Critical review of diagnostic methods used in chronic pancreatic disease

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IT BECK. Critical review of diagnostic methods used in chronic pancreatic disease. Can J Gastroenterol 1995;9(1):51-60. This paper provides a balanced assessment of the various pancreatic function tests and imaging techniques used in the differential diagnosis of chronic pancreatic disease. Function tests that study the digestive capacity of the pancreas (fat absorption of dietary lipids, fluorescein- or radiolabelled fats, bentiromide test, etc) have high specificity, but very low sensitivity. This is because 90% of pancreas has to be destroyed before steatorrhea or creatorrhea occurs. Tests that directly measure pancreatic bicarbonate and protein secretion (secretin test, etc) are more accurate and may detect pancreatic dysfunction even before anatomical changes occur. Measurement of pancreatic enzymes in serum or urine, or the decreased decline of serum amino acids during their incorporation into pancreatic enzymes, are not sufficiently sensitive or specific to help diagnose pancreatic disease. Sensitive and specific tumour markers are not yet available. Thus screening tests are not cost-effective – if they are negative, they do not exclude pancreatic disease; and if positive, they have to be confirmed by more specific tests. Imaging techniques are the most commonly used methods of investigation. The usefulness of abdominal survey films, barium studies, percutaneous transhepatic cholangiography, endoscopic retrograde cholangiopancreatography (ERCP), ultrasonography, computed tomographic scan, magnetic resonance imaging and endoscopic ultrasonography is critically reviewed. Most of the radiological methods can be combined with cytology or biopsy. Histology demonstrating malignancy establishes this diagnosis, but negative biopsies do not exclude malignant tumours. Presently only ERCP and endoscopic ultrasound can diagnose cancers sufficiently early to allow for possible 'curative' surgery, and only endoscopic ultrasound is capable to stage tumours for the assessment of resectability.

Key Words: *Computed tomographic scan, Endoscopic retrograde cholangiopancreatography, Endoscopic ultrasonography, Imaging techniques, Pancreatic biopsies, Pancreatic function tests, Secretin test, Tumour markers*

Analyse critique des méthodes diagnostiques utilisées dans la pancréatite chronique

RÉSUMÉ : Cet article présente une évaluation équilibrée des diverses épreuves de fonction du pancréas et des techniques d'imagerie utilisées pour le diagnostic différentiel de la pancréatite chronique. Les épreuves de fonction qui portent sur la capacité digestive du pancréas (absorption des graisses d'origine alimentaire, fluorescéine ou graisses radiomarquées, épreuve au bentiromide, etc.) s'accompagnent d'un degré élevé de spécificité, mais d'une très faible sensibilité. Cela est dû au fait que 90 % du pancréas doit être détruit avant que ne survienne la stéatorrhée ou la créatorrhée. Les épreuves qui visent une mesure directe des bicarbonates du pancréas et la sécrétion protéique (test de la sécrétine,

voir page suivante

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THIS REVIEW DEALS WITH THE diagnostic modalities used to investigate chronic pancreatic disease and the methods employed to differentiate chronic pancreatitis from carcinoma of the pancreas. Other conditions that lead to pancreatic insufficiency without pancreatitis or cancer (such as cystic fibrosis, primary pancreatic atrophy of childhood, adult pancreatic lipomatosis or isolated lipase-colipase deficiency, etc) will not be discussed although these conditions may also lead to abnormal pancreatic function tests. The subject of the present paper was reviewed in more detail by the author two years ago (1). The present paper is a more general overview and a critical assessment of the methods used and an update on recent developments.

The clinical features of chronic pancreatitis and carcinoma are shown in Figures 1 and 2. The common denominator of both diseases is replacement of functioning parenchyma and the duct system with nonfunctioning tissue: inflammatory tissue and fibrosis in chronic pancreatitis, and tumour in cancer of the pancreas. The clinical symptoms, biochemical abnormalities and anatomical distortions in both conditions are due to ductal obstruction, diminished parenchymal or ductal-cell function and the presence of mass lesions. Except in the case of functioning islet cell tumours (which are not the subject of this review), differentiation between the two conditions may be very difficult (1-3). As shown in Figures 3 and 4, cystic and

etc.) sont plus précises et peuvent déceler une dysfonction pancréatique avant même que ne surviennent des changements anatomiques. La mesure des enzymes pancréatiques sériques ou urinaires ou l'atténuation de la baisse des amino-acides sériques durant leur incorporation aux enzymes pancréatiques ne sont pas suffisamment sensibles ni précises pour contribuer au diagnostic de la pancréatite. Les marqueurs tumoraux sensibles et spécifiques se font encore attendre. Donc, les épreuves de dépistage ne sont pas économiques; si elles sont négatives, elles permettent d'exclure une maladie pancréatique; si elles sont positives, elles doivent encore être confirmées à l'aide d'autres tests plus spécifiques. Les techniques d'imagerie sont les méthodes d'investigation les plus fréquemment utilisées. L'utilité des plaques simples de l'abdomen, des épreuves barytées, de la cholangiographie transhépatique percutanée, de la cholangiopancréatographie endoscopique rétrograde (CPER), l'échographie, la scintigraphie, l'imagerie par résonnance magnétique et l'échographie endoscopique sont passées en revue. La plupart des méthodes radiologiques peuvent être combinées à la cytologie ou à la biopsie. L'histologie permet d'établir un diagnostic de néoplasie le cas échéant, mais les biopsies négatives ne permettent pas d'exclure les tumeurs malignes. À l'heure actuelle, seule la CPER et l'échographie endoscopique peuvent diagnostiquer les cancers suffisamment tôt pour permettre une chirurgie curative possible et seule l'échographie endoscopique peut déterminer si la chirurgie est faisable.

