the appearance of being devoid of reasonable support. Practically tested, as I have endeavoured to test it, it signally fails.

I am glad to express my indebtedness to my Resident Physicians, Drs. Krause, Deuchars, and Lang Todd, for the careful help they have given me in this investigation.

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ON THE RESULTS OF THE "PANCREATIC REACTION,"

AND ON THE DIAGNOSTIC VALUE OF AN ANALYSIS OF THE FÆCES IN DISEASES OF THE PANCREAS.

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In a paper which I read before the Royal Medical and Chirurgical Society on March 13th, 1906, I described an improved method of performing the so-called "pancreatic" reaction in the urine, and gave my experience of the reaction with 100 specimens derived from 94 cases. I now have records of over 1,500 samples of urine derived from 1,475 cases. The large majority were sent to me by medical men in various parts of the country for diagnostic purposes, and it is owing to their kindness in furnishing me with the results of operations and the after-histories of their cases that I am able to compare my analytical findings with the clinical conditions present in most of them. I take this opportunity of thanking them for their courtesy and ready response to my letters of inquiry.

The cases may be divided into eight main groups:

I.—ACUTE PANCREATITIS.

All the 13 cases in this group gave a positive pancreatic reaction; 6 were operated on, and the pancreas was found to be acutely inflamed in all, with disseminated fat necrosis in 5. The diagnosis was confirmed by *post-mortem* examination in 3. Gall stones were discovered in the common bile duct of 2. One had a history of repeated attacks of jaundice with spasm, and had probably suffered from common duct cholelithiasis, but there was no jaundice at the time of the analysis. In 3 the pancreatitis was the sequel of an attack of mumps, but in 4 other cases of the same disease the urine gave no reaction. Two cases gave a history of indigestion and abdominal discomfort extending over several months previous to the attack. Three of the patients operated on died, and 3, including the 2 in which gall stones were found, recovered. All the patients not operated on died, except the 3 in which the pancreatitis followed mumps.

II.—CHRONIC PANCREATITIS.

Chronic pancreatitis is rarely, if ever, a primary disease, but when once it is established it is liable to steadily progress, and may seriously interfere with the metabolic processes of the body, eventually leading to glycosuria in some cases. To merely make a diagnosis of chronic pancreatitis is not enough, the primary cause of the condition must be determined if a successful line of treatment is to be pursued, and by considering the clinical condition together with the results of an analysis of the excreta this can generally be done.

The causes of chronic pancreatitis are numerous, but many of these are rare. I have divided my cases into the following classes:

1. Associated with Gall Stones or Local Malignant Disease.

I have examined specimens of urine from 264 cases in which gall stones were found at operation, and of these

149 (56 per cent.) gave a positive reaction. In 183 cases the gall stones were in the common bile duct, and of these 131 (69.6 per cent.) gave a positive and 57 (30.4 per cent.) a negative pancreatic reaction—percentages which correspond fairly closely with the proportions of cases in which the common bile duct lies embedded in the pancreas (62 per cent.) and runs in a groove on the surface of the gland (38 per cent.) On dividing these cases into groups according to whether bile was or was not detected in the urine, it is found that out of 128 with jaundice 91 (71 per cent.) gave a positive pancreatic reaction, and out of 60 non-jaundiced cases 40 (66.6 per cent.) gave a positive result.

A more or less marked reaction for urobilin is a most useful indication of the probable presence of gall stones in the common bile duct, especially when they are "floating." In this series of 188 cases it was met with in 123 (65.4 per cent.), being more common where the calculi did not give rise to jaundice, namely, 47 cases (78.3 per cent.), than in those in which there was obstruction of the bile flow, namely, 76 cases (59.3 per cent.). A deposit of calcium oxalate crystals was met with in 69 per cent. of those cases in which there was evidence of pancreatitis. Nine of the cases in this group which had given a positive pancreatic reaction during life were examined *post mortem* and the diagnosis of chronic pancreatitis confirmed microscopically. Specimens of urine were obtained after operation in 24 cases, 20 having previously given a positive reaction. In 14 the reaction was found to have disappeared at intervals varying from one to four weeks after the operation, but in 6 it still persisted when the last analysis was made.

Thirollox and Maugerot¹ have maintained that cholecystitis is a common, if not the commonest, cause of pancreatitis, the inflammation spreading by way of the lymphatics from the inflamed gall-bladder to the head of the pancreas. My experience does not confirm this, for out of 76 cases in which gall stones were found in the gall bladder or cystic duct at operation only 18 gave a positive pancreatic reaction and were stated to have pancreatitis; 58 gave a negative result, as did also 17 cases diagnosed clinically as cholecystitis, 6 of which were operated on, that I have included in the miscellaneous group. Bile pigment was found in the urines of 11, including 9 of those that gave a positive pancreatic reaction; 15 gave a reaction for urobilin, and of these 10 gave a pancreatic reaction. Calcium oxalate crystals were met with in the deposit from the urines of all those that gave a positive pancreatic reaction, and in 4 of those with which no reaction was obtained.

A positive pancreatic reaction was given by the urines of 2 out of 8 cases of malignant disease of the common bile duct, and 2 of growth at the ampulla of Vater. Only 1 of the 10 cases in this group gave a reaction for urobilin, and in this the liver was being invaded by the growth.

2. Secondary to Intestinal Disease and Gastric or Duodenal Ulcer.

Chronic pancreatitis is, I believe, most commonly secondary to diseases of the intestine. In most cases there is probably an infection of the pancreatic ducts by direct extension from the duodenum, the pancreatitis being primarily of the catarrhal type. This group includes 403 cases in which the clinical symptoms and results of the analysis of the urine and faeces pointed to there being disease of the intestine other than a malignant growth. Of these the urines of 211 (52 per cent.) gave a positive pancreatic reaction.

