Progress report
Cancer of the pancreas

Carcinoma of the pancreas is now the fourth commonest cancer causing death in the USA, with only cancer of the lung, of the colon and rectum, and of the breast more frequent\(^1\). In the USA the incidence of pancreatic cancer has increased threefold since 1930\(^2,3\), while in England and Wales its incidence has doubled during the same period\(^4\), and in the last 25 years the incidence has also doubled in Norway\(^5\) and increased fourfold in Japan\(^6\). In most western countries an annual incidence of between 9 and 10 cases per 100 000 of the whole population is now found, with a markedly higher incidence (up to 100 per 100 000) in people over 75 years of age\(^7\).

Most patients who develop carcinoma of the pancreas die of the disease within six months of the diagnosis\(^8,9,10,11\). Judging from the results of operative treatment, by the time symptoms develop it is too late for curative treatment in the majority of cases, because the presenting symptoms of pancreatic carcinoma are so vague and nonspecific and also because the pancreas is difficult to examine and investigate. Symptoms have therefore usually been present for months before a diagnosis is made\(^12,13,14,15,16,17,8\). Moreover, metastatic spread appears to occur early in the course of the disease, presumably because the pancreas is abundantly supplied with nerves and venous and lymphatic drainage, so that the carcinoma has usually metastasised at the time of laparotomy.

The present report reviews the aetiology and diagnosis of the commonest carcinoma of the pancreas, which originates from the duct cells, and does not consider the rare endocrine and acinar cell tumours of the pancreas, or cancer arising in periampullary tissues other than pancreas (the lower 2 cm of the bile duct, the ampulla of Vater, and the duodenum adjacent to the papilla of Vater). The latter tumours present clinically in the same way as pancreatic cancer and are diagnosed by the same procedures. However, the prognosis of non-pancreatic periampullary carcinoma is very much better than with carcinoma of the pancreas, and it is therefore always necessary to identify the site of origin of tumours in the region of the head of the pancreas, and to select treatment accordingly\(^18\).

Incidence

In 1976 it is estimated that the incidence of carcinoma of the pancreas will be about 9.5 cases per 100 000 of the population of the USA and Western Europe\(^1,7\). The incidence varies with sex, age, and race. In most countries the incidence is higher in males, with a sex ratio of about two males to each affected female\(^18\). The male preponderance affects all age groups, but becomes progressively less from the age of 35 years\(^20\). The incidence of cancer of the pancreas is very strongly correlated with age, being rare in individuals less than 25 years old, only 42 cases having been reported up to 1974\(^21\), and uncommon below 45, while the occurrence in males over 75 years old is eight to
10 times that in the general population\textsuperscript{19}. The effect of race on the incidence of carcinoma of the pancreas is complicated by racial differences in diet and age distribution. Nevertheless, when age-standardised data are compared, there is a moderate increase in the incidence of pancreatic cancer of Negroes in the USA and Polynesians in Hawaii, and a marked increase in Maoris in New Zealand, compared with their Caucasian counterparts\textsuperscript{22}, whose diet and exposure to environmental carcinogens are presumably not very different.

**Aetiological factors**

**Cigarette smoking**

A number of studies have shown that the incidence of carcinoma of the pancreas in cigarette smokers is about twice that of non-smokers\textsuperscript{23, 24, 25, 26, 27}. Best\textsuperscript{23} showed that the risk of developing pancreatic cancer was proportional to the number of cigarettes smoked, and Kahn\textsuperscript{25} found a similar dose relationship up to 40 cigarettes per day. However, other studies have shown that individuals smoking less than 10-15 cigarettes per day are subjected to the greatest risk, the risk decreasing as the number of cigarettes smoked each day increases, although the risk remains greater than that for non-smokers, regardless of the number of cigarettes smoked\textsuperscript{27}. The inverse relationship between the incidence of pancreatic cancer and number of cigarettes smoked is probably caused by an increased mortality from other diseases related to smoking, such as carcinoma of the lung in persons who smoke very large numbers of cigarettes\textsuperscript{26}. Indirect evidence for an association between smoking and carcinoma of the pancreas has been presented by Krain\textsuperscript{2} who pointed out that the increase in cigarette smoking from 1940 to 1970 paralleled the increase of pancreatic carcinoma and that the median age for pancreatic cancer was 10-15 years earlier in smokers than in non-smokers.