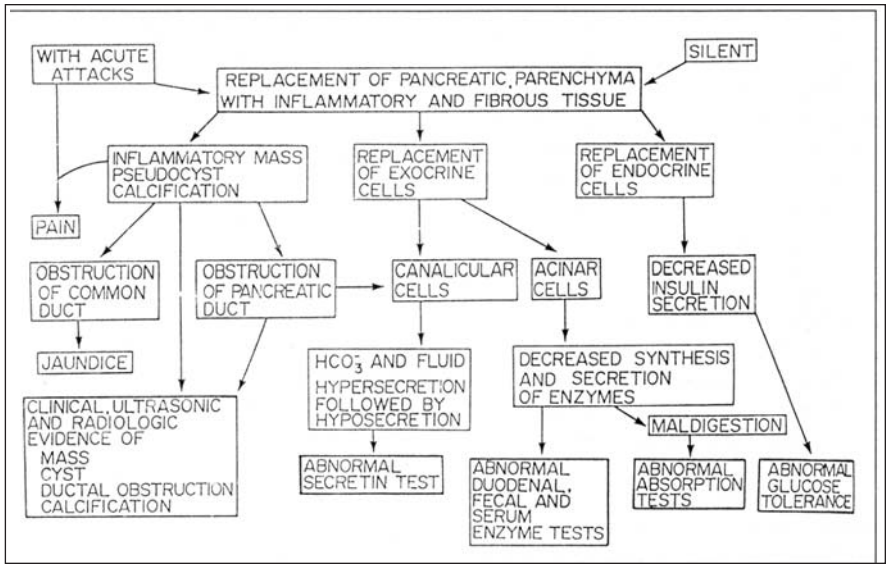


Figure 1) *Clinical and biochemical features caused by the anatomical changes of chronic pancreatitis. Reproduced with permission from reference 1*

solid tumours can occur in chronic pancreatitis as well as in benign and malignant neoplasms (4). Furthermore, calcification can occur in chronic pancreatitis and in several of the benign or malignant tumours. In addition, chronic pancreatitis is a risk factor for pancreatic cancer (2,3).

Once the suspicion of pancreatic disease has been raised on clinical grounds, investigation is warranted to determine whether chronic pancreatic disease is present, and if so, whether this is chronic pancreatitis or carcinoma. The methods employed can be divided into two major categories. The first consists of laboratory tests used to demonstrate abnormal pancreatic function (pancreatic function tests) and immunoassays for tumour markers to differentiate between benign and malignant disease. The second category consists of imaging and biopsy techniques used to establish the anatomical basis for abnormal function. Recent imaging techniques have replaced, to a great extent, the pancreatic function tests, but evaluation and understanding of the usefulness of individual tests is important in the investigation of patients with malabsorption syndrome and in the differentiation of pancreatic maldigestion from malabsorption due to other causes.

LABORATORY TESTS (TABLE 1)

Pancreatic function tests

Tests that assess digestive capacity of the pancreas (Table 2): Tests based on measuring the digestive capacity of the pancreas are less sensitive than those that directly measure pancreatic secretion. This is because the normal pancreas has considerable reserve capacity, and steatorrhea and creatorrhea become biochemically detectable only when lipase and trypsin secretion has been reduced to less than 10% of normal (5), and steatorrhea may not be detectable until 75% of the pancreas has been resected. Thus, fecal fat studies are insensitive in mild chronic pancreatic disease.

Fecal fat balance study: Steatorrhea occurs due to maldigestion (pancreatic disease) and to malabsorption (as a result of many other conditions, including intestinal disease). Differentiation between the two can be achieved by the method described below.

Fecal fat balance study before and during pancreatic replacement therapy: Steatorrhea due to pancreatic disease is diagnosed if fat absorption improves with oral ingestion of pancreatic enzymes. Gastric acid may lower duodenal pH below the level that is optimal for lipase activity, and the simultaneous administration of enzymes and a H_2 receptor antagonist may further improve fat absorption (6).

Colipase, a factor needed for appropriate lipase activity, plays an important role in fat digestion, and steatorrhea may occur in congenital isolated lipase-colipase deficiency (7).

Screening tests for pancreatic maldigestion: These tests, which study fat, starch or peptide digestion, have been developed to simplify the cumbersome fecal fat balance study. Most of them are less sensitive and specific than the 72 h fecal fat excretion.

Macroscopic and microscopic examination of stool: Considering the low sensitivity of the balanced chemical fecal fat determination, one would expect that the qualitative (microscopic) examination of stool is devoid of sensitivity,

