Post-Graduate Medical Journal

LONDON, SEPTEMBER 1944

THE DIAGNOSIS OF CHRONIC PANCREATITIS

By NEVILLE SOUTHWELL, M.A., M.B. (Cambridge), M.R.C.P. (London)

(Medical Tutor and Acting Medical Registrar, Guy's Hospital)

The clinical entity envisaged by the term "chronic pancreatitis" is almost invariably produced by widespread fibrotic changes in the pancreas. The cause for these changes is thought to be predominantly infective, either from the biliary apparatus or the gastro-intestinal tract, although in some cases it does appear that the entry of non-infective bile or the regurgitation of pancreatic juice into the pancreatic duct will produce pancreatic fibrosis.

It might be expected that this sclerosis of the pancreas would be preceded by a more active degeneration of the gland, and in a number of cases in all probability this is so. However, the clinical recognition of this earlier stage presents an almost insoluble problem, and in those cases in which the disease is diagnosed the underlying pathology is nearly always the later schirrous type of pancreas. It is seldom possible to do more than suspect the condition at the earlier stage, and that only by constantly bearing in mind its possibility in those conditions with which chronic pancreatitis has been found to be most often associated.

CLINICAL FEATURES

(a) With early disease.

The onset of chronic pancreatitis is insidious, and the symptoms at the beginning are rarely of a definite nature. Not unnaturally in those cases which are associated with an infective factor in the stomach, intestine, or biliary apparatus, the symptoms are apt to be overshadowed by those of the antecedent condition. Consequently a history of various kinds of dyspepsia may be expected. The story will of course depend upon the primary disease, but probably symptoms suggestive of gall-bladder disease are the commonest. Frequently there are complaints of a vague indigestion and abdominal discomfort with some distension, but not especially indicative of any particular condition. Less often the history may suggest gastric or duodenal ulceration.

There is no single symptom one can mention which is pathognomonic of early pancreatic involvement. It is true that a few cases get pain quite early on, but although the character of this pain may be highly suggestive, the cases in which it occurs comprise only a small proportion of the total. This pain is situated in the epigastrium, and may be of some severity. It is periodic and bears no relation to food, and it tends to pass through to the back. It is often accompanied by nausea.

It is said that undue fatigue after meals is a sign that the pancreas is involved. This fatigue is so overwhelming in some cases that the patient feels compelled to go straight away to rest and sleep after meals, and usually does so.

There is no evidence of pancreatic insufficiency in the stools until widespread damage has been done to the pancreas, consequently at this stage no help can be obtained from biochemical investigations.

(b) With established disease.

As the fibrosing process in the pancreas progresses, clinical indications of its presence become more obvious.

(1) There is usually evidence of pancreatic insufficiency. Food is imperfectly digested, and dyspepsia becomes more pronounced. The intestines tend to become distended with gas, and colicky pains are felt. There is often the passage of a considerable amount of flatus

These symptoms are of course not to be regarded as pathognomonic of pancreatitis, as although their presence in this disease is common, they are also found in most other types of dyspepsia.

Changes in bowel habit, and the macroscopic appearance of the stools are both extremely important features. The bowels are open more frequently than usual, but not as a rule more than two or three times in the day. The stools themselves are often quite characteristic of pancreatic disease. They are fully described later in this article under the heading of steatorrhea.

(2) *Jaundice*.—Jaundice is of considerable importance in pancreatic fibrosis. It occurs in many cases, and at first may possibly be due to simultaneous infection of the biliary passages. Later, however, it slowly and progressively deepens, and irritation of the skin and other notable findings proclaim that the jaundice has become of the obstructive variety. In this case it has been assumed to be due to pressure on the common bile-duct by the fibrosing process in the pancreas.

(3) *Pain*.—Pain in most cases is still inconspicuous. Sometimes, however, it may be severe and paroxysmal; it may be of sufficient intensity to resemble biliary colic. The pain differs inasmuch as it passes through to the back on the left side, often in the region of the shoulder-blade. It is described by the patients as boring in nature.

The cause of the pain in these cases may be a stone or stones in the pancreatic duct, or persistence of subacute necrosis in the gland. It is worth while having an X-ray taken in these cases, as pancreatic calculi are extremely dense and radio-opaque.