The explanation of the presence of a pancreatic reaction in about two-thirds of the cases of intestinal catarrh or enteritis I have examined is, as I have explained, probably an inflammatory condition of the pancreas due to an extension of the catarrh of the intestinal walls along the pancreatic ducts. A similar explanation also probably holds good for those cases of colitis and appendicitis in which a reaction was obtained, for in many instances these conditions are associated with a more or less marked pathological state of the entire length of the intestinal tract. A considerable number of the cases which I have included under the heading of "intestinal catarrh" had in addition some colitis, as an analysis of the faeces showed, but the disease was evidently not very marked clinically, as it was not mentioned in the reply I received to my letter of inquiry. Hyperchlorhydria, as I pointed out some time

ago,³ is a possible cause of pancreatitis. The constant excessive stimulation of the pancreas by the secretin formed by the excess of hydrochloric acid is likely to bring about abnormal physiological activity of the gland, to be followed by degenerative changes if the over-stimulation is long continued. Such I believe to be the explanation of the positive reaction with the 13 cases diagnosed as hyperchlorhydria.

The high proportion (64 per cent.) of cases in which indicanuria was a symptom is interesting, for it has been claimed by some observers that a pathological excess of indican in the urine is an important sign of pancreatic disease, while others have stated that a marked diminution is the rule. My own experience is, however, that neither the one nor the other can be relied upon as a symptom of pancreatitis; but I think that a pathological excess indicates rather the condition of the intestine, and suggests that any pancreatitis that may be present is probably the result of an ascending infection from the duodenum, while the absence of indicanuria points to some other cause. The association of urobilinuria with indicanuria and a positive pancreatic reaction, which occurred in 52 cases, indicates that the infection involved the bile as well as the pancreatic ducts. Twenty-seven of the cases in this group were operated upon, and in 25 the pancreas was said to be enlarged and harder than normal. A positive pancreatic reaction had been obtained with the urines of all. Seven were examined *post mortem*, and pancreatitis found microscopically in 4 which had given a urinary reaction during life; the other 3 had given no reaction, and the pancreas appeared normal. I have not included in this group a number of cases of glycosuria in which there was marked indicanuria, as I propose to deal with the subject of diabetes, and the application of the pancreatic reaction to the examination of urines from such cases, subsequently; but I may now state that I am convinced, from the observations I have made, that diabetes is a very common result of long-continued intestinal catarrh slowly inducing changes in the pancreas.

Catarrhal jaundice is generally assumed to be due to an inflammatory process in the duodenum extending into the ampulla of Vater, which is closed either by a swelling of the mucosa or by a thick plug of mucus. Virchow described such a case, and Osler, among others, has observed a similar condition. However this may be, it may be taken for granted that catarrhal jaundice is usually, if not always, associated with gastro-intestinal disorders, and that, owing to the close relation of the bile and pancreatic ducts, the latter will probably suffer along with the former, so that there is likely to be some pancreatitis.

A diagnosis of catarrhal jaundice was made in 53 of the cases I have examined, and in 42 of these a positive pancreatic reaction was obtained, suggesting that in rather over 79 per cent. the condition was associated with some active degenerative changes in the pancreas. Fifteen of the cases giving a positive reaction were submitted to operation because of the persistence of the jaundice, and in all of these the pancreas was found to be enlarged and harder than normal.

Occasionally one meets with chronic pancreatitis due to direct extension of an inflammatory process from a neighbouring organ, such as the stomach or intestines, but more commonly the pancreatitis in gastric and duodenal ulcer appears to be due to the associated gastro-intestinal catarrh extending to the pancreatic ducts and setting up a catarrhal pancreatitis. I have examined specimens of urine from 50 cases of ulcer of the duodenum and 47 of gastric ulcer, all of which were confirmed by operation; 27 (54 per cent.) of the former and only 5 (10.6 per cent.) of the latter gave a pancreatic reaction. In 2 of the cases of gastric ulcer and 1 of duodenal ulcer the ulcer was said to be eroding the pancreas. In 20 out of the 27 cases of duodenal ulcer there was indicanuria, and in 4 of the cases of gastric ulcer an excess of indican was also found, pointing to abnormal putrefactive changes in the contents of the upper part of the intestine, and suggesting that the pancreatitis was due to a catarrhal condition spreading from the duodenum to the pancreatic ducts. The comparatively high proportion of cases of duodenal ulcer in which a pancreatic reaction was obtained and its rarity in almost exactly the same number of cases of gastric ulcer lends support to this view. The pancreas was examined

post mortem in one of the cases of adherent gastric ulcer, and advanced cirrhotic changes were found spreading a considerable distance into the substance of the gland.

Two other diseases in which I have obtained evidence of pancreatitis, and in which it is probable that the condition is due to an ascending infection from the duodenum, are sprue and pernicious anaemia. The former is well recognized as a disease of the intestine of microbic origin, and many cases of so-called pernicious anaemia are, I believe, dependent upon an abnormal intestinal flora with autointoxication and blood destruction. Out of the 13 cases of sprue, 8 gave a positive reaction, and in 2 of these *post-mortem* examination showed pancreatitis; 4 out of the 6 cases diagnosed as pernicious anaemia gave a pancreatic reaction. In 1 of these examination after death revealed chronic inflammation of the pancreas and an ulcerated condition of the duodenal mucous membrane. Operation on 2 also tended to confirm the diagnosis of chronic pancreatitis.

Chronic pancreatitis in tuberculous cases may arise from deposits of tubercle bacilli carried by the blood stream to the pancreas, but Carnot, Opie, and others have described chronic inflammation of the gland without any specific lesion, and Carnot has experimentally proved that such changes may follow the injection of tubercle bacilli and their toxins into the duct and parenchyma. I have not been able to obtain a necropsy in either of the two cases of tuberculosis of the intestine that gave a positive pancreatic reaction. Six others diagnosed as tuberculosis of the intestine gave a negative reaction, as did also 3 of pulmonary tuberculosis.

The pancreatitis that is occasionally met with as a sequel of typhoid fever is possibly due to a specific infection travelling up the ducts, and I have, therefore, included in this group 8 cases in which typhoid was present at the time of the examination, or the history suggested that it was probably connected with the symptoms of which the patient complained. Six gave a positive pancreatic reaction.