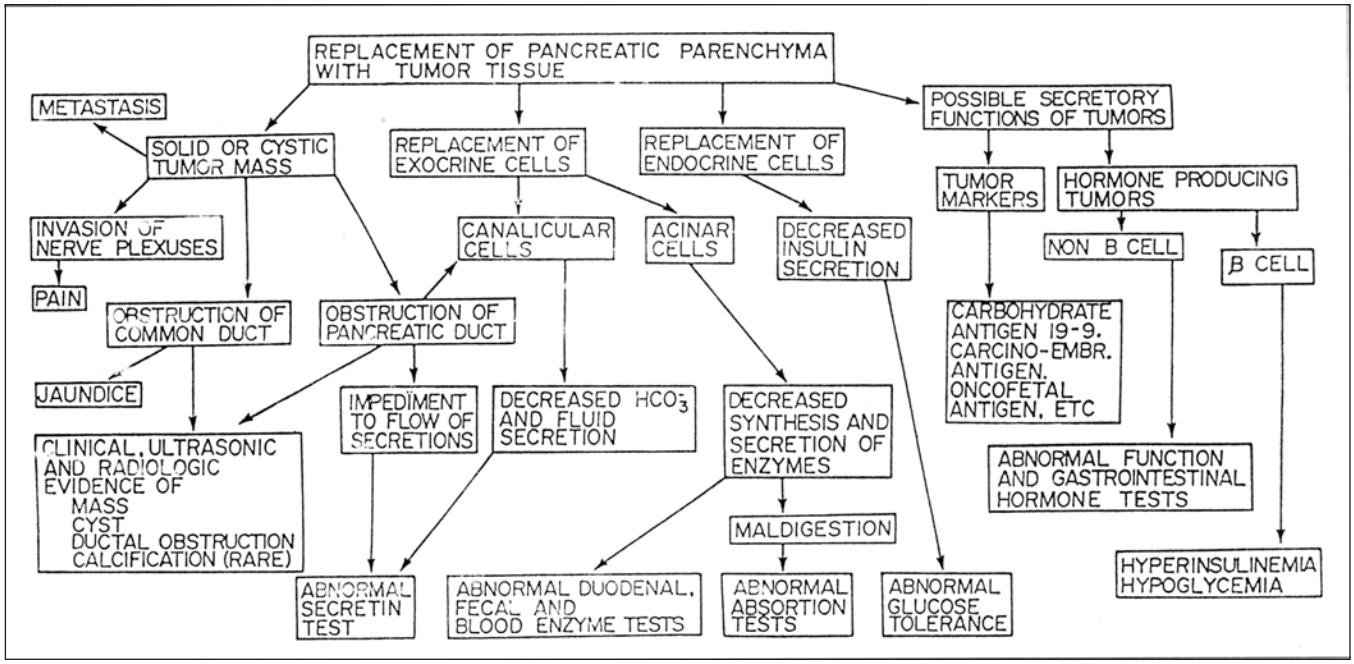


Figure 2) *Chemical and biochemical features caused by the anatomical and hormonal alterations of cancer of the pancreas. Reproduced with permission from reference 1*

and thus may lead to diagnostic confusion.

Pancreolauryl test: This pancreatic function test is based on the digestion of didodecanoic ester of fluorescein by pancreatic lipase. Because 90% of lipase activity has to be destroyed before even the accurate 72 h fecal fat balance study becomes abnormal, it is not astonishing that the sensitivity of the pancreolauryl test (which is based on a single dose of administered fluorescein fat) is low (8). The sensitivity of the test was reported in severe pancreatic disease to be between 80 and 90% but it is much lower in mild chronic pancreatitis (1).

Bentiromide test: This test is based on the digestion of benzoyl-L tyrosil-L-*p*-aminobenzoic acid (NBT-PABA). Because the tyrosil-*p*-aminobenzoic acid bond is specific for chymotrypsin, this synthetic peptide is digested only by chymotrypsin. The hydrolysis of this peptide results in the release of *p*-aminobenzoic acid, which is absorbed and excreted in urine. As this test is based on intraduodenal digestion by chymotrypsin, which is present in the pancreas in great excess, the test becomes positive only in patients with severe pancreatic insufficiency (8,9).

Other screening tests for pancreatic maldigestion: The ^{14}C triolein and fatty

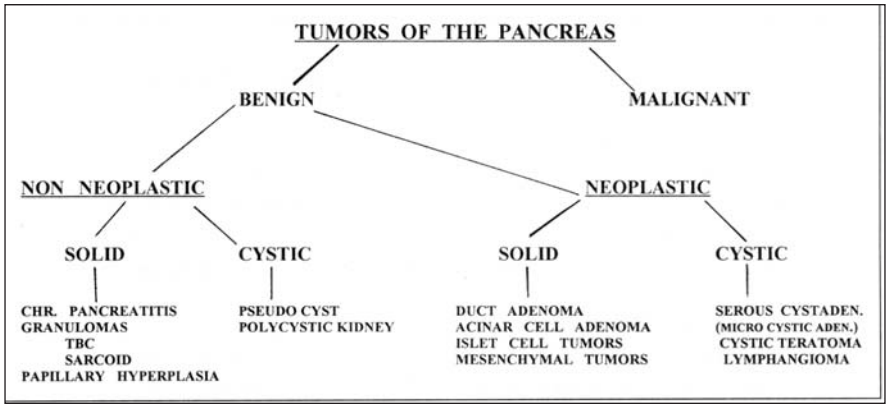


Figure 3) *Classification of benign tumours of the pancreas*

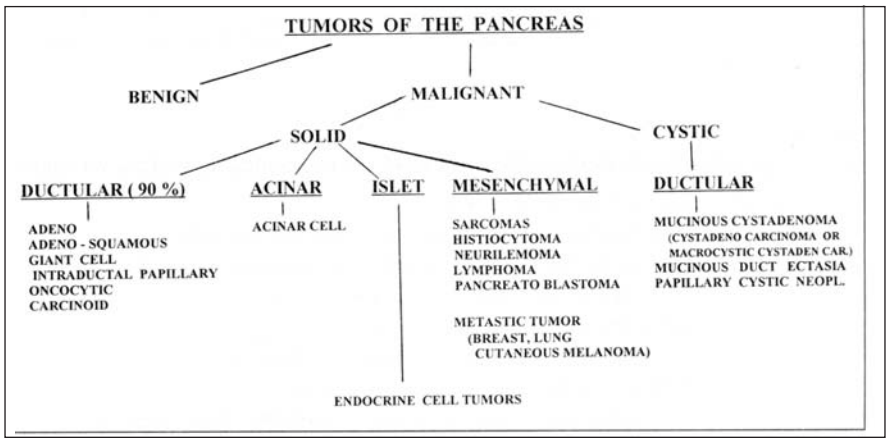


Figure 4) *Classification of malignant tumours of the pancreas*

TABLE 1
Laboratory tests used to investigate chronic pancreatic disease

Pancreatic function tests designed to assess:
Digestive capacity of the pancreas
Pancreatic synthetic and exocrine secretory function
Pancreatic endocrine function
Tests designed to differentiate between chronic pancreatitis and cancer

Modified from reference 1

acid absorption and breath tests (the first depends on duodenal lipase activity and the second on intestinal absorption) have been used to differentiate between maldigestion and malabsorption. However, similar to the nonradioactive ^{13}C-CO_2 breath test for fat and carbohydrate digestion, the ^{14}C fat absorption tests become positive only in patients with severe pancreatic insufficiency (1,2).

Vitamin B_{12} absorption depends on splitting the R protein from cobalamin by pancreatic enzymes. The Schilling test may be abnormal in some patients with severe pancreatic insufficiency; vitamin B_{12} blood levels usually remain normal (10).

