Pancreatic Function Tests

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The study of pancreatic disease provides an interesting paradox; on the one hand the diagnosis of pancreatitis and cancer of the pancreas is frequently overlooked, and on the other the diagnosis is frequently suspected erroneously. To some extent this reflects the rarity of pancreatic disease, but it can also be attributed to the traditional method of diagnosing pancreatic disorders by a process of elimination, a method not without risk as Richard Bright pointed out in 1833, because it presupposes an exact knowledge of other organs, which the clinician may not possess. Since 1833, however, it has become possible to detect the presence of gall-stones and duodenal ulcer with greater certainty, but this is not so with pancreatic disease, which frequently coexists with these two conditions. Gall-stones are a common cause of relapsing acute pancreatitis, and the finding of a duodenal ulcer does not rule out the existence of a pancreatic lesion, since the incidence of duodenal ulcer is increased in both chronic pancreatitis and cancer of the pancreas.

The clinical features of pancreatic disease, and the distinction that must be made between the acute and chronic forms of pancreatitis and, in particular, between relapsing acute pancreatitis and relapsing chronic pancreatitis, have already been described (Howat, 1963). Once pancreatic disease is suspected, the clinician should turn to tests of pancreatic function to establish or disprove his clinical diagnosis, because in the earlier stages of pancreatic disease radiology is of limited value and the findings of sophisticated radio-diagnostic techniques may prove difficult to interpret. To understand how best to use tests of pancreatic function, not only must the indications and limitation of the individual tests be appreciated, but also the clinical situations in which they may prove valuable.

The exocrine pancreas possesses two functions; it produces bicarbonate in association with a considerable volume of fluid, and digestive enzymes in association with a limited volume of fluid. These functions generally diminish proportionately when the pancreas is diseased. In the severer and later stages of both pancreatitis and cancer of the pancreas, endocrine function is also involved and diabetes mellitus is a not infrequent result.

There is no single, simple test of pancreatic function capable of confirming the presence or absence of pancreatic disease, but some pancreatic function tests can delineate the type of pancreatic disease present, and indicate whether

conservative or operative treatment is likely to succeed, hence defining the prognosis in the individual patient. These function tests, however, can only be interpreted in conjunction with the clinical and radiological assessment of the patient, and in this sense no specific or pathognomonic test of pancreatic disease yet exists.

PANCREATIC SCANNING

Pancreatic scanning (Bouchier, 1968; Brown *et al.*, 1968) is still in its infancy but, theoretically, modifications and refinements may increase its accuracy so as to provide a screening test of pancreatic function that can be analysed quantitatively by computer. It is at present best carried out with ^{75}Se —selenomethionine, which is incorporated into the enzymatic proteins of the acinar cell, but is also accepted by the liver. Visualisation of the pancreas with present techniques is adequate in about 75 per cent of cases. Failure to visualise the pancreas may be due to an overlying enlarged liver, but in a few patients in whom pancreatic function is apparently normal the pancreas may not be visualised adequately. It is, therefore, difficult in the individual case to attribute non-visualisation to a pathological pancreas, although it is known that after recent severe pancreatitis uptake is diffusely reduced. Greater stress should be laid on pancreatic displacements and localised filling defects indicative of pancreatic neoplasm. At present, positive features are more reliable than negative findings, but false positive results ('cold spots') have been recorded in the normal pancreas. Although the isotope tends, during excretion, to be localised in the central or periductal area of the pancreas, so far no method has permitted adequate radiological visualisation of the ducts of the pancreas in man.

USES OF TESTS OF PANCREATIC FUNCTION

The presence of active pancreatitis is usually confirmed by estimating the values of amylase and lipase in serum or urine, or both. Elevation of these values accompanies the release of these enzymes into the interstitial tissue of the pancreas, from which they pass by way of the lymphatics and thoracic duct into the systemic blood stream and are excreted by the normal kidney. A raised serum amylase is not pathognomonic of acute pancreatitis, as it is raised in parotitis and, occasionally, in perforation of a peptic ulcer and in other acute abdominal catastrophes. Elevated serum amylase and lipase are found in gall-stones, in hepatic disease and after administration of opiates. In both acute and chronic insufficiency the values of these enzymes in serum and urine may be dissociated and this may also occur in macroamylasaemia when the serum content of amylase is high but the urinary values are low,

which can be attributed to the binding of amylase in a macromolecular complex too large to be excreted in urine (Wilding *et al.*, 1964; Berk *et al.*, 1967). There is little evidence that measurement of isoamylases in serum is of practical use, and the estimation of trypsin and of antitryptic titres in serum is of no practical value in the clinical assessment of acute pancreatitis; indeed, opinions differ as to whether the release of active trypsin is a significant factor in the pathogenesis of acute pancreatitis.