Nearly all observers are agreed that the pancreas is frequently affected in cirrhosis of the liver. Klippel and Lefas have concluded, as the result of their observations, that the two are due to the same etiological factor, but that the pancreatic condition is independent of, and not secondary to, the lesion in the liver. As alcohol is generally acknowledged to be a common exciting cause of cirrhosis of the liver, and its use to excess gives rise to disturbances of the gastro-intestinal tract, it is not a very far cry to assume the possible dependence of the associated inflammatory changes in the pancreas upon an ascending infection from the duodenum along the pancreatic ducts, at least in some cases. I have, therefore, included 21 cases in which there was said to be cirrhosis of the liver and pancreas in this group. Fourteen of these gave a positive pancreatic reaction. In all of these the state of the liver and pancreas was determined at operation, and in 1, which had given a positive result, a *post-mortem* examination was made. I may also add 7 cases of cirrhosis of the liver that gave no reaction, but were not examined on the operating table or in the *post-mortem* room.

In the large majority of cases already mentioned the results of the pancreatic reaction were borne out by the clinical condition and observations made at operation or in the *post-mortem* room; but I now come to a group of 11 in which, although I am assured that the pancreas was enlarged and hard, no pancreatic reaction was obtained. These I have put down as cirrhosis of the pancreas, as I believe they were cases in which, although there was more or less cirrhosis the result of past inflammation, no active degenerative changes were going on in the gland substance at the time the urine was examined. To these may be added the 5 cases with gall stones in the common bile duct in which no pancreatic reaction was obtained, but the pancreas was found to be enlarged and thickened at operation, and the 5 cases in which there was cirrhosis of the liver and pancreas with a negative reaction mentioned above.

3. Associated with Diseases of the Heart, Vessels, or Lungs.

Basing his conclusions on the *post-mortem* records of Guy's Hospital, Hale White is of opinion that disturbances

of the circulation are much commoner than other causes of "congestion, cirrhosis, and hardening of the pancreas"; but in my experience circulatory disturbances are relatively uncommon causes of pancreatic troubles. Fleiner and Hoppe-Seyler both state that arterial diseases cause nutritive changes in the parenchyma, which degenerates and is replaced by fibrous tissue. I have, however, only met with 10 cases giving a positive pancreatic reaction in which it was stated that the pancreatitis which was suspected to be present was probably dependent upon arterio-sclerosis. Long-standing difficulties of venous flow, due to chronic disease of the heart, liver, or lungs, may cause fibrosis of the pancreas, as of other organs, but Opie is of opinion that passive congestion is an unimportant factor in the production of chronic pancreatitis. I have examined the urine from 6 cases in which chronic pancreatitis was said to be associated with heart disease, and obtained a positive reaction in all of them.

4. Secondary to Metastatic Deposits.

In common with other organs of the body, the pancreas is liable to be the seat of metastatic deposits of growth from malignant disease occurring in other tissues, and it may also be invaded by growths situated in the stomach, duodenum, and neighbouring organs. The resulting inflammatory changes are usually local, but give rise to alterations in the urine, which can be recognized by the pancreatic reaction. I have examined the urine from 92 cases of malignant disease, and obtained a positive pancreatic reaction in 34 (37 per cent.). Sugar was found in the urine of 2 of these cases. One of these is of particular interest, for it demonstrated very clearly the dependence of the pancreatic reaction on degenerative changes in the pancreas and its disappearance with the destruction of the gland when advanced glycosuria has been established. The patient was first seen in December, 1906. There was then an abdominal tumour, which it was thought might be pancreatic, but an examination of the urine gave no pancreatic reaction, and there was at that time no sugar. An exploratory operation was performed by Mr. Mayo Robson, and a growth of the first part of the duodenum found, but it was said to be quite free from the pancreas. On January 18th a second specimen of urine was examined and found to be free from sugar, but it gave a well-marked pancreatic reaction, suggesting that the pancreas was then involved in the disease. At the request of the patient's friends, the abdomen was reopened a few days later, and it was then found that the growth had invaded the pancreas. In the early part of May examination of the urine showed 5.25 per cent. of sugar, and a modified pancreatic reaction gave a positive result. A month later the sugar had increased to 7 per cent., and a much less marked pancreatic reaction was obtained. In July the urine contained 7.25 per cent. of sugar, and the pancreatic reaction gave only a few crystals. In August 7.5 per cent. of sugar was present, and no crystals were found on carrying out the modified pancreatic reaction. In October the urine contained 9.5 per cent. of sugar, and the pancreatic reaction was negative. The patient died deeply jaundiced on November 5th.

In 63 cases the urine gave a positive pancreatic reaction, but I have not received any reply to my inquiries as to the final diagnosis and subsequent course of the case, and so cannot say whether there was clinical evidence of pancreatitis or not.

III.—PANCREATIC CALCULI.

Pancreatic calculi are exceedingly rare. In 1903 Oser was only able to collect 70 recorded cases. The calculi probably arise as a consequence of morbid changes in the pancreatic secretion consequent upon inflammatory alterations in the glands and ducts.⁸ It has been supposed that, like gall stones, they are the result of infection of the ducts by micro-organisms. I have had the opportunity of examining the urine from 3 cases in which pancreatic calculi were discovered at operation, and 1 in which they were found *post mortem*. Three gave a positive pancreatic reaction, and 1 in which there was a large amount of sugar, and the whole pancreas appeared to be represented by fibrous tissue, gave a negative result.

IV.—PANCREATIC CYSTS.

Chronic pancreatitis is present in many cases of simple cyst of the pancreas, and there is no doubt, both on experi-

mental and clinical grounds, that it is a frequent, and probably the most common, cause of the condition.⁴ Cysts are, however, only likely to occur in the later stages of the disease when a considerable amount of fibrous tissue has formed. This, by its contraction, may cause constriction of the ducts in some places, while other parts are pulled upon and dilated, the pancreatic secretion will then tend to accumulate in the dilated portions and undergo chemical changes by which its physical characters are altered and its absorption interfered with. It is unlikely, therefore, that a cyst of the pancreas will be associated with a positive pancreatic reaction unless active degenerative changes are going on in the gland as the result of the pressure effects it may produce in the remainder of the organ or the cause of the pancreatitis still persists. Of the 4 cases of pancreatic cyst that I have examined the urines of 2 gave a positive pancreatic reaction and in 2 it was negative. One of the latter had, however, been operated on and the cyst drained for some three months before I saw him, when he still had a fistula. I had the opportunity of examining the urine and faeces from one of the cases giving a positive result three years after the first analysis. The urine then contained 4.5 per cent. of sugar, although it had been quite free before. A positive pancreatic reaction was still obtained, suggesting that the active degenerative changes associated with the presence of the cyst in the first instance were still progressing and were likely to bring about still more marked glycosuria. In one case, which was diagnosed clinically as a pancreatic cyst, but the urine of which gave no pancreatic reaction, the tumour proved at operation to be a mass of tuberculous glands pushing forward the pancreas, and in another a hydatid cyst of the liver, which had been similarly diagnosed, caused no pancreatic reaction in the urine.