Other tests of malabsorption: Clinically significant malabsorption of proteins and fat-soluble vitamins occurs only rarely in chronic pancreatic disease. Thus, serum albumin is usually normal, and carotene (for vitamin A), serum calcium, phosphate and alkaline phosphatase (for vitamin D) and prothrombin time (for vitamin K) are usually normal. However, plasma vitamin E levels and the vitamin E:total plasma lipid ratio are abnormally low in 75% of patients with chronic alcoholic pancreatitis and in 91% of those with steatorrhea. Although it has been suggested that this determination may be a practical means of detecting steatorrhea in patients with alcoholic chronic pancreatitis (11), fecal fat balance still remains the standard for abnormal fat excretion. Low folate levels, if present, are usually related to excessive alcohol consumption rather than pancreatic insufficiency.

Differentiation of malabsorption from pancreatic maldigestion can be achieved by tests that depend on intestinal absorption rather than digestion. Thus, the xylose absorption test and lactose tolerance tests are normal in pancreatic insufficiency.

Tests of pancreatic exocrine secretory and synthetic function (Table 3): Tests in this category are based on the secretory and synthetic function of the pancreas. Assessment of this function can be done either by directly determining the composition of pancreatic secretion obtained by peroral intubation, or by deducing secretory functions from the concentration of enzymes or their substrate in blood, urine or stool.

Tests requiring duodenal intubation: Stimulation of pancreatic secretions can be achieved either by parenterally administered hormones or by stimulating the pancreatic secretions with intraduodenally administered food.

Direct stimulation of the pancreas with parenterally administered hormones: The first changes of chronic pancreatitis occur in the ductal cells. Because secretin-stimulated bicarbonate secretion depends on ductal function, the most accurate method to assess pancreatic function is the intraduodenal measurement of the secretin-stimulated pancreatic bicarbonate secretion. Based on over 5000 cases the sensitivity of the tests was 90% and the specificity was 94%. False positive results occurred in patients with vagotomy, gastric surgery, diabetes and inaccurate tube placement (12). 'False positive' results may not necessarily be falsely positive. Abnormal pancreatic function after vagotomy or gastric sur-

TABLE 2
Tests designed to investigate the digestive capability of the pancreas

Fecal fat excretion (does not differentiate between pancreatic and other types of malabsorption)
Fecal fat excretion before and during pancreatic replacement therapy
Screening tests
Macroscopic and microscopic examination of stool
Starch digestion test for amylase (hydrogen, ^{14}C-CO_2 breath test)
^{131}I-triolein and fatty acid digestion and absorption test (blood and urine)
^{14}C-triolein and fatty acid digestion and absorption test (^{14}C-CO_2 breath test)
1,3 distearyl-2 carboxyl-^{13}C octanoyl glyceryl test for digestion by lipase (^{13}C-CO_2 breath test)
Fluorescein dilauryl test for digestion by lipase
N-benzoyl-L-tyrosyl-L-p-aminobenzoic acid (NBT-PABA) urinary excretion test
Other tests of malabsorption that may be positive in chronic pancreatitis
Low serum protein
Malabsorption of fat-soluble vitamins
Vitamin A: Low serum carotene
Vitamin D: Low serum calcium, elevated alkaline phosphatase
Vitamin K: Prolonged prothrombin time
B_{12} absorption (Schilling test and double-labelled Schilling test)

Modified from reference 1

TABLE 3
Tests designed to study pancreatic synthetic and exocrine secretory function

Tests requiring duodenal intubation ('invasive')
Direct stimulation with secretin, cholecystokinin, caerulein, bombesin
Indirect stimulation: Lundh test meal, fatty acid or amino acid test meals
Tests not requiring duodenal intubation ('noninvasive')
Fecal enzyme determination: chymotrypsin
Serum or plasma levels (with or without provocative testing) of:
Substances required in synthetic activity: amino acids
Substances synthesized: pancreatic amylase, trypsinogen, lipase, pancreatic polypeptide

Modified from reference 1

gery may relate to abnormal neuroendocrine control of pancreatic secretions. Evidence is accumulating that a high proportion of insulin-dependent diabetics may have exocrine pancreatic dysfunction, including ductular abnormalities (13). Hypersecretion was observed in patients with cirrhosis. False negatives were mainly due to inaccurate tube placement, which can be avoided by careful fluoroscopy (12). The secretin test becomes positive before any other function test, and an abnormal secretin test precedes the earliest structural abnormalities that can be demonstrated by endoscopic retrograde pancreatography (14).

The hormones cholecystokinin (CCK), caerulein and bombesin stimulate enzyme secretion by alveolar cells. Diminished hormone stimulated intraduodenal enzyme concentration occurs early in pancreatic insufficiency. These tests, however, have not been as well standardized as the secretin test (12).

Other 'invasive' tests requiring duodenal intubation have been proposed. For instance, the above-mentioned hormones increase secretion of calcium and lactoferrin, and abnormally high concentrations can be measured in duodenal juice of patients with early chronic pancreatitis. However, duodenal lactoferrin levels are also elevated in patients with duodenitis (1,2). A pancreatic function test was developed incorporating ^{75}Se methionine into pancreatic proteins. Increased ^{75}Se methionine labelled protein excretion into the duodenal juice has been reported to occur in early chronic pancreatitis, but this observation has not yet been confirmed (1,2).

Indirect stimulation tests: The indirect test described by Lundh (15) measures the secretory response to an intraduodenally administered liquid test meal. Diminished enzyme secretion in response to the test meal occurs in pancreatic insufficiency. However, indirect pancreatic secretory stimulation depends on the release of secretin and CCK from the duodenal mucosa, which may be impaired in patients with duodenal mucosal abnormalities. False positive results have been reported in patients with celiac disease. Tests based on duodenal perfusion with fatty acids or amino acids have the same limitations.

Tests that do not require duodenal intubation: Because 'invasive tests' are difficult to perform and some patients resist prolonged nasoduodenal intubation, investigators have attempted to develop sensitive and specific tests that can be performed without intubation.

Fecal chymotrypsin: The overall proteolytic activity in feces reflects the activities of a mixture of bacterial, pancreatic and other peptidases. Therefore, a method using specific substances for fecal chymotrypsin activity is more specific. Unfortunately, fecal chymotrypsin becomes abnormal only in advanced pancreatic disease (1,2).