The mechanism by which cigarettes cause pancreatic carcinoma is not known, but the most likely explanation is that a pancreatic carcinogen is present in tobacco smoke. The carcinogen appears to be very potent, in view of the finding that the risk of pancreatic carcinoma is increased almost threefold in men by smoking 10 cigarettes per day or less\textsuperscript{26}, but the carcinogen must presumably act over a long period of time, as, at high levels of cigarettes smoking, death from other causes occurs before carcinoma of the pancreas develops. Wynder has also suggested that smoking may have an indirect carcinogenic effect on the pancreas through the effect of the increased concentration of blood lipids which follows heavy smoking, as the concentrations of blood lipids may be related to the development of pancreatic cancer\textsuperscript{28}.

An association between the risk of developing pancreatic carcinoma and the smoking of cigars and pipes\textsuperscript{23, 29} or cigars alone\textsuperscript{25} was reported, though the number of subjects was small. If this association denotes a real relationship, carcinoma of the pancreas differs from carcinoma of the lung in that deep inhalation of the smoke is not necessary for its development, perhaps because the carcinogen is highly potent and can be readily absorbed from the mouth or upper respiratory tract.

**Diet**

Evidence for an important role of diet in the causation of carcinoma of the pancreas has been provided by studies indicating a significant correlation between the average per capita intake of fat and the national incidence of the
disease. In addition, retrospective studies have shown an increased intake of protein in patients with carcinoma of the pancreas in Japan. It has been suggested that the rapidly rising incidence of this disease in Japan is a consequence of the westernisation of the diet since dietary studies show a steadily increasing intake of fat and animal protein after 1950, during which time the incidence of carcinoma of the pancreas has increased fourfold.

A comparison between the national consumption of coffee and the incidence of carcinoma of the pancreas showed a significant correlation in males, but no correlation in females. No correlation was found between tea consumption and incidence of the disease in either sex.

No satisfactory mechanism has been proposed to explain the relationship between diet and the incidence of carcinoma of the pancreas, though it may be possible to reduce the likelihood of developing pancreatic carcinoma in groups at risk (the elderly, or the diabetic) by dietary manipulation, if the aetiological factors can be identified. It is possible that modern processed foods contain carcinogens specific for the pancreas, particularly as chemicals which cause a high incidence of pancreatic cancer in other species have been described. The most potent of these are nitrosamines, and the recent finding that nitrosamines can be formed during cooking and in the stomach from nitrates used in the preservation of meat suggests a possible dietary source of these carcinogens. However, the organ specificity of the nitrosamines depends on their chemical nature and the species in which they are tested. No information is available about the organ specificity of these chemicals in the human and there is no evidence for the presence in man of the nitrosamines which cause pancreatic cancer in other species.

If potential pancreatic carcinogens are present in the environment, it is possible that the composition of the diet could augment or potentiate the action of these carcinogens. Thus, it is known that chronic administration of cholecystokinin-pancreozymin (CCK) causes pancreatic hypertrophy and hyperplasia. It is possible that a diet rich in fat and protein (both potent stimulants of CCK-PZ release) might increase cell turnover in the pancreas and thus increase the susceptibility of the pancreas to carcinogens. In this connection, we have recently demonstrated that raw soya flour greatly sensitises the pancreas of rats to the carcinogenic action of azaserine, presumably because the pancreatic hyperplasia evoked by the trypsin inhibitor of the raw soya flour potentiates the action of the carcinogen.

**DIABETES MELLITUS**
The incidence of carcinoma of the pancreas in patients with diabetes mellitus appears to be about twice that in the general population. The most extensive study of this problem is that of Kessler, in which a standardised mortality ratio of 1.82 for carcinoma of the pancreas was found for a population of 21,447 diabetics studied in Boston between 1930 and 1959. The mortality ratio was lower for males (1.47) than for females (2.13) but was significantly raised above normal for both subgroups. As in the case of heavy cigarette smokers, the lower incidence in males probably reflects earlier death from other causes. No other malignancy showed an increased incidence in the total diabetic population or in either sex subgroup and the overall rate of death from malignancy was not raised in the diabetic subjects. Other studies showed a similar increased incidence of carcinoma of the pancreas in diabetic
subjects\textsuperscript{41,42}, while Levin and Connelly provide indirect evidence for this relationship\textsuperscript{40}.