The height of the elevation of amylase and lipase in serum and urine cannot be correlated with the severity of an attack of acute pancreatitis because the highest values are found in relapsing acute pancreatitis, in which the pathological process is not as a rule severe, and in which pancreatic function returns to normal in the intervals between attacks (Howat, 1963, 1965). The degree of severity is gauged by the acute electrolyte disturbances that accompany acute haemorrhagic pancreatitis, in particular the fall in serum calcium from the third to the eleventh days of the attack. Calcium is fixed by the fatty acid liberated in severe cases by lipolysis of the peri-pancreatic fat, and the concentration of readily mobilised calcium in serum falls. The extent of this fall can be used to measure the severity of an attack and therefore as an index of prognosis. The rapid development or exacerbation of diabetes mellitus during the course of acute pancreatitis is roughly commensurate with the severity of the attack.

To be of value, the serum enzymes should be measured early in the attack, since the rise may be evanescent and transient. The duration of an attack of acute pancreatitis cannot always be estimated from serial serum enzyme values. Persistently high values lasting more than seven to ten days after an attack of acute pancreatitis could indicate a pseudocyst complicating the pancreatitis, or that an obstructive lesion, such as a duct cancer or small cancer of the head of the pancreas, is responsible for the attack of pancreatitis.

A marked rise of serum deoxyribonuclease I activity, which may be sustained from one to three weeks after the onset of the attack, is an indication of pancreatic necrosis (Kowlessar and McEvoy, 1956) and methaemalbumin released by pancreatic digestion of the haemorrhagic exudate may appear in the serum of severe and fatal cases of acute haemorrhagic pancreatitis (Mazumdar, 1961; Northam *et al.*, 1962). Neither of these, however, is useful in the practical management of the patient.

Obstruction of the pancreatic duct by stone, stricture or a cancer is accompanied by a progressive deterioration of function, in part due to atrophy, but sometimes associated with chronic pancreatitis. In early obstruction, when pancreatic integrity is relatively intact, the serum enzymes may be

raised, but, as the gland deteriorates, this elevation is less often found. Attempts have been made to make this elevation of serum amylase and lipase more sensitive in the early duct obstruction associated with cancer of the pancreas and sometimes with chronic pancreatitis by stimulating the pancreas with secretin and pancreozymin. This simple evocative test (Burton *et al.*, 1960b) is most valuable in the first ten days of obstructive jaundice due to ampullary carcinoma, before pancreatic function deteriorates. When a positive glucose tolerance test indicates increasing pancreatic damage, the test more often tends to be negative. Taken together, the simple evocative test and the glucose tolerance test are positive in 85–90 per cent of cases of chronic pancreatitis and cancer of the pancreas at all stages. It must be remembered, however, that the evocative test is not specific for pancreatic disease, but may also be positive in hepatic and biliary disease and in some other pathological conditions. There is no place in clinical study for the obstructive-evocative test which combines the use of pancreatic stimulants with morphine.

Pancreatic secretory capacity can be estimated indirectly by balance and tolerance tests which demonstrate impaired digestion or absorption of the main foodstuffs, starch, protein and fat. Neither balance tests in which fat and nitrogen are measured nor tolerance test procedures using fat and starch provide early evidence of pancreatic dysfunction. In advanced pancreatic insufficiency, when steatorrhoea is present, fat balance studies are most useful in estimating the response to substitution therapy by pancreatic extracts. Direct methods are of incomparably greater value in assessing the secretory capacity of the exocrine pancreas. After intubating the duodenum the pancreas is stimulated and the quantity and character of the duodenal contents are assessed. The pancreatic stimulus used by Lundh (1962) is a standard meal of 6 per cent fat, 5 per cent protein and 15 per cent carbohydrate, with polyethylene glycol as reference substance. Samples are taken from the upper jejunum or duodenum at ten-minute intervals in the first hour and less frequently in the second hour. Low concentrations of trypsin are found in chronic pancreatitis and cancer of the pancreas. The Lundh test is an adequate guide to established pancreatic insufficiency.

