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
GULL, "Fatty stools from disease of the mesenteric glands," Guy's Hospital Reports (1855), I, 369.
HARRISON, Chemical methods in clinical medicine, 1937.
HURST, "Syphilis of the pancreas," Fried's Text-book of Medicine, 1941.
RYLE, The Natural History of Disease (1930), 127.
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
glandular and interstitial tissue. There is widespread thrombosis of vessels with hyalinisation. In the milder cases which survive there may be marked polymorphonuclear infiltration.

**Chronic Pancreatitis.**

This condition may be found following an attack of acute pancreatitis, or it may be the result of arterio-sclerosis, or it may be found in association with cirrhosis of the liver. It may also be seen following long-standing obstruction of the main duct by a pancreatic calculus, or by a gallstone impacted in the ampulla of Vater.

Macroscopically in all cases the pancreas is firmer than usual, and in most cases it is also shrunken.

Microscopically there is an extensive fibrosis which may affect the gland in two ways—it may be predominantly interlobular or intralobular, although frequently both changes are combined in the same case. The glandular acini are usually affected more than the islets of Langerhans, although these may be affected in the later stages. In the fibrosis following obstruction of the pancreatic duct, fibrosis of the islets is rare. If associated with haemachromatosis, haemosiderin is deposited in the connective tissue.

**2. New Growths**

**Islet-cell Adenoma.**

This is associated with the clinical picture of hypoglycaemia. It is generally situated in the body or tail of the gland, and is an encapsulated tumour found on the superficial surface. Microscopically it consists of branching trabeculae separated by strands of fibrous tissue rich in blood vessels. The cells are basophilic and resemble normal B cells; they are polyhedral or columnar with abundant granular cytoplasm containing round or oval nuclei which stain deeply with haematoxylin.

Although usually innocent, the adenoma may both recur locally or metastasise in the liver.

**Carcinoma.**

This usually occurs in the head of the gland, and is an adeno-carcinoma of the scirrhus type, although sometimes the encephaloid type is encountered. Metastases are usually found in the retroperitoneal glands and liver.

**3. Rarer Pathological Conditions of the Pancreas.**

**Congenital cystic disease** of the pancreas is usually found in combination with cysts in the liver or as part of Lindau's syndrome. Cysts of the pancreas may occur as the result of an acute pancreatic necrosis.

**Dermoid** and **hydatid cysts** of the pancreas have been reported. **Syphilis** and **Tubercle** may also affect the gland.

**INVESTIGATIONS OF VALUE IN CASES OF PANCREATIC DISEASE**

These investigations test the efficiency of the internal and external secretions. The *external secretion* is an alkaline medium containing enzymes amylase, lipase and trypsin. It is poured into the duodenum and becomes mixed with bile. Hence information about it can be obtained by examination of the *duodenal fluid* and *faeces*. A certain amount is absorbed into the *blood* and thence passes to the *urine*, therefore these must also be examined.

**1. Faeces.**

Although the pancreatic juice contains vitally important enzymes, compensation takes place to a certain extent when there is deficiency of this secretion, thus the appearance of the faeces is variable. Usually, however, the food will remain largely undigested, so that there is an increase in the bulk of the stool. Owing to the intestinal hurry due to this bulkiness, there is not the normal loss of water during the passage through the intestine. It is also more acid in reaction. The evidence of this failure of digestion will be shown by the presence of unaltered protein and an increase in fat, which will be largely unsplit.
(a) **Macroscopical examination.**—The stools are characteristically palé, bulky and fatty, with an extremely offensive odour. True fatty stools are liquid when passed and set on cooling, but they are not watery. In severe cases the neutral fat will separate out as a yellowish oil.

(b) **Microscopical examination.**—Mention has already been made of the fact that deficiency of external secretion leads to a failure of the fat splitting enzyme, hence search must be made for the presence of neutral fat. These fat globules tend to rise to the surface, their size is variable and they are highly refractile. It is important to make certain that the patient is not receiving paraffin oil or other oily substance before reporting the presence of neutral fat. In addition, fatty acid crystals which have an acicular appearance are sometimes seen owing to the frequency of a combination of liver and pancreatic disease. An even more useful test of pancreatic insufficiency is the finding of undigested muscle fibres. A true creatorrhoea must be distinguished from woody fibres of certain vegetables. In the former the striations are well marked and regular, whereas the ends of the fibres are irregular, while in the latter the striations are coarser and irregular and the ends are rounded.

(c) **Chemical examination.**—This consists in the estimation of the fat and nitrogen. In routine clinical work it is usual to estimate these while the patient is on a normal diet, but more information can be obtained by balanced studies, using the Schmidt diet. This diet has been further modified by Pratt, and consists of 102 gm. of protein, 132 gm. of fat, and 180 gm. of carbohydrate, giving a total of 2,324 calories. It is given for three days. With breakfast on the first day the patient receives 0.3 gm. of carmine in a capsule. On the fourth morning he receives charcoal. All faeces from the first coloured with carmine to the first coloured with charcoal are saved. Normally 94 per cent of fat and 92 per cent of nitrogen are absorbed, i.e. the residue should contain 6 per cent of fat and 8 per cent of nitrogen. In complete obstruction of the pancreatic ducts, however, 50 per cent or more of fat and nitrogen may be present. Whereas in obstructive jaundice, although the high proportion of fat may be present, the faecal nitrogen is essentially normal.