The development of diabetes \textit{de novo}, or the development of instability in a previously controlled diabetic, about the time of appearance of symptoms of carcinoma of the pancreas has been frequently noted\textsuperscript{43,44,45,46,47}. While the mechanism involved is obscure\textsuperscript{43,48,49}, it is probable that the diabetes is the result of some process initiated by the tumour. In the study of Kessler\textsuperscript{40}, patients with carcinoma who developed diabetes were largely eliminated by selecting for study only subjects who had survived at least one year after diagnosis of diabetes. Nevertheless, some patients did develop cancer in the year after diagnosis of diabetes, and if these were eliminated from analysis the mortality ratio for male subjects (1.27) was no longer significantly raised, although that for females (1.82) remained significantly greater than expected. In the subjects in whom the date of onset of symptomatic carcinoma could be accurately determined to be more than one year after development of diabetes (22 of 30 males and 33 of 48 females) the average survival after onset of diabetes was $11.4 \pm 2.9$ years\textsuperscript{40}, and the diabetes therefore almost certainly preceded the development of carcinoma.

No satisfactory mechanism has been proposed to explain why diabetes mellitus predisposes to carcinoma of the pancreas, although functional links between the endocrine and exocrine pancreas have been suggested\textsuperscript{50}. The intriguing possibility that animal insulin or an impurity in the product might be carcinogenic to the pancreas has been proposed\textsuperscript{40}.

**Pancreatitis**

There is no evidence that pancreatitis, either acute or chronic, predisposes to carcinoma of the pancreas, although inflammation of some part of the pancreas is extremely common in association with carcinoma\textsuperscript{51,52}. Indeed, carcinoma of the pancreas may sometimes present with the symptoms of acute pancreatitis and in these patients the diagnosis of the underlying malignant condition may be delayed by many months. In the series of 255 patients with pancreatic cancer reported by Gambill\textsuperscript{5}, 26 had symptoms of pancreatitis\textsuperscript{53}. In these 26 patients symptoms were present for an average of eight months before the carcinoma was diagnosed, giving a prediagnostic symptomatology almost twice as long as in the remaining 90\% of cases. However, even in patients complaining of symptoms suggesting pancreatitis, laparotomy was of limited value in the diagnosis, as in 10 of the 26 patients laparotomy was reported to show only acute pancreatitis, and a final diagnosis of carcinoma was not made until three to 24 months (mean five months) later.

Rarely, carcinoma may develop in patients with longstanding chronic pancreatitis but the association is almost certainly fortuitous\textsuperscript{54,55}. Robinson, Scott, and Rosenfeld in 1970\textsuperscript{56} could find only 15 authenticated cases of this combination of diseases. If there is any link between the diseases it may be that chronic alcoholism predisposes to both conditions, as an increased alcoholic intake has been reported in patients with carcinoma of the pancreas\textsuperscript{57}. However, a recent study of the cause of death in alcoholics showed no increase in the incidence of carcinoma of the pancreas\textsuperscript{58}.

**Carcinogens**

Carcinoma of the pancreas can be readily induced in experimental animals by the implantation of carcinogens directly into the pancreas\textsuperscript{59,60}. Of greater
significance is the recent finding that a small number of carcinogens cause a high incidence of pancreatic carcinoma after systemic administration under experimental conditions. Methyl nitrosourea causes carcinoma of the pancreas in guinea-pigs after a long latent period of 1.5 to two years, although the duration can be reduced in a specific highly susceptible strain (strain 13)\(^{31}\). A number of metabolites of di-n-propyl nitrosamines cause pancreatic carcinoma in the hamster\(^{42}\). The most potent are 2, 2' dihydroxy-di-n-propyl nitrosamine (DHPN)\(^{43}\) and 2, 2' dioxypropyl-n-propyl nitrosamine (DOPN)\(^{44}\), both of which cause carcinoma of the pancreas in virtually all animals exposed to these chemicals for six months or less. In the case of DHPN, tumours also commonly occur elsewhere, but with DOPN very few other organs are affected. These pancreatic carcinomas are of ductal origin and thus resemble the human tumours. DHPN is peculiarly species specific, having only a low carcinogenicity for the pancreas of the rat\(^{45}\), although other related compounds are more potently carcinogenic in this species\(^{45}\). The carcinogenicity of DOPN in species other than hamster has not yet been reported.