(4) *Tenderness*.—This is never a striking feature in chronic pancreatitis. It may be present in a minor degree in those cases in which there is much pain, and then the point of maximal tenderness is in the epigastrium in the mid-line, or just to the right of it.

(5) *Pressure*.—In a small number of cases pressure is exerted by the fibrotic head of the pancreas on the portal vein or even the duodenum. In these circumstances there will be consequent ascites, or symptoms and signs of pyloric obstruction.

(6) *Diabetes*.—Diabetes is a most uncommon complication of chronic pancreatitis. It does sometimes occur in very chronic cases, but on the whole the presence of glycosuria is more often associated with acute or subacute necrosis of the gland.

(7) *The gall-bladder*.—There is usually some enlargement of the gall-bladder, but in practice it is difficult to be certain of this on palpation. It is not uncommon to find an enlarged liver which may feel unduly firm or even hard. In cases associated with gall-stones the gall-bladder will of course be small.

LABORATORY INVESTIGATIONS

The functions of the pancreas are to provide an internal secretion—*insulin*, and an external secretion—*pancreatic juice*, which contains ferments acting on the three main groups of food-stuffs, namely *lipase* on fats; *trypsin* on proteins; and *diastase* on carbohydrates. The clinician is often able to obtain valuable confirmatory evidence of a presumptive diagnosis of pancreatic disease from the laboratory tests of pancreatic efficiency. Unfortunately from this point of view the pancreas, like most other organs, has a considerable reserve of power, and only extensive disease will result in appreciable impairment of its function. For this reason it will be apparent that although evidence of impaired pancreatic function may clinch the diagnosis, normal pancreatic efficiency tests do not negative the diagnosis.

Defects of internal secretion.

(1) *Hyperglycaemia*.—It is exceptional to find glycosuria in chronic pancreatitis. If a diabetic sugar curve is present it certainly means very extensive pancreatic fibrosis indeed.

(2) *Loewi's test*.—In 1908 Loewi introduced his interesting adrenaline mydriatic test. Adrenaline of course, in the normal subject, produces no alteration in the size of the pupil when dropped into the conjunctival sac. Working in Vienna, Loewi produced mydriasis in depancreatized cats and dogs after instilling adrenaline into the eye. In the human subject the procedure is to drop two or three drops of 1:1000 adrenaline solution into the conjunctival sac of one eye. A positive result is indicated by conspicuous dilatation of the pupil in half to one hour. The test is only positive in a small proportion of cases of chronic pancreatitis, but if it is so, it offers valuable confirmatory evidence of pancreatic damage. It is interesting to note that the test may be positive in diabetes and in Graves' disease. That the latter condition has

an occasional association with chronic pancreatitis is suggested by the rare occurrence of exophthalmos and a positive Von Graefe's sign in chronic pancreatitis. Moebius and Stellwag's signs may also be positive in both diseases.

Defects of external secretion.

(1) *Steatorrhoea*.—Steatorrhoea is probably the most important single sign of pancreatic insufficiency. It was recognised as a sign of pancreatic disease by Kuntzmann as early as 1820, and in 1832 Richard Bright noted it independently.

(a) Naked-eye appearance of the stools.

The stools are always large, and may be extremely large. They are liquid when they are first passed, and they set on cooling. The fat remains separate from the faecal material, and is visible as fat, a fact noted by Bright. This separation is a valuable sign of pancreatic steatorrhoea, and is not found in the steatorrhoea due to malabsorption.

(b) Microscopical appearance of the stools.

Oily globules, but no excess of fatty acid crystals are visible under the microscope.

(c) Chemical findings in the stools.

In the dried faeces of the normal subject not above 25 to 30 per cent is composed of fat, of which proportion not more than 20 to 25 per cent is present in the form of unsplit fat. In disease of the pancreas there is an increase in the total fat content of the stools, and more particularly an excessive proportion of unsplit fat. The amount of fat may total 70 to 80 per cent of the faeces, and of this fat as much as 40 to 70 per cent is unsplit.

