem warranted in the human as were reached in the dog (*ref.* 3, 4 and 5).

11. That the internal secretion is produced by the islands of Langerhans, or some other pancreatic structure (man and dog).

12. That while the pancreas proper may be greatly degenerated these islands probably remain intact (man and dog).

13. That when there is no irritation these islands continue to secrete and no pancreatic reaction is found (man).

14. That irritation causes inhibition of the secreting properties of these islands, evidenced by the pancreatic reaction (man).

15. That removal of this irritation allows the patient to recover health (man).

16. Therefore the external secretion of the pancreatic gland is not more essential to either human or dog than the internal secretion.

Analytical.—1. In 62 cases of pancreatitis the urinary reaction was positive in 82 per cent. and negative in 18 per cent.

2. Positive reactions were obtained in all cases of subacute and all of the more marked chronic types of pancreatitis.

3. The negative results were obtained in cases of moderate localized chronic pancreatitis of interlobular type.

Statistical.—1. 293 cases of pancreatitis, stones were present in 77 per cent.; 52 per cent. in the gall-bladder and 25 per cent. in the common duct. Cholecystitis was marked in 33 per cent., *per se* and plus other factors.

2. In 3095 operations on the gall-bladder and biliary tract 9.5 per cent. of the cases were accompanied by gross changes in the pancreas. In 394 operations in which stone was found in the common duct 19 per cent. were accompanied by gross changes in the pancreas.

Inferential.—1. The disturbance of internal secretion of the pancreas is responsible for the pancreatic reaction; that this may be effected by reflex irritation as well as by direct, which may prove the forerunner of gross changes in the gland.

2. A typically positive reaction with a negative control is almost pathognomonic of pancreatic derangement. The converse is not shown.

My thanks are due to Dr. W. J. Mayo for suggesting the above study and placing at my disposal his clinical material; to Dr. L. B. Wilson, Director of the Pathological Laboratory, for his advice and personal interest, and to Dr. George Eusterman for his valuable assistance in the experimental work.