V. PANCREATIC INFANTILISM.

I have examined the urine and faeces from one case diagnosed as pancreatic infantilism,⁵ and obtained a positive pancreatic reaction with the former.

VI.—MALIGNANT DISEASE OF THE PANCREAS.

The difficulty of successfully diagnosing cancer of the pancreas from chronic pancreatitis on the clinical data alone, especially when the latter is associated with obstruction of the common bile duct, is generally acknowledged to be very great. In the large majority of instances the laboratory analyses furnish information which is more conclusive than can be obtained in any other way. In cases of primary malignant disease of the pancreas the urinary pancreatic reaction is usually negative, but in a certain percentage a positive result is obtained, owing probably to the inflammatory reaction set up in the adjacent gland tissue by the irritation of the growth and the blocking of the duct. Of the 73 cases diagnosed as cancer of the pancreas that I have examined, the urines of 24 (33 per cent.) gave a positive reaction, and 49 (67 per cent.) a negative reaction. The diagnosis was confirmed by operation in 18, and by *post-mortem* examination in 7. Two of the latter had given a positive result and 5 a negative reaction, which corresponds with the proportions diagnosed clinically and at operation, which had given a positive and negative result respectively. Bile was present in the urines of 67, usually in large quantities, but only 5 gave a reaction for urobilin, which contrasts markedly with the cases in which the obstruction of the bile ducts was due to gall stones. It will be seen from these results that while the pancreatic reaction in the urine is of value as showing the presence or absence of pancreatitis in a case of persistent jaundice, it does not differentiate between those in which the inflammation is the result of malignant disease and those in which it is of simple origin. To attain this end the whole of the results secured by a complete qualitative and quantitative analysis of the urine and faeces must be considered, and these again be checked by a consideration of the clinical signs and symptoms.

VII.—MISCELLANEOUS.

In a miscellaneous group of 467 cases 461 gave a negative pancreatic reaction. Many of these were sent to me because it was thought, from the clinical condition, that there was some inflammation of the pancreas, but subsequent observation tended to disprove this and support the opinion based upon the urinary analysis in about one-third of the

cases. In the remaining two-thirds I have not received any reply to my letters of inquiry. Of the 6 cases that gave a positive reaction, 3 were suffering from diffuse peritonitis, 1 from pneumonia, 1 was a case of abscess of the liver, and 1 had pyaemia. It is possible that the pancreas was also affected in these cases, for in diffuse peritonitis and pyaemia involvement of the gland is not improbable, while in pneumonia histological changes have been observed by Chauffard and Ravaut,⁶ and Trevor,⁷ but the destruction of an excess of nucleo-proteid-containing material might also conceivably account for the positive urinary reaction.

VIII.—NORMAL.

In the last group are specimens of urine from 50 presumably healthy individuals, none of which gave a positive pancreatic reaction.

On bringing forward the results of my observations on the urine in diseases of the pancreas in 1904 I stated that "a much more extended experience dealing with a considerably larger number of cases than it has been possible so far to obtain, will be necessary before the exact value of the test can be determined," and I think that I can now safely say that this has been done. My results during the five years since this was written, which I have collected in this paper, confirm the claim I then made that the reaction is "clinically useful," especially in its improved form. I have repeatedly, and from the first, stated that I do not believe that the "pancreatic reaction" is pathognomonic, or that taken alone it will enable a correct opinion to be formed in every instance, but I do think that when the results of an examination of the urine are considered in conjunction with the clinical symptoms and an analysis of the faeces a trustworthy diagnosis is capable of being arrived at in nearly every case of pancreatic disease. I lay considerable stress on the analysis of the faeces, for from the information so obtained one can infer the extent, and often the nature, of the pancreatic mischief, and also obtain confirmatory indications as to the cause.

With regard to the pancreatic reaction itself, my clinical experience and the results of the experiments I have carried out point to its being due to the destruction of substances with a glyco-nucleo-proteid content which yield a pentose in hydrolysis with acids, and, since the percentage of pentose in the dry weight of the pancreas is nearly five times as great as in any other organ of the body and it is more loosely combined and more readily set free than the corresponding sugar in other tissues, the reaction is obtained with very much greater frequency and more constantly in lesions involving active degenerative changes in that organ than in others. A single positive reaction cannot be accepted as a conclusive indication of a pancreatic affection, but is strong corroborative evidence of clinical signs pointing in that direction. The affections that are likely to give rise to a positive reaction are usually so readily differentiated from pancreatic disease clinically that there is little or no chance of confusion on that account. Cirrhosis of the pancreas will not give rise to a reaction unless there is also some active inflammation going on at the same time, and that is probably why a negative result is sometimes obtained when the gland is found to be enlarged and hard at operation. So, too, in cancer of the pancreas there is usually no reaction, for no destruction of gland substance takes place to set free the glyco-nucleo-proteid content of the cells unless the pressure of the growth or obstruction of the duct sets up a secondary inflammation.

ANALYSIS OF THE FAECES.

The assistance in diagnosis that may be gained by an analysis of the urine in cases of suspected pancreatic disease has been acknowledged for some time by a number of independent observers, but the importance of an examination of the faeces in such cases is not generally recognized. This is partly due to a natural disinclination to undertake such examinations, but is probably also contributed to by the somewhat conflicting statements of different authors who have made such analyses. I shall endeavour to explain the causes of these differences, and to prove that, when taken in conjunction with the clinical symptoms and the results of an analysis of the urine, and particularly the "pancreatic" reaction, a quantitative and qualitative analysis of the faeces may help in the

diagnosis of affections of the pancreas and also indicate their nature and cause.