(2) *Creatorrhoea*.—The passage of undigested meat fibres in the stools is known as creatorrhoea. This indicates deficient protein breakdown by trypsin. The patient must of course have been on a diet which includes meat or poultry for a day or two before the investigation is made. Creatorrhoea may accompany severe diarrhoea from any cause, but in combination with steatorrhoea its presence is of considerable significance; moreover it is not affected by blocking of the bile-duct.

(3) *Urinary diastase*.—A unit of diastase is the amount which will digest 1 c.c. of 0.1 per cent soluble starch in 30 minutes at 37 degrees C., so that no blue colour is obtained on adding iodine. The diastatic index is the number of units in 1 c.c. of urine, and normally varies between 5 and 30. The index is raised in most forms of pancreatic disease, especially the acute forms, although in chronic pancreatitis it is seldom grossly raised, and may occasionally even be low. The test should, however, be made as a routine, and a 24-hour specimen will be required.

Laparotomy.

A number of cases diagnosed as chronic pancreatitis will ultimately undergo laparotomy. These will be jaundiced patients in whom the jaundice has persisted for 2 to 3 months. The object of the operation is twofold. In the first place the distressing symptoms of the jaundice can be relieved by cholecyst-enterostomy, and in the second place the operation will have considerable value from the diagnostic and thus the prognostic aspect, as the surgeon will be able to examine the pancreas. Even so there will be some cases in which doubt still exists or mistakes are made, and only the subsequent course of the illness after palliative cholecyst-enterostomy will decide whether the case has been one of carcinoma of the pancreas or chronic pancreatitis.

DIFFERENTIAL DIAGNOSIS

Other causes of steatorrhoea can as a rule be distinguished clinically and by the chemical analysis of the stools, in which the characteristic abnormal split to unsplit fat ratio of pancreatic disease will be lacking.

(1) Sprue.

Apart from the existence of steatorrhoea there are few common features, and many points of difference. The history of residence abroad, the frequency of glossitis, the existence of the different types of anaemia, the achlorhydria, the occasional presence of clubbing of the fingers, are some of the striking clinical features which will be absent in chronic pancreatitis.

(2) Idiopathic steatorrhoea. (Non-tropical sprue, or Gee's disease.)

Here again there is little likelihood of confusion. Many of the features already noted in sprue may be present in idiopathic steatorrhoea, and there may also be additional clinical points of distinction from chronic pancreatitis, such as the presence of a particularly sallow complexion, or even real pigmentation or dermatitis. Tetany, bending of bones, and other evidence of calcium lack, even spontaneous fracture may occur.

(3) Lacteal obstruction.

Differentiation of chronic pancreatitis from lacteal obstruction may present considerably more difficulty than is the case with sprue or idiopathic steatorrhoea, because the clinical picture is by no means so well defined.

Lacteal obstruction as a cause of steatorrhoea was recognised as long ago as 1853 by Gull, who described a case in the Guy's Hospital Reports. He was well aware of the difference of the steatorrhoea in this condition and chronic pancreatitis, and described the stools in the two diseased. Referring to a case of lacteal obstruction due to mesenteric glandular tuberculosis, he wrote:—

"The bowels were generally moved three times in the twenty-four hours. The evacuations were pultaceous or liquid, of a dull chalky colour, frothing like soap when a stream of water was poured on them. Under the microscope they were seen to contain muscular fibre in different stages of disintegration, starch cells, and finely divided oily and granular matter like chyle, and inflammatory exudation."

The presence of meat-fibres in the stools in lacteal obstruction may suggest the creatorrhoea of pancreatic disease. It is not uncommon in the former condition, and is simply a manifestation of the diarrhoea.

Apart from the character of the stools a feature which may serve to differentiate chronic pancreatitis from the other forms of steatorrhoea is the occurrence in the latter of tetany. Tetany is probably due to excessive excretion of calcium soaps, which should not take place when unsplit fats are passed.

Lacteal obstruction is usually due to tuberculous disease of the mesenteric glands, very much less often to non-specific fibrosis, and extremely rarely to Hodgkins disease or lymphosarcoma. Consequently in any case of steatorrhoea the cause of which is not apparent, a careful search should be made elsewhere in the body for the presence of these diseases, especially in the lungs, joints and glands.