The best means currently available in clinical practice to demonstrate early impairment of pancreatic function are the secretin test and secretin-pancreozymin test (Burton *et al.*, 1960a). The principle of the secretin test is the same as laid down thirty years ago by Ågren and Lagerlöf (1936) and Lagerlöf (1942), and necessitates duodenal intubation with a double lumen tube and continuous aspiration of the stomach and duodenum for a period of some one and a half hours. Accurate siting of the tube by fluoroscopy is

necessary, and the giving of biological preparations intravenously requires constant medical attendance. The technique, once acquired, is not difficult to perform but is time-consuming and trying for the nervous patient. The quantitative recovery of the duodenal contents and the output of bicarbonate, and enzyme if pancreozymin is used, provide an accurate and reproducible estimate of pancreatic function. A diminished maximal bicarbonate concentration and post-secretin bicarbonate output and a reduced post-pancreozymin enzyme output, if permanent or found in the intervals of remission of pain, are characteristic of chronic pancreatitis, while a reduced volume is a feature of duct obstruction (Howat, 1966). Recent attempts to increase the sensitivity of the secretin test by prolonging the infusion of secretin to ensure maximal secretory capacity appear at present to be of marginal value to the clinician, and the expense and the discomfort to the patient of unduly prolonging the test are increased. However, the recent synthesis of secretin makes this concept attractive. The use of pancreozymin in addition to secretin permits an assessment of acinar function, and at the same time gives valuable information about the integrity of the gall bladder (the cholecystokinin test of Burton *et al.*, 1960c).

CLINICAL PROBLEMS

The clinician is primarily concerned with pancreatic function tests as an aid to diagnosis or to confirm a tentative clinical diagnosis. Tests for elevated serum amylase and lipase or urinary amylase, although not specific tests, are, when taken in conjunction with the clinical features, of great assistance in arriving at the often overlooked diagnosis of acute pancreatitis.

The clinician is frequently concerned that a previous attack of upper abdominal pain may have been due to an attack of pancreatitis. In the absence of pseudocyst or abscess, confirmation is often difficult to obtain, since, in the absence of complications, complete restitution of function accompanies the restitution of structure that takes place after acute pancreatitis. Even in severe necrosis, when surgery has eradicated the complications, a return to normal, albeit with some scarring, takes place. It is therefore important, during attacks of pain in the upper abdomen, to obtain serum for enzyme estimations and to repeat these even when the patient is in an interval of freedom from pain. Minor elevations above the normal for the individual may prove to be significant, although similar rises may accompany biliary pain. The most common cause of relapsing acute pancreatitis is the presence of gall-stones, removal of which terminates the attacks. Indeed, many patients are relieved of relapsing acute pancreatitis by surgery without the surgeon suspecting that pancreatitis has ever been present.

TABLE 1. Secretin-Pancreozymin Test

	Number of patients	Decreased in duodenal contents			
		Volume	Maximal HCO_3	Post-secretin output HCO_3	Post-pancreozymin output of amylase
Acute pancreatitis	40	2 (4)*	6	7 (7)*	3 (1)*
Chronic pancreatitis	30	17 (1)*	27	28	24
Cancer of pancreas	34	21	23	26 (1)*	28

* Significant increase. The test was carried out in some of the patients in the acute pancreatic group when active pancreatitis was still present. In a few increased values were present.

During the painful attacks that characterise relapsing chronic pancreatitis and in early cancer of the pancreas and cancer of the ampulla of Vater, serial enzyme studies are again helpful, and the simple evocative test in which the enzymes are measured in serum in response to secretin and pancreozymin

Fig. 1. Secretin-Pancreozymin Test in Relapsing Chronic Pancreatitis without duct obstruction. The left hand columns of each pair represent the mean volume of duodenal contents (ml/60 min); the mean maximal concentration of bicarbonate (m.moles/l); the post-secretin output of bicarbonate (m.moles) and the mean post-pancreozymin output of amylase (Nörby units). The hatched area represents ± 2 S.D. The same symbols and conventions are used in Fig. 2.

may suggest the diagnosis. This test should be combined with an oral glucose tolerance test and a secretin-pancreozymin test, if one is contemplated.