Serum or plasma amino acids: During amino acid incorporation into newly synthesized pancreatic protein, a fall in plasma amino acid levels occurs after secretin and pancreozymin stimulation. Slowing of the rate of plasma amino acid decrease may suggest exocrine pancreatic insufficiency. Unfortunately, overlaps occur between normal patients and those with pancreatic diseases (1,16).

Serum and urine levels of pancreatic enzymes: Serum and urinary isoamylase and lipase are useful in the diagnosis of acute pancreatitis. However, these enzymes are of no help in the diagnosis of chronic pancreatitis or pancreatic neoplasm, except during an acute relapse or the presence of pseudocysts where these enzymes may remain elevated during the active presence of a pseudocyst.

Tests assessing endocrine pancreatic function: Frank diabetes does not occur in chronic pancreatic disease until approximately 90% of the islets have been destroyed. Therefore, demonstration of carbohydrate intolerance is not helpful for the early diagnosis of pancreatic disease. Both insulin and glucose levels vary considerably in patients with chronic pancreatitis, and their levels do not provide useful information (2).

Tumour markers for differentiating cancer from chronic pancreatitis

Many attempts have been made to develop diagnostic techniques that do not require laparotomy or biopsy. Serum and duodenal tumour markers initially appeared the most promising; however, many of the proposed tests, such as carcinoembryonic antigen (CEA), pancreatic oncofetal antigen and ribonuclease, are not sufficiently sensitive to provide a differential diagnosis (17).

More promising are the carbohydrate antigens, especially CA 19-9, the marker that has the closest association with pancreatic cancer (17,18). It has been reported that this carbohydrate antigen has a sensitivity of 78% in resectable and 91% in unresectable pancreatic cancer. The specificity of the test is 92%. Unfortunately, the test has a relatively low sensitivity in early detectable lesions, so it cannot be used as a screening test. The antigen was originally extracted from a colon cancer, is positive, and is expressed in cancers of the colon (19) and other gastrointestinal carcinomas. The monoclonal antibody is expensive, and the test does not appear to be cost-effective at present.

METHODS TO DETERMINE THE ANATOMICAL BASIS FOR ABNORMAL FUNCTION

Imaging techniques (Table 4)

Indirect radiological methods: Conventional x-ray techniques cannot differentiate between the densities of pancreatic and peripancreatic tissues. Therefore, except when the pancreas is calcified, the abdominal survey film does not show the pancreas. Attempts to visualize pancreatic anatomy directly by isotope scanning techniques (^{75}Se methionine) do not provide images that could accurately differentiate normal from diseased pancreas. Therefore, before the existance of ultrasound and computed tomography (CT) scan, direct visualization of the pancreas was not possible. Up to the late 1970s, radiological diagnosis of pancreatic disease depended entirely on 'indirect methods'. These were based on detection of distortion, compression or invasion by benign or malignant masses of hollow organs (stomach, duodenum, colon), ducts (pancreatic or common

TABLE 4
Imaging techniques

Indirect
Barium meal
Barium enema
Angiography
Percutaneous transhepatic cholangiography
Endoscopic retrograde cholangiopancreatography
Direct
Abdominal survey film (if calcified)
Ultrasonography
Computerized tomography (CT) scan
CT scan with dynamic scanning
Magnetic resonance imaging
Endoscopic ultrasonography

TABLE 5
Ultrasonic and computerized tomographic scan of chronic pancreatitis (CP) and cancer

	CP	Cancer
Mass	+	+++
Inhomogeneity	+	+
Cystic lesions	+++	+
Calcification	+	+
Abnormal common duct	+	+
Abnormal pancreatic duct		
Smooth dilation	+	+++
Beaded dilation	+	+++
Irregular dilation	+++	+

+Rare; ++Common; +++Frequent

duct) or blood vessels filled with contrast material.

Barium meal and barium enema: Barium studies of the stomach and duodenum may demonstrate deformities of the posterior wall of the stomach, and of the bulbar, postbulbar and peripapillary regions of the duodenum. Differentiation between cancer and chronic pancreatitis is difficult. Occasionally, large pseudocysts or tumours may compress or invade the colon, resulting in abnormalities of the barium enema.

Angiography: Ultrasonography and CT scanning have, for all practical purposes, replaced angiography in the diagnosis of pancreatic disease.

Percutaneous transhepatic cholangiography: Chronic pancreatic disease may distort or obstruct the transpancreatic portion of the common bile duct. Injection of dye into the intrahepatic duct system via the percutaneous route provides excellent visualization of the common duct. The method is relatively safe, the complication rate due to sepsis, bile leak and bleeding is around 3%, and the mortality is less than 0.2%. Until the introduction of endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC) was the method of choice for investigating patients with obstructive jaundice (20). Since ERCP is now becoming increasingly available in primary and secondary care hospitals, the use of PTC has been relegated to patients in whom ERCP has failed. Clearly, the advantage of ERCP over PTC is that ERCP provides the opportunity for therapeutic intervention, with sphincterotomy or stenting in the same sitting. Furthermore, for pancreatic disease, ERCP is superior because it allows for direct visualization not only of the common bile duct, but also of the pancreatic duct.

ERCP: ERCP plays a principal role in the overall investigation of pancreatic disease. The main indications for ERCP are to: differentiate between chronic pancreatitis and carcinoma in patients with abnormal CT scan or ultrasound; differentiate between hepatobiliary and pancreatic diseases in patients with obstructive jaundice; assess ductal anatomy preoperatively in patients with chronic pancreatitis; prove or disprove the presence of pancreatic disease in patients in whom, based on history and function tests, there is a high degree of suspicion of pancreatic disease but whose ultrasound and CT scans are normal (21).

The major recent advances are in the therapeutic applications of this technique. The classic indication for papillotomy is the presence of common bile duct stones. Recently, sphincter of Oddi spasm has been recognized as a possible cause of recurrent abdominal pain and pancreatitis. It has been suggested that if sphincter of Oddi motility study is abnormal, symptoms may be relieved or relapsing pancreatitis alleviated by sphincterotomy. If a malignancy causes jaundice with symptoms, palliative treatment with stenting is safer and less invasive than surgical bypass procedures. Newer stents allow for less frequent clogging of the insert (21). However, the usefulness of pancreatic stone removal and dilation of the duct remains to be proven.