For systematically administered chemicals to cause carcinoma of the pancreas they must reach the organ through the blood stream or the ductal system or both. Wynder and his colleagues\(^{28}\) have proposed the hypothesis that carcinogens are produced in the liver by the metabolic conversion of inactive precursors from, for example, tobacco. These active carcinogens are excreted in the bile and reach the pancreas by reflux into the pancreatic duct. After many years' exposure, carcinoma develops in the ducts\(^ {59}\). The hypothesis accounts for the specificity of carcinogens for the pancreas and also explains the apparently high incidence of carcinoma in the head of the pancreas, compared with body or tail\(^ {60}\). However, Bates\(^ {67}\) points out that most carcinogens which are excreted by the liver are converted into water soluble, non-carcinogenic compounds before being excreted in the bile, and that reconversion to active carcinogens would be necessary before they could act in the pancreatic ductal system. Bates\(^ {67}\) also suggests that the seemingly higher incidence of carcinoma of the head of the pancreas may result from a sampling error, as usually only carcinoma of the pancreas arising in the head can be detected early, at a time when the site of origin of the tumour can be determined with certainty.

If the carcinogen is carried in the bloodstream, it could be organ selective for the pancreas as a result of some metabolically specific process in the pancreas. Many chemicals become carcinogenic only after metabolic conversion from procarcinogens at their site of action\(^ {54,68,69}\). It is possible that the pancreatic ductal cells are peculiarly capable of metabolising the chemicals which are carcinogenic there, but this has not yet been demonstrated. The ductal cells do not have any known biochemical peculiarity apart from their capacity to secrete bicarbonate in large amounts, a function which may be linked to carcinogenicity at this site by the recent highly speculative suggestion that intracellular pH may be a factor in the development of carcinoma\(^ {70}\).

A specific ductal site of action of carcinogens may also be determined by the possibility that pancreatic cells concentrate the carcinogens more than other cells. It has been shown that the bicarbonate transport system of the duct cells will also transport lipid-soluble weak organic acids\(^ {71}\). Carcinogens with appropriate chemical properties might therefore be concentrated either in the cell or in the duct lumen adjacent to the cells. Similarly, it has been shown that the acinar cells take up aminoacids and amines avidly\(^ {72}\), and,
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probably as a result of this, certain aminoacid derivatives are potent carcinogens for the acinar cells in rats. However, the tumours which develop are histologically distinct from the ductal cell tumours seen in humans.

Whatever the mechanism, it is apparent that potent carcinogens with organ specificity for the pancreas of animals have been discovered. While similar carcinogens acting on the human pancreas have not been identified, there is presumptive evidence that such compounds do occur. Thus carcinoma of the pancreas is commoner in workers in the chemical industry than in the general public, and these workers are exposed to a wide variety of potential carcinogens in their work. The identification of these carcinogens is also an important area for further search, in the hope that such carcinogens can be identified and eliminated.

Diagnosis

SYMPTOMS
Carcinoma of the pancreas may develop in the head, body, or tail of the pancreas, with the head of the organ involved in 60-80% of reported cases and the body and tail in the remainder. The symptoms produced by the cancer depend to some extent on the site of the tumour, although pain, jaundice, and loss of weight are the major symptoms, whatever the anatomical site of the carcinoma.

Pain
Pain occurs as a presenting symptom in between 50 and 80% of patients and occurs at some time in the course of the disease in between 75 and 90% of patients. Pain without other symptoms has been alleged to be more frequent in carcinoma of the body and tail than in carcinoma of the head of the pancreas but is such a frequent symptom in carcinoma of the head of the pancreas that the mere presence of pain is of no value in predicting the site of the tumour. The pain may be maximal in abdomen or back. The characteristics of the abdominal pain have been described by Gullick and Berk and analysed by Thompson and Rodgers, who found that the pain was variable in location and severity, but most frequently occurred as a dull aching or boring pain in the epigastrium, was steadily progressive, and often increased in severity at night. Gullick found that the pain of carcinoma of the head of the pancreas was often aggravated by the ingestion of food, while the pain of carcinoma of the body and tail of the pancreas was worse when recumbent and was relieved by sitting forward. Berk noted a similar effect of posture but did not relate this feature to the site of origin of the tumour.

The pain may be maximal in the right and left upper quadrant. Gullick found, in his series of 100 cases, that pain from carcinoma of the head of the pancreas was invariably located in the epigastrium and/or right upper quadrant, while carcinoma of the body and tail resulted in pain in the epigastrium and/or left upper quadrant. He noted, however, that such a characteristic difference in the location of the pain had not been found by other authors. Nevertheless, Duff also reported a marked tendency of pain to radiate to the left side of the abdomen in carcinoma of the body and tail of the pancreas.