The other group of cases in which the possibility of chronic pancreatitis will arise is those in which an obstructive jaundice of uncertain origin has persisted for some considerable time.

(1) Catarrhal jaundice.

The differentiation from catarrhal jaundice presents little difficulty. The acute onset with temperature and malaise, the nausea and vomiting, the tenderness, and the short clinical course with full recovery will be sufficient distinction.

(2) Gall-bladder disease.

Obstructive jaundice with severe pain should suggest gall-stones in spite of the occasional occurrence of paroxysmal pain in chronic pancreatitis. The distribution of the pain is, of course, quite different in the two conditions, although left-sided pain is not unknown in gall-bladder disease. The radiographic findings will be of the greatest assistance. It is important to be cautious in the use of cholecystography in patients suffering from obstructive jaundice. Where severe liver damage is present alarming reactions may follow the cholecystogram, even in some cases a state of hepatic coma.

(3) Carcinoma of the pancreas.

In many cases it is possible to decide that the pancreas is diseased, but it may be extremely difficult to say whether the lesion is neoplastic or fibrotic. In both conditions there may be steatorrhoea or jaundice, or both. In both conditions the gall bladder is likely to be enlarged, except in those cases in which chronic pancreatitis is a sequel to, or existing in, association with inflammation of the gall-bladder.

Differentiation between the two conditions cannot be made on any single or particular factor, but rather upon the clinical condition as a whole. A patient with carcinoma of the pancreas is usually very much more ill than is the case with the fibrotic condition. There is a much greater degree of weakness and loss of weight with progressive emaciation in pancreatic carcinoma than is the case in chronic pancreatitis.

Pain if present at all is a much more prominent feature in carcinoma than in pancreatitis. The pain has the characteristics of pancreatic pain already described. It differs from the pain of pancreatitis both in its intensity and its persistence. It is referred to by patients as a "boring" pain, and is felt deep in the abdomen. Like the pain of chronic pancreatitis, it extends through to the back, but it is more often bilateral than confined to the left side. Nevertheless it cannot be said that pain is a particularly frequent feature of carcinoma any more than pancreatitis, in fact in a number of cases, perhaps the majority, it is completely absent.

Chemical examination of the stools in carcinoma of the head of the pancreas may show a complete absence of stercobilin. This is not as a rule the case in chronic pancreatitis, where even with a severe degree of obstructive jaundice it is usual to find some stercobilin present, if only a small amount.

Examination of the stools for occult blood may be of some assistance. It is not uncommon to find persistent occult blood in the stools in cases of carcinoma of the pancreas, whereas this is not the case in chronic pancreatitis, unless the pancreatitis is secondary to invasion of the pancreas from an ulcer of the stomach or a neoplasm, and in most cases it will be possible to decide whether or not this is so.

Chronic morbid changes may rarely occur in the pancreas in a number of diseases besides the condition of "chronic pancreatitis." These diseases affect the pancreas in varying degree, but in none of them is there much likelihood of confusion with chronic pancreatitis, consequently they may be mentioned briefly only.

(1) Mumps.

There is some doubt whether the pancreas is ever permanently affected by mumps. Acute pancreatic involvement during the attack of mumps is real enough, although it is rare. In fact, in a series of 6,000 cases Radin was able to find only 14 cases of pancreatitis. But these were acute cases, and R. E. Smith, writing on mumps in the Guy's Hospital Reports, was able to note no more than eight cases recorded in the literature in which pancreatic insufficiency followed mumps, and all these cases suffered from a glycosuria; in none was the external secretion of the pancreas permanently affected.

(2) Syphilis.

Syphilitic cirrhosis of the pancreas is rare, but definitely does occur. It is found in both congenital and acquired syphilis, and is more commonly found in the former. When it is present in congenital syphilis it is usually associated with cirrhosis of the liver. Evidence of pancreatic insufficiency may follow, and according to Hurst the pancreas is affected in no less than 20 per cent of cases of syphilis of the newborn.