As some of the features of chronic pancreatitis and pancreatic cancer are similar, differential diagnosis between the two may not always be easy. The most important diagnostic features are the changes that occur in the duct system. The pancreatic duct of normal subjects is regular, with terminal tapering. Multiple irregularities of the major and secondary pancreatic ducts are usually diagnostic of chronic pancreatitis, and dilated ducts due to partially obstructive tumour are sharply delineated and have a smooth contour. However, as these smoothly dilated ducts may take on a 'bead-like' appearance, the ductal changes caused by cancer or chronic pancreatitis may sometimes be difficult to distinguish. The diagnosis becomes easier if the ductal changes of chronic pancreatitis occur in the absence of a localized obstruction. According to several studies, the accuracy of ERCP in differentiating benign from malignant changes is between 62 and 92%. The higher diagnostic accuracy (92%) reported in 1987 than in previous years may be related to improved technique and more accurate interpretation of radiological images (22).

Direct visualization of the pancreas – *Abdominal survey film:* This examination is useful as an indirect method to diagnose acute pancreatitis. The usual findings are localized ileus (sentinel loop) or the cut-off sign of the colon. Routine films cannot distinguish the pancreas from surrounding soft tissues. However, once calcification occurs, direct visualization becomes possible. Calcium may be localized in a single area or extend throughout the organ. As to the differential diagnostic value of calcification, calcium deposits occur most frequently in chronic pancreatitis; however, they may also be present in the walls of pseudocysts, cystic neo-

plasms and in the parenchyma of carcinomas.

***Ultrasonography*:** Echographic diagnosis of both chronic pancreatitis and pancreatic carcinoma is dependent on changes in size and contour of the gland, echoreflectivity of the parenchyma and alteration of ductal anatomy (Table 5). Unfortunately, the shape, size and position of the organ may differ from one normal individual to another, and echoreflectivity increases with age. In chronic pancreatitis, changes in gland size are not always diagnostic because this condition may cause pancreatic atrophy or enlargement. Alterations of contour may be difficult, because the age-dependent increases in echogenicity of the gland may render delineation of the pancreas from peripancreatic fibrous tissue difficult. A solid pancreatic mass of a tumour cannot always be differentiated from that of a focal mass caused by inflammation. Also, cystic tumours may be difficult to differentiate from pseudocysts.

Interpretation of ultrasonographic changes in the ducts are subject to the same limitations were described for the ductal characteristics observed in ERCP. In a retrospective analysis of 27 patients with proven chronic pancreatitis, similar ductal abnormalities were found in patients with or without pancreatic insufficiency, and in 13% of patients with chronic pancreatitis the ultrasound was normal (23).

***Computerized axial tomography*:** Computerized axial tomography (CAT) is one of the most accurate direct methods to assess the pancreas. However, for the same reasons as described for ultrasound, except for the classic examples of each disease, the differential diagnosis of chronic pancreatitis from carcinoma may be difficult and not always possible (Table 5). Mass lesions may be caused by inflammation or tumour, cystic changes may be due to pseudocysts or cystic neoplasia, and changes in ductal anatomy in chronic pancreatitis may resemble those seen in carcinoma of the pancreas (24).

Dynamic scanning (25) employs rapid intravenous injection of 150 mL of iodinated contrast material. Starting immediately after the intravenous injection of the bolus, cuts are made at 1 cm intervals with a rapid scan sequence of less than 2 s. This allows assessment of the relationship of a mass to the surrounding vasculature, and detects invasion of arteries or veins, infarctions and perfusion defects. A correct diagnosis of pancreatic cancer has been reported in 91% of 174 patients with a frequency of false positive and false negative results of 8 and 1%, respectively. Unfortunately, the accuracy of this method was studied in patients with advanced cancer, and only six of the 174 patients had resectable disease. Thus, even this improvement in diagnosis using CAT scanning does not allow for the early diagnosis of resectable cancer (25). Of special diagnostic interest are benign and malignant cystic lesions of the pancreas (Figures 3,4); their x-ray characteristics are reviewed in Table 6. Combined with ERCP, some of these tumours are easily recognizable and may have characteristic appearance such as classic pseudocyst of chronic pancreatitis (Figure 5), the sunburst calcification of the frequently benign serous cystadenomas (Figure 6) and the large thick fluid-filled cysts of mucinous cystadeno carcinomas (Figure 7).

TABLE 6
Cystic tumours

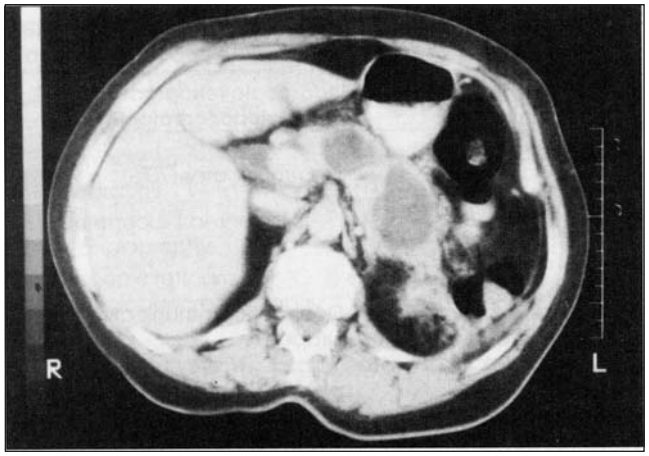
	Ultrasound/computed tomographic scan	Endoscopic retrograde cholangiopancreatography
Pseudo cyst		
Simple	–Single –Homogeneous	–Communicates (70%)
Complicated	–Hemorrhage –Multiloculated –May calcify	
Serous cystadenoma (microcystic cystaden)	–Lobulated, large –Multiple small cysts –'Sunburst' calcification	–Does not communicate –Draped
Mucinous cystadeno CA (macrocystic cystaden CA)	–Large cysts –Thick fluid –Dystrophic calcification	–Does not communicate –Draped –Obstructed
Mucinous ductal ectasia	–Tumour in duct –Cystic dilation of duct	–Communicates –Thick fluid, draped –Cystic dilation of duct
Papillary cystic tumour	–Tumour in duct –Obstruction –May cause acute pancreatitis	–Obstruction –Draped –Cystic dilation of duct –Possible pseudocyst

Based on reference 4

***Magnetic resonance imaging*:** Examination of the pancreas with magnetic resonance imaging (MRI) has been limited due to distortion by respiratory motion and difficulty in distinguishing between the bowel and pancreas. The head and body can be seen reasonably well, but the tail is often not visualized. At present, the diagnostic capability of the CT scan is superior to that of MRI (26).