2. Duodenal fluid.

(a) **Technique of obtaining duodenal fluid.**—A special duodenal tube such as that of Lagerlof and Agren may be used. This is a double tube with one going into the stomach and one into the duodenum. On the other hand, satisfactory specimens can be obtained by using an ordinary flexible tube of the Ryle pattern, with a metal olive at one end, which in addition to being marked at 16 ins. and 20 ins. is also marked at 28 ins. and 32 ins. The patient should be fasted from 9 p.m. At 9 a.m. the tube is passed into the stomach and the resting juice is removed. The stomach is then washed out with two quantities of 250 c.c. of distilled water. The patient is then instructed to lie on his right side and is given a book to read. At the same time he should swallow the tube at the rate of about a cm. a minute, then in twenty minutes the tube should be in the duodenum. The duodenal contents should then be aspirated.

A simple method of testing for enzyme activity has been described by Lueders.

**Lipase** is determined by adding 0.1 c.c. of duodenal contents to an emulsion of olive oil containing 1 c.c. of 0.1 N NaOH and phenolphthalein. As the fatty acid is liberated the sodium hydroxide is neutralised and the pink colour of the phenolphthalein disappears. Normally this requires five minutes or less.

**Trypsin** is estimated by adding 0.5 c.c. of 0.1 N NaOH to a gelatine substrate. The alkali in this case is neutralised by the liberated amino acids, and should occur in five minutes.

**Amylase** estimation is interfered with by swallowed saliva.

Agren and Lagerlof described a test of pancreatic function based on stimulation with secretin and quantitative recovery of the duodenal juice. They used a purified crystalline secretin injected intravenously, and gave 16 cat units per kgm. of body weight, taking about one minute for the injection. No signs of anaphylactic effect occurred. Almost immediately the secretion increases. The colour changes from light yellowish brown to a very light yellow. The spontaneous secretion is very viscous, but the secretin juice is watery, becoming thicker as the secretin decreases. The maximum secretion occurs within five to ten minutes of the injection, and usually about 130 c.c. of duodenal contents are obtained. Later, Lagerlof showed that the volume of the juice and the bicarbonate contents are very constant and are not easily disturbed. The enzymes, however, show independent variations.
In disease two types of reactions may be found:—

(1) Depression of the diastase action only, as in the early stages of acute pancreatitis.

(2) Depression of the volume, bicarbonate and diastase action as in advanced carcinoma of the body of the pancreas.

3. Urine.

All cases of suspected pancreatic disease should have a specimen of urine tested for the presence of sugar, but, except in chronic cases, glycosuria is rare.

Estimation of urinary diastase.—In acute pancreatitis the amount of diastase in the blood is greatly increased, but owing to its rapid excretion in the urine, estimation of it in the latter is of more value. In the acute disease, the estimation of diastase on a single specimen of urine is often conclusive, but in the chronic case a 24-hour specimen is needed. A disadvantage of this test is the fact that as in any abdominal catastrophe associated with shock and vomiting, secretion of urine is depressed, and as Norby has pointed out, “the amount of amylase in the urine per unit of time was constant for the same person when the diuresis amounted to 1–2 c.c. per minute. It fell as diuresis decreased,” hence in acute abdominal conditions uncertainty exists as to where the urinary diastase becomes pathological. However, it is a useful investigation, and in this country it is usual to employ a modified Wohlgemuth’s method. The principle of this depends on the hydrolysis of starch by the diastase with the production of erythrodextrin, achroodextrin, and maltose. The end-point being the dilution at which no starch is left. A unit is that amount of diastase which will digest 1 c.c. of 0.1 per cent solution of starch (1 mgm.) in thirty minutes at 37 C. The diastatic index is the number of units in 1 c.c. of urine. Normally the diastatic index is 6.7–33.3 units. An index over 50 is suspicious and over 100 definitely abnormal.

In carrying out this test it is necessary to work at the optimum pH for the enzyme.


Proteolytic enzymes in the blood are mainly derived from the leucocytes. It is impossible, therefore, to estimate the trypsin with any degree of accuracy. Similarly the lipase estimation is uncertain. The blood amylase, however, can be estimated with sufficient accuracy to make it of clinical value. This can be done by Wohlgemuth’s method as for urine. Norby has evolved a method based on the estimation of the maltose formed when starch is broken down by amylase. Other methods are dependent on the measurement of the remaining substrate after the action of amylase and the measurement of the viscosity of the substrate. It must be remembered that increased blood amylase values may also occur in a proportion of patients with disorders affecting other organs in the neighbourhood of the pancreas.