The acquired form was described by Warthin. He collected 150 cases, and considered that syphilis is the most common cause of chronic pancreatitis, a view not generally accepted. Diabetes may follow, or more often deficiency of the external secretion. It is probably a good plan to have the W.R. done in any case of suspected chronic pancreatitis.

(3) Haemochromatosis.

The rare condition originally called Bronzed Diabetes and characterised by pigmentation of the skin, diabetes, sex changes, siderosis, sex incidence in males only, and cirrhosis of the liver, also shows a marked cirrhotic change in the pancreas. The haemosiderin deposited in the pancreas leads to destruction of the cells, followed by increase in the connective tissue, and proliferation of the unaffected cells. The diabetes may or may not be due to destruction of the islets by fibrosis, but in no case is there evidence of insufficiency of the external pancreatic secretion.

Conclusion

It should be emphasised that chronic pancreatitis is an uncommon disease. There is an impression among many physicians to-day that it may be more rare than it was; certainly it is diagnosed less frequently than in the past. For instance, in the five years preceding the war, only nine cases at Guy's have been so diagnosed. Ryle considers that the importance of pancreatic disease as a cause of steatorrhoea has been over-emphasised. He notes that in his own experience failure of absorption is by far the commonest cause of steatorrhoea.

It is therefore all the more important to make a diagnosis of chronic pancreatitis only after careful deliberation. It is interesting to recollect that as long ago as 1871 Wardell wrote that "no symptoms are pathognomonic of pancreatic disease; an assemblage of symptoms indicates the probability of its lesion." The same applies to-day, and the variability of the clinical picture militates against basing the diagnosis upon any single observation, for no finding is constant. As far as the laboratory investigations go, normal results of the pancreatic efficiency tests do not exclude pancreatic disease. One positive test is suggestive, and several are highly significant.

In the main, diagnosis must still rest upon careful balancing of the available evidence for and against chronic pancreatitis, with the help in jaundiced cases of the additional information, both immediate and remote, provided by laparotomy.

REFERENCES

- CAMMIDGE, "Chronic pancreatitis," *Lancet* (1911), 1, 1495.
 GARROD, "The diagnosis of disease of the pancreas," *B.M.J.* (1920), 1, 459.
 GULL, "Fatty stools from disease of the mesenteric glands," *Guy's Hospital Reports* (1855), 1, 369.
 HARRISON, *Chemical methods in clinical medicine*, 1937.
 HURST, "Syphilis of the pancreas," *Price's Text-book of Medicine*, 1941.
 RYLE, *The Natural History of Disease* (1936), 151.
 SMITH, "Mumps," *Guy's Hospital Reports*, 1937, 447.

THE CLINICAL PATHOLOGY OF PANCREATIC DISEASE (EXCLUDING DIABETES)

By SHEILA M. NEWSTEAD, M.B., B.S., M.R.C.P.

(Pathologist, Royal Hospital, Richmond, Surrey)

MORBID ANATOMY

The pancreas is composed of two types of tissue, the glandular or acinar, which produces the external secretion, and the islets of Langerhans, which produce the internal secretion.

1. Inflammatory Conditions

Acute Pancreatitis.

Some authors speak of this as acute pancreatic necrosis, whilst others divide it into three types, viz., haemorrhagic, gangrenous, or suppurative. Necrosis is certainly the dominant histological feature, and whether it is haemorrhagic, gangrenous, or suppurative will depend on the length of time that the patient survives and the presence or absence of super-added infection.

Macroscopically the pancreas is swollen, friable and purplish in colour. Often there is extensive haemorrhage, sometimes patchy in distribution, and at other times almost uniform throughout. Again in other cases there may be no change visible to the naked eye. There is often evidence of haemorrhage into the surrounding tissues, and even in mild cases there is oedema of the adjacent connective tissue.

On the surface of the pancreas and in the surrounding mesenteric fat there are small opaque white areas of fat necrosis. The liberated pancreatic juice splits the fat into glycerol and fatty acids, and the latter combine with calcium to form insoluble soaps.

Often there is evidence of a pathological biliary tract, and gall-stones are present in 40-70 per cent of cases.

Microscopically, necrosis, haemorrhage and inflammation may all be present, the extent of each varying from case to case. Usually the necrosis is predominant and affects both the