A recent report indicates that MRI can noninvasively visualize the biliary tract by subjecting the images obtained in the axial plane to a computer generated projection of the cholangiogram in a coronal plane. With today's techniques, the images are not as clear as with invasive visualization of the ducts, and several episodes of 17 to 20 s breath holding are necessary to obtain an image (27).

***Endoscopic ultrasonography*:** Endoscopic ultrasonography involves the attachment of an ultrasound transducer to the endoscope. The scope is introduced into the duodenum or into the posterior wall of the stomach. Under direct endoscopic observation an echogram of the pancreas is created, which is well seen because it appears adjacent to the endoscopic image. Echograms of the relation of the pancreas to the bili-



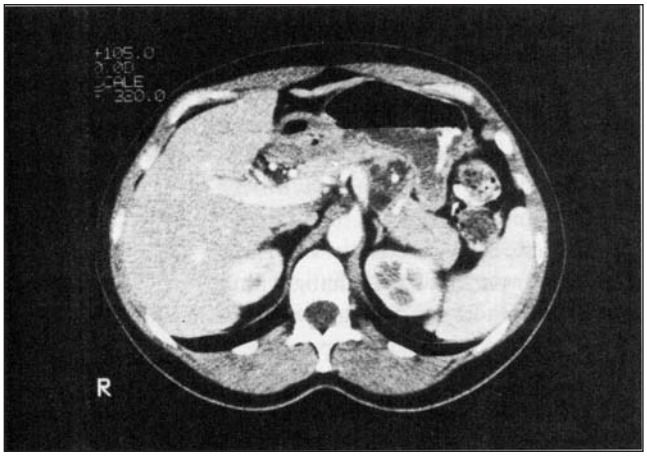
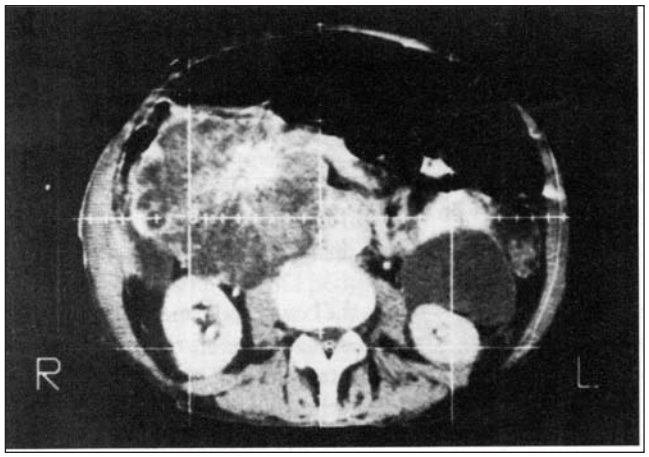


Figure 7) *Computed tomographic scan of mucinous cystadeno carcinoma. Note the multiloculated fluid-filled large cysts*



Top left Figure 5) *Computed tomographic scan of two large pseudocysts of the pancreas. Note the sharply delineated outline of the cysts*

Bottom left Figure 6) *Computed tomographic scan of a serous cystadenoma. Note the 'sunburst' calcification within the cyst*

TABLE 7
Methods to obtain material for histology

Cytology from duodenal juice
Cytology from pancreas obtained during endoscopic retrograde cholangiopancreatography by collection during secretin stimulation brushing
Cytology by ultrasonography or computed tomographic scan guided thin needle biopsy
Cytology obtained during endoscopic ultrasonography
Biopsy obtained during endoscopic retrograde cholangiopancreatography
Biopsy obtained during surgery

ary system, portal vein, arteries and the aorta can be obtained. Differentiation of malignant and benign tumours of the pancreas is possible for masses of 30 mm diameter, and even as small as 20 mm. It is somewhat less sensitive for tumours of less than 20 mm diameter (28,29).

It is unlikely that this examination will ever become the primary method to detect small and fully resectable cancers, because it is never used before some other technique (ERCP, CT scan, etc) has already raised the suspicion of a tumour. However, by now endoscopic ultrasonography has proven to be the best method to assess peripancreatic local invasion and help to decide preoperatively on resectability of the tumour (28,29).

Methods to establish histopathological diagnosis

The many methods that have been used to provide specimens for histological diagnosis are shown in Table 7. Every method has certain specific limitations. Cytology from duodenal juice has a very low yield of cells. Cytology obtained by cannulation of the pancreatic duct during ERCP is cumbersome. A cytology brush or the recently developed biopsy forceps can be introduced easily into the head of the pancreas during ERCP. However, obtaining specimens from other parts of the gland may be difficult and often impossible (30).

The major disadvantage of the ultrasound or CT scan thin needle biopsy is that it may be difficult to differentiate tumour mass from pericancerous edema on the scan. If the latter is biopsied a false negative cytology is obtained (31). Reports have also indicated that occasionally the tumour may spread along the needle tract (32). The major disadvantage is that these biopsies are carried out only once the tumour is large enough to be seen on ultrasound or CT scan, and in most instances, by then it is too late for curative removal of the malignancy. Thus,

in most instances these biopsies are only used to confirm by histology the presence of unresectable cancer. Direct cytology is now possible during endoscopic ultrasonography (33). The aspiration needle is inserted directly into the small tumour. Although data from a prospective study are not yet available, this method may surpass the accuracy of other types of biopsies.