The points to which I wish particularly to draw attention are the following:

Appearance.

The frequent, bulky, soft, white motions of advanced pancreatic disease are very typical, and to an experienced eye present characters differing from those seen in biliary obstruction, *tabes mesenterica*, and other disorders with which they might be confused. They are usually whiter, more glistening, and have a peculiar odour, resembling that of rancid bacon. Such typical stools are, however, rare; first, because there is very frequently an associated obstruction of the bile flow, which alters their characters, and secondly, disease of the pancreas sufficiently advanced to give rise to such typical stools is comparatively uncommon. In the majority of cases of pancreatic disease, apart from those associated with biliary obstruction, the faeces show no characteristic change to the naked eye even when chemical analysis reveals considerable alteration in their composition.

Reaction.

The reaction of the normal faeces is amphoteric, faintly alkaline or faintly acid. A strongly alkaline or acid reaction is pathological. As a rule the stools in pancreatic disease are acid, the intensity of the reaction depending upon the degree to which the digestive functions of the gland are interfered with. I have met with two cases with markedly acid stools in which the irritation of the lower bowel was so great that it had to be washed out several times a day to allay the discomfort. In some cases the reaction is either amphoteric or alkaline, occasionally strongly alkaline, but in these the pancreatic disease is associated with biliary obstruction, in which the stools are usually alkaline, or is secondary to an intestinal catarrh, which generally gives rise to faeces with a markedly alkaline reaction.

Microscopical Examination.

Microscopical examination of the bulky white stool of advanced pancreatic disease shows numerous fat globules, fatty acid crystals, and undigested muscle fibres. Muscle fibres, provided that the patient is not an excessive meat eater and the digestive functions of the stomach are being normally carried out, are particularly characteristic, and are best and most frequently seen in cases of malignant disease of the pancreas. Fat in the form of undigested globules is also fairly characteristic, but it must be remembered that fatty stools are also met with in biliary obstruction, apart from disease of the pancreas; in diseases of the intestinal tract where absorption is interfered with, such as sprue, tuberculosis, or malignant disease of the intestine where the retro-peritoneal lymph glands are involved and there is blocking of the lymph flow; and in persons on a milk diet, or who are taking much cod-liver or olive oil. The earlier stages of diseases of the pancreas produce little or no change in the microscopical characters of the stools.

Chemical Analysis.

Since the preparation of fats for absorption by the intestine is peculiarly a function of the pancreatic juice, it is to an investigation of the undigested fat in the faeces that attention has been chiefly directed in searching for signs of disease of the pancreas. The method I employ is that which I first described in 1905.⁸

Total Fat.

The percentage of total fat in the dry weight of the faeces in cases of disease of the pancreas has been found to vary very much by different observers. This has been partly due to their investigating different forms and stages of pancreatic disease, and to their not making allowance for the cause of the disease and the modifications that it may bring about in fat digestion and absorption. I have endeavoured to overcome this difficulty by arranging my cases in groups according to the cause as far as possible.

Very wide variations in the percentage of total fat have been met with in my cases, not only in different forms of pancreatic disease, but also in patients suffering from the same disorders. The average percentage has, however, been abnormally high in nearly every class.

The highest percentage has been encountered in malignant disease of the pancreas, an average of 71.3 per cent. of total fat being found in my 38 cases. Chronic pancreatitis appears in severe cases to interfere with fat digestion and absorption almost as much as malignant disease of the gland, the average in 52 cases of chronic pancreatitis associated with gall stones in the common duct and jaundice being 56.6 per cent., and in 8 cases of cirrhosis of the pancreas 36.2 per cent. Müller has attributed the steatorrhoea in pancreatic cases with jaundice entirely to absence of bile.⁹ A very considerable increase of fat in the stools may result from simple biliary obstruction, but the increase is usually greater when there is an associated affection of the pancreas. Although the average of total fat in my cases was nearly always abnormally high in every group in which disease of the pancreas was present, and the highest readings obtained were very markedly in excess of the normal limit of about 25 per cent., the lowest were not infrequently much under the normal limit of about 15 per cent. This is at first sight contrary to what might be expected, but the explanation is that these were cases in an early stage where as yet the secretion of the pancreatic ferments had not been interfered with, but was, in all probability, rather increased; for just as in the early stages of parotitis there is an increased flow of saliva, so in catarrhal pancreatitis there is probably also an increased flow of pancreatic juice, so that fat digestion is rather increased than diminished. In support of this supposition, it may be pointed out that the lowest readings were obtained in cases of intestinal catarrh, duodenal or gastric ulcer, and catarrhal jaundice, in which it is probable that the pancreatitis was due to catarrhal inflammation spreading from the duodenum along the pancreatic ducts. In these cases, however, the abnormal activity of fat-splitting bacteria in the intestine has also to be taken into account, and may afford an additional explanation.

Relation of Unsaponified to Saponified Fats.

The presence of an excess of unabsorbed fat in the faeces is suggestive of pancreatic disease, but a normal and even a subnormal proportion does not exclude it, especially in the early stages of a catarrhal inflammation. As I have already mentioned, steatorrhoea is also met with in other diseases, so that alone it is not of very great diagnostic value. The relation existing between the percentages of unsaponified and saponified fats is much more important, and even when an abnormally low percentage of total fat is present in the stool, a disturbance of this relation may help to confirm a diagnosis of disease of the pancreas. In normal faeces the unsaponified and saponified fats are present in approximately equal amounts, and any marked change in this relation is indicative of a disturbance of digestion. The effect of interference with the functions of the pancreas is, as might be supposed from a consideration of its work in digestion, to increase the proportion of unsaponified fat, while obstruction of the bile flow and intestinal catarrhs tend to raise the percentage of saponified fat.

The change produced by coexistent pancreatic disease and biliary obstruction depends upon the relative extent and standing of the two conditions. In cancer of the pancreas, where, as a rule, there is complete blocking of the common bile duct and serious interference with the functions of the pancreas, since the growth is most commonly situated in the head of the gland, the proportions of unsaponified and saponified fat are frequently nearly equal. Chronic pancreatitis, due to the presence of gall stones in the common bile duct and associated with obstructive jaundice, gave an excess of unsaponified fat in 29 of my cases and an excess of saponified fat in 21. Here, again, very wide variations in the percentages of each were met with, depending apparently upon the extent to which the bile flow was interfered with and the amount of damage of the pancreas.