Impaired digestion and absorption of food, such as steatorrhoea, are late manifestations of pancreatic insufficiency, although both chronic pancreatitis and cancer of the pancreas, by far the most common causes of impaired pancreatic function in the adult, may present in this way. Perhaps the easiest way to distinguish pancreatic steatorrhoea from malabsorptive steatorrhoea is to perform a glucose tolerance test, the values of which are frequently raised at this stage of pancreatic disease but are depressed in idiopathic steatorrhoea. The presence of calculi in the pancreatic ducts, visible on tomography of the pancreatic site, is a valuable aid to the diagnosis of chronic pancreatitis. In this context, as in diabetes mellitus secondary to chronic pancreatitis, serum enzyme studies are usually equivocal or uninformative, and recourse must be made to the secretin-pancreozymin test to obtain duodenal contents.

The secretin-pancreozymin test is a remarkably sensitive test of pancreatic dysfunction in both chronic pancreatitis and cancer of the pancreas (Table 1). The characteristic feature of chronic pancreatitis is a diminished maximal

Fig. 2. Secretin-Pancreozymin Test in Relapsing Chronic Pancreatitis with duct obstruction. See Fig. 1 for symbols and conventions.

bicarbonate concentration and output of bicarbonate following secretin (Fig. 1). This finding distinguishes relapsing chronic pancreatitis from relapsing acute pancreatitis, the course and treatment of which are different. The secretin-pancreozymin test provides additional information; if the

TABLE 2. Obstructive Jaundice (67) Cases

	No.	Cholecystokinin test			Secretin-pancreozymin test	
		> 100	< 100	0	Normal	Abnormal
Gall-stones	19	0	17	2	15	4
Cancer of biliary tract	10	0	0	10	10	0
Cancer of ampulla of Vater	6	2	2	1	1	4
Cancer of head of pancreas	23	1	3	19	2	21
Other causes	9					

volume of the duodenal contents is also diminished, there is *prima facie* evidence of duct obstruction, due to stone or stricture or cancer (Fig. 2), and from the clinical assessment of the patient it is not usually difficult to determine which of these is present. A low volume may be the only finding to suggest a simple stricture obstructing the main pancreatic duct. A reduced enzyme output in the post-pancreozymin samples provides a more sensitive index of pancreatic dysfunction in cancer of the pancreas than in chronic pancreatitis.

Not only does the secretin-pancreozymin test provide a direct quantitative assessment of pancreatic function, but pancreozymin extracts contain cholecystokinin, which has been used to devise a test of gall-bladder and biliary function that is particularly valuable in the definitive diagnosis of the causes of obstructive jaundice (Table 2). Used in conjunction with the secretin-pancreozymin test, the cholecystokinin test can indicate the presence of extrahepatic biliary obstruction, whether the cause is gall-stones or malignancy, and further distinguishes between cancer originating in the bile ducts and in the pancreas. It is particularly helpful in the pre-operative diagnosis of cancer of the hepatic ducts. Finally, cytological studies of the duodenal contents may provide confirmatory evidence of the presence of cancer in about half the cases of pancreatic cancer at the time of testing, although tetracycline fluorescence is less helpful in duodenal contents that contain bile (Burton and Cunliffe, 1966).

CONCLUSION

In the study of the acute forms of pancreatitis, reliance must be placed on securing confirmation of the diagnosis from the elevated enzymes in serum.

In the chronic forms of pancreatic disease in adults, in chronic pancreatitis and cancer of the pancreas, the secretin-pancreozymin test in experienced hands affords information which far outweighs the time taken and the discomfort to the patient, since from this test an accurate assessment of the pathological process, in both pancreas and biliary tract, is made, the correct treatment is indicated, and the prognosis given.

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Book Reviews

Diseases of Man Acquired from his Pets by B. BISSERU, MSc, PhD, MB, BS, MRCS, MRCP Ed, DTM & H, DObst RCOG. William Heinemann. Price 84s. 482 pages.

The title of this book does not do justice to its contents. It is about much more than man's pets. Such animals as centipedes, harvest mites, sharks and jellyfish could hardly be called 'pets', although the author cites a fantastic list of creatures that have at one time or another been kept as pets. This book is about those diseases of man where animals (all creatures included) play some part in their causation. This is a big field, covering the greater part of tropical medicine as well as all those diseases in temperate climates where animals and humans are involved.