Gambill tabulated the site of occurrence of pain in 239 patients with pancreatic carcinoma. He recorded the pain as mid-epigastric in 46%; as upper
abdominal in 23%; as lower abdominal in 20%; as right upper quadrant in 18%; and as left upper quadrant in 13% of patients at some time during the course of the disease, with an overall incidence of abdominal pain of 80%.

Pain referred to the back is less frequent than abdominal pain, occurring as a presenting symptom in from 15% to 30% of patients and in up to 60% of patients at some time in the course of the disease. The pain rarely occurs alone, but is usually associated with abdominal pain. The pain is usually constant and situated in the lumbar region and is more frequent in patients with carcinoma of the body and tail of the pancreas than in those with tumours in the head of the organ.

Jaundice
Jaundice is the first symptom of carcinoma of the pancreas in 10 to 30% of patients. By the time the patient is first seen by the doctor, jaundice is present in 30 to 65% and occurs at some time in the course of the disease in 90% of patients. The jaundice is often accompanied by pain. Pain preceded the jaundice by an average of 13 weeks in two-thirds of the icteric patients reported by Douglass and Holyoke and also preceded jaundice in 83% of the patients in whom the order of appearance of symptoms could be accurately determined by Berk. Although other studies report up to 50% of the jaundice to be painless early in the disease, most show that less than 20% remain pain-free during the course of the disease.

The jaundice is usually progressive until relieved by surgery, but spontaneous fluctuations in the degree of icterus early in the course of the disease have been reported in about 10% of patients. The jaundice may be accompanied by pruritus which may be very troublesome. Jaundice is much more common in carcinoma of the head of the pancreas than in carcinoma of the body or tail of the organ. The incidence of jaundice at some time in the course of the disease is between 80 and 90% in patients with carcinoma of the head of the pancreas, while it may be as low as 5% at the time of diagnosis in tumours of the body and tail. Most studies, however, report an incidence of jaundice of between 20 and 50% at some stage of the disease in the latter group. The jaundice associated with carcinoma of the body and tail of the pancreas is often caused by secondary spread of the tumour to the liver and to lymph nodes around the bile duct, and usually presents only in the last few weeks of life.

Loss of weight
Loss of weight is probably the commonest symptom of carcinoma of the pancreas and usually precedes other symptoms. Most studies report that loss of weight afflicts 70 to 90% of patients by the time of diagnosis, though occasionally a lower incidence is reported. These differences in incidence may reflect differences in the criteria used to define weight loss.

The weight loss is usually rapid and progressive. Berk collected data on 813 patients and found an average weekly loss of 3.1 kg with an average total loss of 11.9 kg, while when survival is prolonged weight loss may be as great as 30 kg. The rate and total amount of weight lost is not dependent on the site of the tumour, similar weight loss being seen in carcinoma of the body and tail of the pancreas, as in carcinoma of the head of the organ. Nor is the extent of the weight loss directly related to the extent of the tumour,
as severe weight loss is sometimes found in patients with resectable tumours.\(^{84,77}\)

The cause of the extensive weight loss seen in carcinoma of the pancreas has not been fully explained. Anorexia is undoubtedly a factor, but most studies find the incidence of anorexia to be less than 50% so that anorexia is less common than loss of weight.\(^{79,15,78,40}\) Malnutrition caused by exocrine insufficiency of the pancreas is also a factor, but the degree of weight loss is as severe in carcinoma of the body and tail of the pancreas, when malnutrition should be minimal, as in carcinoma of the head of the pancreas when obstruction to the pancreatic and/or biliary duct may cause massive malnutrition and malabsorption. Furthermore, frank steatorrhea is uncommon, occurring in only about 10% of patients.\(^{8,83,49}\)

**Other symptoms**

Among other symptoms noted by Gambill in his review of 239 patients with carcinoma of the pancreas were subjective epigastric bloating and flatulence (31%), weakness or fatigue or both (31%), diarrhoea (25%), vomiting (23%), and constipation (11%). Only the first two were consistently early symptoms. Other studies confirm the approximate frequency of these symptoms in carcinoma of the head of the pancreas.\(^{12,77,78}\) In carcinoma of the body and tail of the pancreas bloating and flatulence seem less frequent, though an incidence of the other symptoms similar to that found with carcinoma of the head of the organ is reported.\(^{18}\)