I have examined the faeces from 7 cases of growth of the common bile duct. In 5 of these there was no evidence of involvement of the pancreas, and the saponified fat was found to be considerably in excess of the unsaponified fat. Of the two in which the pancreas was involved in the growth, and the urine gave a well-marked pancreatic reaction, one showed an excess of saponified and the other of unsaponified fat, but as the last-named was on an

entirely milk diet the results are not strictly comparable with the others, since the experiments of Abelmänn¹⁰ have shown that in depancreatized animals from 30 to 53 per cent. of a natural emulsion, such as milk, is absorbed, and that when a portion of the gland has been left as much as 80 per cent. may be digested.

Another factor which plays an important part in determining the relation between the unsaponified and saponified fats in the faeces is the distribution and activity of the intestinal flora. Owing to the defensive action of the stomach juices and the rapid passage of the chyme through the upper intestine in a healthy person comparatively few bacteria are met with until within a foot or two of the colon. In this region, and in the large intestine, a certain amount of fat saponification normally goes on from the action of bacteria of the colon group. In acute and chronic pathological conditions of the gastro-intestinal tract the altered state of the secretions allows an ascent of micro-organisms above the level of their normal habitat,¹¹ and, owing to their increased number and probably also to alterations in their chemical activities, the saponification of fats is more energetically carried out, so that in cases of gastro-intestinal catarrh it is the rule to find a more or less marked excess of saponified over unsaponified fat in the faeces. Even when pancreatitis is present and there are other indications that the digestive functions of the gland are interfered with, the excess of unsaponified fat that might be expected is often replaced by an abnormally high percentage of soaps owing to the fat-splitting action of the intestinal bacteria.

It is obvious that when there is interference with the functions of the pancreas from cirrhosis consequent on past inflammatory changes and also an abnormal activity of the fat-splitting bacteria of the intestine the relation between the saponified and unsaponified fats will vary with the relative intensity of the two, and no hard and fast rule can be laid down—each case must be judged on its merits and the indications to be obtained by other methods of analysis and examination.

The varying relations found in my cases of duodenal and gastric ulcer are examples of this, and the same explanation probably holds good for the cases of sprue and pernicious anaemia that I have examined. Stones in the common bile duct and gall bladder have frequently not been found to be associated with a disturbance in the relation between the saponified and unsaponified fats in the direction that might theoretically be expected, especially when there has been no obstruction of the bile flow, and I am inclined to think that this may be due to the abnormal activity of fat-splitting bacteria, for in such cases there is generally evidence of cholangitis, and this, as well as the gall-stone formation, is probably consequent upon invasion of the biliary tract by intestinal organisms which have ascended beyond their normal limit to the level of the common bile duct.

In the early stages of catarrhal pancreatitis there is probably an increased flow of pancreatic juice, and in such cases it is the rule to find that the saponified are in excess of the unsaponified fats, often very markedly so, even when there is no evidence of abnormal bacterial activity in the intestine. This is probably due to the excess of pancreatic juice causing a higher proportion than normal of the fats to undergo saponification; and, although much of this is absorbed, leading to a low total fat reading, a higher proportion than usual appears in the faeces.

Inorganic Ash.

The excretion of calcium and magnesium salts appears to take place mainly by way of the intestinal mucous membrane, and particularly through the large intestine. Normally the proportion of inorganic ash in the faeces lies between 10 and 15 per cent., but when from any cause there is a catarrh of the intestinal walls this percentage is increased, and I have met with readings as high as 45 and 46 per cent. These have usually been cases where there has been well-marked chronic colitis. The occasional association of intestinal sand with muco-membranous colitis, and more rarely with diarrhoea, was pointed out by Dieulafoy, but I believe I was the first to show that an increase in the proportion of inorganic ash occurs in all cases of colitis.¹² Such an increase was found in each of the 30 cases of colitis that I have examined, the average for the 30 being 25.3 per cent. In appendicitis, intestinal

catarrh, and growth of the intestine, particularly of the colon, a similar, although less marked, increase has usually been met with, probably because in these too there is some colitis. For although clinically the disease may appear to be more or less localized in some particular part of the intestine, it is not unlikely that other regions are also involved to a less extent; and that this is so is suggested by the occasional association of pancreatitis, as indicated by the urinary reaction, with appendicitis, and of chronic colitis with enteritis or duodenal ulcer. An excess of inorganic ash in the faeces is therefore indicative of an intestinal catarrh and more particularly of a catarrh of the colon. In such cases the stools are usually strongly alkaline in reaction.

Bile Pigment.

Bile is the chief ingredient that takes any considerable part in furnishing the colour of the stools. Its chief pigment as excreted is bilirubin. A part of this is promptly oxidized, either in the bile passages or soon after it reaches the intestine, into biliverdin and allied bodies, and, under the influence of bacteria and enzymes in the intestine, these are reduced to hydrobilirubin (stercobilin), which constitutes the normal yellowish-brown pigment of the faeces. Bile pigment, as such, never appears in the normal faeces, and in health is not met with below the caecum. Interference with the bile flow is therefore an important factor in producing alterations in the colour of the faeces, the well-known "clay-coloured" stools of biliary obstruction being the result. Since many cases of pancreatic disease in which white stools exist are associated with more or less complete blocking of the common bile duct by gall stones or growth in the head of the pancreas, the lack of bile pigment is without doubt a frequent contributory cause in their production. I have, however, met with cases of pancreatitis with white stools where there was no jaundice or biliary obstruction, and in which a chemical examination of the stools showed a well-marked reaction for stercobilin, also others in which it was demonstrated that a return of the biliary secretions to the intestine by means of a cholecystenterostomy was not sufficient to bring about a return of the normal colour when the pancreatic juice was still absent. Both in these and the clay-coloured faeces of simple biliary obstruction the large excess of unabsorbed fat is an additional and important cause of their abnormal physical characters.¹³ The whiter, more glistening appearance of the faeces in typical cases of pancreatic disease is, I believe, to be attributed to the existence of the fat largely in the form of free fatty acid crystals, which act upon light in the same way as snow and other finely crystalline substances that appear white in mass. Another factor which must not be overlooked, that also plays an important part in the production of the pseudo-acholic stools met with in other conditions where there is no icterus and possibly also no interference with fat digestion and absorption, is the action of bacteria on the faecal pigments. A certain amount of the hydrobilirubin of the faeces frequently, and perhaps always, undergoes further reduction to a colourless body, called by von Nencki "leuco-urobilin," through the action of bacteria, and it is probable that under pathological conditions this reduction may be so marked that little or no coloured pigment remains.¹⁴ I have shown by a series of experiments that the bacteria present in the white stools of pancreatic disease have the power of decolorizing normal brown stools when grown under anaerobic conditions,¹⁵ and I believe that it is to the abnormal activity of such bacteria that the absence of colour is due to a considerable extent in such cases.