The blood sugar should also be estimated. Manifest diabetes seldom develops after acute pancreatic disease, and glycosuria only occurs in 5–20 per cent of these cases. Milder disorders of sugar metabolism, such as a pathological blood sugar curve are common and may persist for some time. Similar abnormal sugar curves may also occur in chronic pancreatitis.

5. Artificial substances used for estimating pancreatic function.

These tests are dependent on the theory that certain artificial substances when administered orally will appear undigested in the faeces when the pancreatic secretion fails to reach the intestine.

(a) Sahli’s “Glutoid Capsule” Test.—Iodiform, salol or methylene blue is administered in a gelatine hardened capsule which would be dissolved by normal pancreatic juice with excretion of the dye in the urine. Most observers agree on the unreliability of this test owing to the fact that the “hardness” of the capsules and the speed of their passage through the intestines are variable factors.

(b) Schmidt’s “Beef cube” Test.—This is based on the theory that cell nuclei are digested by pancreatic secretion. For proper interpretation these capsules must remain not less than 6 or more than 30 hours in the intestine. Other investigators have used thymus gland nuclei.

(c) Wintermitz “Sajodin” Test.—In this test the calcium salt of iodo-behenic acid is hydrolysed by pancreatic juice in the presence of bile salts. Detection of iodine in the urine after five hours is proof of hydrolysis having taken place. However, in occlusion of the bile ducts with the patency of the pancreatic ducts, a negative result will be obtained.
Tests of Deficiency of Internal secretion

Mention has already been made of the value of blood sugar estimations and the examination of the urine in pancreatic disease. In addition, some authors place reliability on *Loewi's Test*. This is based on the antagonistic action of the pancreas and suprarenal. He showed that if the pancreas is absent, the sympathetic is more irritable. After carefully examining both eyes, and noting the size and reaction of the pupils to light and accommodation, 2 drops of 1 in 1000 adrenalin are instilled into one eye. The pupil is examined every 15 minutes for one hour. Normally no dilatation takes place. In a positive case, eccentric dilatation occurs. Positive results may be found in gall-bladder disease and hyperthyroidism as well as in pancreatic disease.

X-ray Evidence

In addition to excluding disease of other organs, radiography may help in the diagnosis of pancreatic disease.

A straight X-ray may show a stone or calcification in an old fat necrosis.

A barium meal may show deformity of the duodenum from a cyst or tumour. In more advanced cases the stomach or colon may be displaced.

Cannon shows that the emptying of the normal stomach is slowest after a fatty meal. Northmann and Wendt noted that in the depancreatized dog, fat left the stomach with great rapidity.

In conclusion, the following is a brief summary of the tests most likely to be of value in the most frequently encountered pancreatic diseases.

1. Acute Pancreatic Necrosis.

   (a) The urinary diastase on a single specimen of urine. It is usually over 100 units per c.c. and may reach 2,000.

   The blood amylase increases rapidly in the first two hours, and is maximum in twenty-four hours. A raised value may be found in biliary disease. On the other hand, a normal value in the first two days rules out acute pancreatic disease.

   Loewi's test may be positive. Hyperglycaemia and glycosuria may occur.

   The secretin test may be of value in the follow-up of a suspected case of pancreatitis. Lagerlof givesfigures of one in which five days after the acute attack the volume of the duodenal fluid and its bicarbonate content were normal, but the diastase value was low. Six weeks later all values were normal.

2. Chronic Pancreatitis.

   The faeces may show varying degrees of creatorrhoea and steatorrhoea, but the urinary diastase is usually normal.


   (a) *Adenoma of islets of Langerhans.*—The outstanding abnormality of this condition is a hypoglycaemia. Often an overnight fast is sufficient to show a low blood sugar in the morning, but in other cases confirmatory evidence may be shown by the sensitivity to insulin, and if an insulin tolerance test is performed, the reduction in the blood sugar is normal, but the recovery from the low level is deficient or almost absent.

   (b) *Carcinoma of the pancreas.*—In this condition the results of the investigations are variable. As carcinoma frequently attacks the head of the gland the common bile duct is obstructed, and the picture is altered by the interruption of the flow of bile. The faeces may then show a steatorrhea with a normal proportion of split and unsplit fat. Usually there is no disturbance of either internal or external secretion until the disease is well advanced. In the later stages the secretin test shows a diminution of volume, bicarbonate content and enzyme activity.

REFERENCES

1. BOYD, A textbook of Surgical Pathology.
2. COOPE, R. (1927), *The Diagnosis of Pancreatic Disease*.
4. LAGERLOF, (1942), *Pancreatic Function*.
The Clinical Pathology of Pancreatic Disease (excluding Diabetes)
Sheila M. Newstead

Postgrad Med J 1944 20: 255-259
doi: 10.1136/pgmj.20.226.255

Updated information and services can be found at:
http://pmj.bmj.com/content/20/226/255.citation

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/