All these methods have a common defect: they exhibit low sensitivity but high specificity. In other words, if no cancer cells are found, malignancy is not excluded with certainty, but the presence of cancer cells provides an unquestionable diagnosis of malignancy. The major limitation is that many of these tumours are desmogenic and cancer cells may be difficult to find. This also holds, not only for aspiration cytology, but also for surgical biopsies (34).

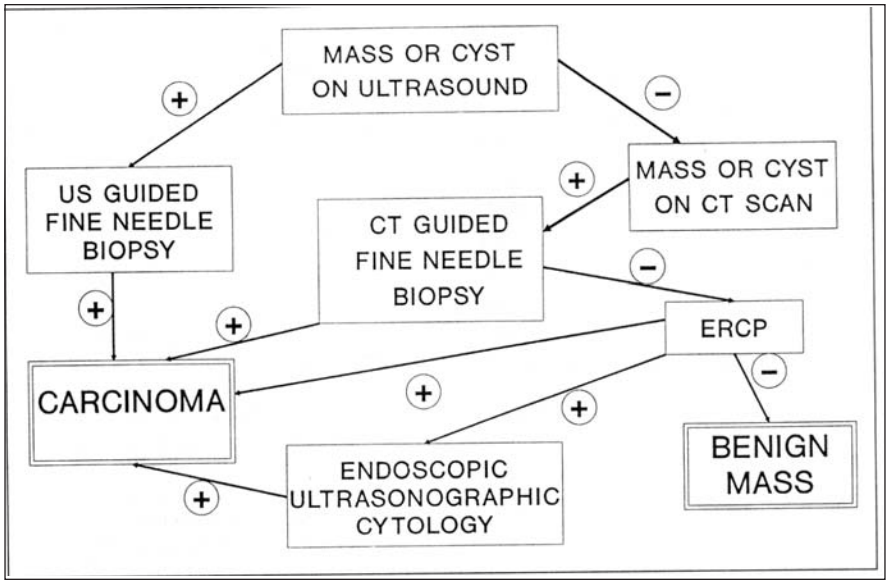


Figure 8) *Algorithm to differentiate carcinoma from chronic pancreatitis. CT Computed tomography; ERCP Endoscopic retrograde cholangiopancreatography; US Ultrasonography*

CLINICAL APPROACH TO DIAGNOSIS

There are three questions that need to be answered during investigation: first, whether chronic pancreatic disease is present; second, whether this is benign or malignant; and finally, whether a malignant neoplasm is still curatively resectable. Before the introduction of ultrasound and CT scan, patients were referred to gastroenterologists because of abdominal pain, diarrhea, weight loss or jaundice. The gastroenterologist's job was to diagnose these complex problems by means of laboratory investigation, indirect imaging techniques and, since the 1970s, by ERCP. This has changed with the introduction of both echography and CT scanning.

Presently, patients are referred because of suspected pancreatic disease detected as an incidental finding on ultrasound or CT scan, frequently ordered for reasons unrelated to suspected pancreatic disease. These patients do not need pancreatic investigation to prove the presence of pancreatic disease and, in contrast to past practice, will not undergo function tests but will proceed directly to ERCP.

There are, however, patients who are still referred for investigation of symptoms suggestive of pancreatic disease without previous work-up. In these patients, the first examination ordered is the abdominal ultrasound. If this is negative, a CT scan is carried out. If this is also normal and if pancreatic disease is strongly suspected, an ERCP follows. If this is also negative, in the presence of a strong clinical suspicion, a secretin test is carried out.

Some clinicians still use pancreatic function tests and even recent research papers have used them (11,16,35). This is why these tests were reviewed in the first section of the paper, even though there may be little indication for their utilization. Specifically, because of their poor predictive value, presently available 'screening tests' are not cost-effective. For all practical purposes there are only two pancreatic function tests that are still of use: the 72 h fecal fat balance before and during pancreatic enzyme administration and the secretin test. The first is used in the course of investigations of patients with steatorrhea. Because the secretin test is more sensitive than any of the imaging methods (14), it is used where chronic pancreatitis is suspected but the ERCP is still normal.

The methods used to achieve the second objective, ie, to differentiate between chronic pancreatitis and carcinoma, is reviewed in the algorithm shown in Figure 8. If a mass is found on ultrasound, a guided fine-needle biopsy is carried out. A positive biopsy for a tumour is diagnostic, but a negative one does not exclude malignancy. If the ultrasound is negative, a dynamic CT scan may demonstrate the lesion and a CT guided biopsy may provide a diagnosis for malignancy. If, however, the biopsy yields no malignant cells, an ERCP is carried out to assess ductal anatomy. The role of endoscopic ultrasonography combined with endoscopic ultrasound guided cytology needs to be further evaluated. The main diagnostic role of this test will be to assess the nature of tumours or cysts that are too small for regular echography or CT scan guided fine-needle biopsy.

The third objective of investigation is to establish whether a malignancy is resectable in patients in whom distant metastases have been excluded. In the past, angiography used to be employed to assess vascular invasion. As endoscopic ultrasound becomes more and more established, this will become the method of choice because it can assess most accurately size, vascular invasion and lymph node involvement.

In spite of the major advances in methods of investigation, mortality due to cancer of the pancreas has not diminished during the past 20 years (36). This is because cancers of the pancreas can grow to considerable size before they cause symptoms. Once symptoms

are present, it is still difficult to differentiate chronic pancreatitis from cancer unless the cytology is positive. None of the tests can diagnose cancers less than 2 cm in diameter, except in the rare instance where a small tumour obstructs the papilla. Those tests that can diagnose small and resectable tumours, ie, ERCP and endoscopic echography, are done only once a suspicion of pancreatic disease has arisen on the basis of less sensitive investigations. Even if tumours are discovered early, surgery is difficult and has considerable mortality, and radiotherapy and chemotherapy remain ineffective. Until a very sensitive and accurate screening blood test that can detect very small cancers has been developed and until improvement in therapy has been achieved, the high mortality due to cancer of the pancreas will remain unaltered.

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