It is obvious from these considerations that mere inspection of the stools is not a reliable guide as to the amount of bile pigment that is reaching the intestine, and for purposes of diagnosis this is most important to determine. Hydrobilirubin gives the same chemical reactions as the urinary pigment urobilin, with which it is closely allied, and it is only by applying these chemical tests that the presence of complete biliary obstruction can be determined with certainty.¹⁶

A more or less marked reaction for hydrobilirubin was obtained in all my cases, except 22 of malignant disease of the pancreas and 1 of cancer of the common bile duct, even when the faeces were quite white to the naked eye. In those where there was biliary obstruction from gall stones the

intensity of the reaction varied with the degree of jaundice, but traces at least were found in every one, and in all but 10 a fairly well-marked reaction was obtained, showing that rarely, if ever, does impaction of gall stones in the common bile duct produce absolute blocking. On the other hand, out of 38 cases of cancer of the pancreas complete obstruction of the duct was met with in 22, traces of hydrobilirubin were met with in 13, and in 3 only was a well-marked reaction obtained, and in these 3 the growth was situated in the tail or body of the gland. As a rule, malignant disease of the common bile duct and gall bladder does not produce the complete blocking of the bile flow usually associated with cancer of the head of the pancreas, probably because the growth in these cases is of a soft character and allows a certain amount of bile to percolate through it.

Occult Blood.

In the last few years considerable attention has been devoted to the examination of the faeces for occult blood, that is to say, for traces of blood too small to be recognized by other than chemical means, and for this purpose the guaiac, aloin, and benzidine tests have been chiefly employed. The guaiac and aloin tests are about equal in sensitiveness, both responding to dilutions of 1 to 25,000, and are useful as controls for the simpler and more sensitive benzidine test, which reacts with 1 part in 200,000 of blood. If the benzidine test is negative, it may be concluded that no blood is present, and it is not necessary to proceed further, but if it is positive, it is advisable that the result should be controlled by the aloin or guaiac test. If these are also positive, the presence of occult blood is indicated, but if, on the other hand, they are negative, the presence of occult blood should be regarded as doubtful, and a further examination be made on a future occasion. Hence, a positive benzidine test shows nothing unless corroborated by one or both of the other tests, but a negative benzidine test is proof positive of the absence of occult blood.¹⁷

I have examined 579 specimens of faeces with these tests, and obtained evidence of the presence of blood in 89. It has been said that occult blood is found in the faeces constantly in malignant disease of the gastro-intestinal tract, whereas in simple ulceration it is only met with at intervals. My experience would tend to confirm this, for out of 25 cases of malignant disease of the intestine I found it in 22, in 23 of growth of the stomach it was present in 18, but in 21 cases of duodenal ulcer a positive result was only obtained in 5, and in 16 cases of ulcer of the stomach in 5. In several of the cases of simple ulcer a series of five or six examinations on succeeding days was made before a trace of blood was found. Cancer of the pancreas is very frequently associated with the presence of occult blood in the stools. In 25 of my 38 cases a positive result was obtained. The haemorrhagic tendency that is known to be present in chronic pancreatitis is sometimes shown by the presence of blood in the faeces, and in advanced cases serious haemorrhage may take place from the intestinal and other mucous membranes; in 2 of my cases such haemorrhage was the cause of death. This haemorrhagic tendency was the probable explanation of the positive reaction for blood given by the stools of 2 of my cases of chronic pancreatitis associated with jaundice and the presence of gall stones in the common duct, and 4 cases of pancreatitis in which there was no biliary obstruction. I was able to detect blood in the faeces of 4 out of the 7 cases of malignant disease of the gall bladder, and in 2 out of the 6 cases of growth of the common duct that I have examined.

Pancreatic Insufficiency Tests.

Early in the year 1908 Schlecht¹⁸ described a method of estimating the functional activity of the pancreas, based upon the observation of Müller,¹⁹ that it was possible to detect the presence of trypsin in the faeces by its action on a serum plate. I have employed this test in a number of cases and have found that, on the whole, it is satisfactory, but the necessity for using a serum plate is a drawback. I have therefore been using lately a modification introduced by Gross,²⁰ which is based upon the fact that pure casein, which is readily soluble in an alkali, is promptly precipitated by acetic acid from such a solution, in contrast to its digestion products. I have employed

this test in about 60 cases of suspected pancreatic disease, and find it a useful additional aid in diagnosis.

More recently Heiberg²¹ has introduced a modification of Gross's test, in which a series of progressive dilutions of the faecal extract are incubated for a fixed time with the same quantity of casein solution. This method has the merit of frequently shortening the time of the examination, and also enables the various samples to be examined together and compared. I have made use of this test, along with Gross's method, in the last 30 specimens that I have examined, and I find that the results compare very well. For the reasons I have mentioned, I think that Heiberg's method is to be preferred.

It must be remembered that these insufficiency tests only indicate very gross changes in the digestive functions of the pancreas, and so are only of limited value when taken alone, but when considered in conjunction with other methods of examining the faeces and urine they certainly assist one in arriving at a more reliable opinion as to the condition of the gland.

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GALL STONES: ACUTE PANCREATITIS: RECOVERY.

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THE following case appeared at the time to be one of great obscurity, and was not made clear until a laparotomy was performed.