**Signs**

In carcinoma of the head of the pancreas the commonest physical findings are jaundice, a palpable enlarged liver, and abdominal tenderness. In earlier studies an enlarged liver was found in about 60% of cases\(^{15,78,77}\) but in the more recent report of Gambill\(^{8}\) hepatomegaly was found in only 19% of the patients. Abdominal tenderness is less frequent, the reported incidence ranging from 24% to 49%.\(^{77}\) A palpable gallbladder is found in 12% to 37% of cases, with a higher incidence in jaundiced patients.\(^{12}\) Thrombophlebitis occurs in less than 10% of patients.\(^{8,78,49}\)

Hepatomegaly is less common in carcinoma of the body and tail of the pancreas but an abdominal mass can be felt in 40 to 50% of patients\(^{77,15}\) by the time a diagnosis is made. As symptoms from carcinoma of body or tail of pancreas are usually absent until widespread dissemination has occurred, physical signs of metastatic spread are common when the patient first seeks medical advice. In the 150 cases reported by Die Goyens, 106 (70-6%) had signs of distant spread at the initial examination, including hepatomegaly, enlarged supraclavicular lymph nodes, metastasis to the rectal shelf, and ascites.\(^{15}\)

The development of diabetes mellitus, or difficulties with the control of established diabetes, have been frequently observed in early carcinoma of the pancreas, often before other symptoms or signs appear.\(^{43,44,45,46,42,16,47}\) The sudden appearance of diabetes in a middle-aged or elderly patient with no family history of the disease, particularly if associated with weight loss or vague abdominal symptoms, is therefore an indication for the presence of a pancreatic malignancy.

**INVESTIGATIONS**

At the present time the most diagnostically precise techniques for the detec-
tion of carcinoma of the pancreas are pancreatic secretory studies, selective angiography, endoscopic retrograde cholangiopancreatography (ERCP) and laparotomy.

**Pancreatic secretory studies**
Duodenal intubation and aspiration of duodenal contents have been used for the purpose of confirming the diagnosis of pancreatic cancer for about three decades. It has been assumed that decrease in some index of pancreatic secretory capacity, as manifest by the secretory response to the small intestinal hormone secretin, and more recently secretin combined with cholecystokinin-pancreozymin, reflects the pancreatic ductal obstruction caused by the cancer. Thus, a number of reports have demonstrated that, in patients with pancreatic cancer, the rate of secretion is impaired, so that the volume of the aspirated duodenal contents in response to the hormones is less than normal, while the concentrations of bicarbonate and enzymes in the aspirated juice remain normal or are not altered as much as secretory rate, thus differing from the secretory pattern shown by patients with chronic pancreatitis in whom the principal defect is impairment of the secretion of bicarbonate. More recent analysis of the secretory response to combined secretin and CCK showed that advanced pancreatic cancer, even in anicteric patients, was associated with marked overall pancreatic achylia indistinguishable from the secretory response of patients with chronic pancreatitis. Less severe functional impairment of the pancreas was manifest by significantly more marked impairment of enzyme secretion than of bicarbonate secretion in patients with pancreatic cancer, compared with chronic pancreatitis. However, none of the reported series contain sufficient information about early pancreatic cancer to permit evaluation of the role of secretory tests in the detection of operable pancreatic neoplasms.

Secretory studies have been combined with cytological examination of the duodenal aspirate. Histological examination of the centrifuged sediment has been claimed to provide confirmation of pancreatic cancer in a variable proportion of cases. Histological techniques have been extended by studies of fluorescence after the administration of tetracycline, as neoplastic cells are claimed to fluoresce in these circumstances. A further very recent extension of combined secretory and cytological techniques has involved the use of retrograde endoscopic cannulation of the pancreatic duct, which permits collection of pancreatic juice uncontaminated by other secretions. The pancreatic juice can be collected after stimulation of secretion with secretin and CCK for chemical and enzymic analysis. For cytological examination, either the centrifuged sediment of the secretory pancreatic juice, or the debris collected in the bristles of fine brushes inserted into the pancreatic duct through the endoscopic cannula, can be examined histologically for neoplastic cells. It is clear that histological evidence obtained by these means or by direct biopsy provides the only unequivocal confirmation of the presence of pancreatic neoplastic disease.