On September 20th, 1909, I was called to a married woman, aged 35, who complained of acute spasmodic pain in the upper part of the abdomen and of constant retching and vomiting of all foodstuffs.

Previous History.

Her previous history gave evidence of a gouty diathesis with a disposition to asthma and muscular pains. Two years ago she had had an acute attack of abdominal pain, attributed to appendicitis, which entirely cleared up. She had a similar attack in the spring of 1909, which also cleared up. She stated that for several months she had had a constant dull pain under the right lower ribs, as if "there were something to come away," that she had had daily effortless vomiting of food, bringing up simply acid gastric contents, never any blood; that the bowels had always been constipated, requiring daily aperients. She had never been jaundiced, had had frequent attacks of distension of the abdomen, with flatulent eructations and rapid pulse-rate. She had always suffered from menorrhagia, and had had two children, the younger being 18 months old; at the last confinement she had phlegmasia dolens in both legs and pleurisy on the right side. Latterly she has fallen into very poor health.

Present Illness.

The present illness began with acute pain in the upper part of the abdomen, coming on spasmodically, leaving in the intervals a dull pain in the epigastrium; vomiting and retching was continuous; the bowels had not been moved for two days. The temperature was 99.6°, pulse 110, respirations 18; the abdomen was generally distended and tender all over, but tenderness on pressure was more marked over a point to the right of the umbilicus and a point in the epigastrium midway between the umbilicus and the right costal arch. There was no jaundice, the skin perspired freely, the heart, lungs, and urine were normal. She was ordered an opium mixture, which was vomited, and fluid nourishment.

Course.

On September 21st I found that vomiting continued, though a little fluid nourishment had been retained. Temperature normal, pulse 90; the distension of the abdomen continued, also the tenderness over the areas mentioned. The bowels freely moved with a cascara mixture. This attack subsided in three days; solids were taken easily, though occasionally vomited, and she was able to get up on a couch, but a certain amount of distension of the abdomen and the tenderness at the painful spots remained.

On September 30th she was again attacked with the same symptoms, and next day the symptoms were more severe, the abdomen more distended and more tender; temperature 99.6°; pulse 110. The bowels had been relieved by aperients and she was given morphine $\frac{1}{2}$ grain. She had no sleep for two nights.

Mr. Moynihan, of Leeds, saw her in consultation on October 3rd. The abdomen was very distended but moving slightly with respiration; the painful areas to the right of the umbilicus and in the right of the epigastrium were very tender. Temperature 100°; pulse 114 to 120; respiration normal. There was also a sensation of great soreness over the lower ribs on both sides. Mr. Moynihan considered the condition one of appendicitis primarily, complicated with gall stones, and advised waiting for the acute symptoms to pass and an operation in a quiet interval.

The same night the patient became very ill. The temperature on the morning of October 4th was 100.2°; pulse, 130. She had had a sleepless night, with great pain in the abdomen, so much so that $\frac{1}{2}$ grain of morphine was injected. The knees were drawn up, and the abdomen was much distended, very painful to touch, though still moving slightly with respiration. All food by the mouth was stopped, and nutrient enemata with saline solution given by the rectum. The patient developed the facies abdominalis, and for the first time was slightly jaundiced. An operation was again considered, but rejected, it being thought advisable to wait for the subsidence of the acute symptoms.

For two days this condition continued, when the symptoms began to subside, first fluids and then solids being taken by the mouth. The temperature varied from 98.4° to 100.2°, and the pulse from 100 to 128.

On October 6th the patient complained of acute pain over the lower ribs on the left side and just about the splenic area. The skin was acutely painful to the touch; a thin layer of fluid was made out over the base of the left lung. Firmly applied strapping relieved the pain and enabled the patient to breathe comfortably.

On October 10th the patient was taking soft solids; temperature normal and pulse 100. The jaundice had disappeared but the pain in the left side continued; the abdomen had subsided, but became suddenly distended at times, the distension being invariably relieved by turpentine enemata; the before-mentioned painful areas still remained tender.

This condition continued until October 21st, when all the symptoms returned with full force—retching, copious vomiting, and hiccough—with the same peristaltic pain and distension in the abdomen; pulse 110 to 126, temperature 100.2°. Her aspect was that of acute illness—dusky lips and dusky patch on each cheek, the legs were drawn up, and pain was complained of with the slightest movement, though the abdomen still moved slightly with respiration.

Operation.

This condition continued until October 23rd, when a laparotomy was performed by Mr. Moynihan. An incision was made in the right linea semilunaris from the costal border to just below the umbilicus. The appendix was first searched for; the caecum was pulled up and the appendix removed; there were some adhesions about its base, and it was long and of a small lumen. There was no other change. It was noticed that the whole of the large intestine was much distended. The gall bladder was next examined; small gall stones were felt in it. A general survey of the abdomen was then made; some adhesions were discovered about the tail of the pancreas, and on separating these several ounces of blood escaped, showing that there had been a recent haemorrhage about the pancreas at the splenic end. Patches of fat necrosis were then found scattered about the omental and mesenteric fat, more marked in the neighbourhood of the haemorrhage; there was a patch on the mesentery of the removed appendix; on gently examining the whole pancreas it was found very much swollen, but there were no further haemorrhages. The gall bladder was then opened, and some dozen or so small rounded gall stones removed; the bile ducts were explored and found free from stones; the ampulla of Vater was found empty. A large rubber tube was then inserted into the gall bladder, which was drained in the usual way. The pulse-rate during the operation rose to 150.

After-History.

The patient made an uneventful recovery; the gall bladder was drained for three months, and then allowed to close.

MISS ELLEN ELIZABETH BOND, of Lancaster, who died last May, has set aside the residue of her estate, amounting to about £10,000, on trust for the erection of a sanatorium for the relief and cure of consumptives. There is a proviso that if a more beneficial cure has in the interim been found than the open-air treatment, then the money shall go to a home for incurables. She desires the home shall be erected in the neighbourhood of Lancaster, and that the residents of the latter borough shall have first claim; further, that the sanatorium be called "The James Bond Sanatorium for Consumptives," and that rooms be called after her brothers, John Bond and Edward Thomas Bond. The testatrix makes certain suggestions to the trustees, but specifies that they are not binding, the trustees having absolute discretion in the matter.