**Selective angiography**
In its most sophisticated form selective injection of radio-opaque dye into branches of the coeliac artery is capable of detecting tumours as small as 1.5 cm in diameter, at which stage resection with a hope of surgical cure is
possible. To obtain this degree of resolution, multiple selective cannulation of the vessels supplying the pancreas is necessary, with pharmacological enhancement of pancreatic flow where such selective cannulation is not possible. Using this technique, MacGregor and Hawkins were able to diagnose carcinoma in 42 of 45 subjects later shown to have carcinoma at laparotomy. In the same study, another 30 subjects suspected clinically of having carcinoma were found to have no carcinoma by angiography, and 28 of these were still alive more than one year after radiography, suggesting that indeed no carcinoma was present. Other workers have shown similar high success rates in diagnosing carcinoma of the pancreas by angiography.

Other advantages of selective angiography include the detection of carcinoma in the body and tail of the pancreas in cases in which secretory studies have been equivocal. Angiography will usually localise the tumour precisely within the pancreas and may also detect metastatic spread to the liver. From this information and from the degree of involvement of the large pancreatic vessels, it is often possible to make a preoperative decision about the resectability of the tumour and the most favourable surgical procedure to use.

Selective angiography has the disadvantage that the technique is complex, expensive, and time-consuming, especially if the highest resolution is sought, as the cannulation of multiple arteries is then necessary. Moreover, the interpretation of the angiograms is difficult, and, as a result, considerable experience is necessary before the greatest accuracy in diagnosis is attained. The full potential of selective pancreatic angiography can therefore be realised only in large centres where the procedure is frequently employed. The morbidity of the technique in skilled hands appears to be acceptably low.

Duodenoscopy and endoscopic retrograde cholangiopancreatography
Duodenoscopy with a side-viewing endoscope allows visualisation and biopsy of the ampulla of Vater, and carcinoma may therefore be directly diagnosed. If the ampulla is visualised it may be possible to cannulate the biliary and pancreatic duct through the endoscope and to inject radio-opaque contrast medium to outline the biliary and pancreatic ductal systems. In carcinoma of the pancreas, radiological abnormalities include strictures of the pancreatic ducts, obstruction of the main ducts, and pancreatic field defects. With experience, this technique is rapid (20-30 minutes) and has an acceptably low morbidity, though meticulous attention to detail is necessary to reduce the incidence of post-cannulation pancreatitis.

Endoscopic cannulation of the pancreatic duct also allows collection of pancreatic juice from within the ducts for biochemical and cytological analysis. The cells collected in this way may show excellent morphological detail and may permit the unequivocal diagnosis of malignancy. Recently the morphological diagnosis of pancreatic cancer has been improved by examination of brushing of the duct walls obtained with soft brushes passed through the cannulae. Brushing provides a richer yield of better preserved cells, so that a more confident diagnosis of the presence of malignancy is often possible.

Retrograde injection of radio-opaque dye into the ductal system allows a diagnosis of carcinoma to be made in 70-80% of cases, and cytology increases the diagnostic accuracy to about 90% of cases. However, cannulation of the pancreatic duct is not always possible, most studies reporting an 80-90% success rate, though rates up to 96% have been reported.
Since most pancreatic carcinomas arise from ductal tissue ERCP can detect early carcinoma at a time when resection is possible\textsuperscript{103,116,107}. Like angiography, ERCP will detect tumours in all areas of the pancreas if the ductal system is completely outlined\textsuperscript{116,107}. Angiography and ERCP provide complementary data and, used together, appear to offer the greatest probability for detection of early carcinoma\textsuperscript{103,106,117}.

**Laparotomy**

Laparotomy must be regarded as a routine diagnostic investigation of patients with unexplained persistent abdominal pain, especially if associated with weight loss, as well as being the preliminary to treatment when the diagnosis has been confirmed by other studies. A number of reports have indicated that patients with carcinoma of the pancreas are usually investigated for several months before a diagnosis is made. When the diagnosis is finally confirmed the tumour is usually inoperable and the average survival after diagnosis is less than six months\textsuperscript{118,81,119,8,15,120,66,9,78,82,121,15,122,10,11,17,123}. In view of the rapid spread of the tumour, early diagnosis and total excision offers the only hope of cure. Long-term survival after surgical treatment was excessively rare in the past, but in recent years early diagnosis and excision have resulted in a few cases who have survived for several years\textsuperscript{118,119,99,49,123}.

Even laparotomy may not provide a definitive diagnosis of carcinoma of the pancreas. Chronic pancreatitis may produce an ironhard mass of inflammatory tissue in the head of the pancreas, indistinguishable from carcinoma by palpation\textsuperscript{59}. Biopsy of such a mass may not show neoplastic tissue, even if present, as carcinoma is often surrounded by a wide area of pancreatitis\textsuperscript{51,52}. Nevertheless, a recent study suggests that a wedge biopsy of a suspicious lesion is relatively safe, and is a valuable and accurate procedure in over 90\% of cases\textsuperscript{124}. Needle biopsy, from multiple sites if necessary, also offers a safe and accurate means of determining whether a mass is neoplastic\textsuperscript{125,126}, but if the tumour has spread to the lymph nodes, biopsy from this site is preferred\textsuperscript{119,127}.

**Other techniques**

Hypotonic duodenography is useful in evaluating lesions of the ampulla of Vater, and a diagnostic accuracy of up to 80\% for lesions in this region has been reported\textsuperscript{128}. However, although barium studies may demonstrate carcinoma of the head of the pancreas, the cancer is usually of considerable size before it distorts the duodenal mucosa\textsuperscript{128,49}. Standard barium studies are of limited value, except in excluding other causes of the presenting symptoms. Computerised axial tomography, using the EMI scanner, may become a powerful tool for investigation of the pancreas but is still in its developmental stages for studying abdominal organs\textsuperscript{129,130}.

Ultrasonic scanning offers a rapid, noninvasive technique for studying the pancreas, but at the present stage of its development this technique is unable to provide the resolution needed to detect early resectable carcinoma\textsuperscript{131}. Similarly, radioisotopic scanning lacks the resolution needed to detect early carcinoma\textsuperscript{132}.

**Tumour associated antigen assay**

All of the described investigative procedures are at present unsuitable as screening procedures for the detection of carcinoma of the pancreas and are
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employed only when symptoms suggestive of pancreatic pathology are present, so that it is already too late for curative resection in the majority of patients. There is therefore a need for a simple and accurate test which can be applied routinely as a screening test to detect pancreatic carcinoma before symptoms develop. For this purpose serum levels of a tumour associated antigen have been studied.

Carcinoembryonic antigen (CEA) has been most extensively investigated in patients with carcinoma of the pancreas. The blood concentrations of CEA are raised in the majority of patients with carcinoma of the pancreas and the quantitative assay of this protein may help in the differential diagnosis of pancreatic disease. However, false positive and false negative results are frequently observed. Serum levels of CEA are often raised in chronic pancreatitis and other non-malignant disease (though usually to a lesser degree than in carcinoma of the pancreas) and in carcinoma elsewhere, while a significant number of patients with early carcinoma of the pancreas show normal CEA levels. In view of these false positive and negative results, CEA assay cannot at present be regarded as useful in the routine screening for pancreatic malignancy in the general population. Nevertheless, CEA assay may have a place as a screening test in patients with nonspecific gastrointestinal complaints as, in one report, 37 of 81 such patients with raised CEA levels developed overt gastrointestinal malignancies, including carcinoma of the pancreas, during a two-year period of follow-up. Currently, CEA levels in duodenal secretions and pancreatic juice are also being studied in an attempt to improve the specificity of this assay for carcinoma of the pancreas.

A second, apparently more specific, antigen associated with carcinoma of the pancreas has recently been described by Banwo, Versey, and Hobbs, who found oncofetal antigen in 36 of 37 patients with proven carcinoma of the pancreas, with no false positive assays. A subsequent report confirms that the antigen is present in a high proportion (42/59) of patients with carcinoma of the pancreas and biliary tract, but indicates that false positive tests are also found in other diseases.

Prognosis

Most studies have shown a mean survival after diagnosis of less than six months. Baylor and Berg analysed the survival characteristics of 5000 cases of carcinoma of the pancreas, 86% of which were adenocarcinoma or 'carcinoma, not otherwise specified'. For all histological types of nonendocrine cancer less than 50% survived six months after diagnosis, and, except for papillary adenocarcinoma (1.3% of total), less than 10% survived one year. The prognosis was worse in patients with disseminated carcinoma at the time of diagnosis, but even in the 10% of patients with carcinoma localised to the pancreas at the time of diagnosis only about 40% survived six months, 20% one year, and less than 2% for five years. In patients with distant metastases, 15% survived six months, 5% one year, and all were dead within 2.5 years.

Survival may be increased by surgical intervention. A number of studies suggest that, if the tumour has not spread to involve the portal lymph lodes, bile duct, or portal vein, resection of the tumour improves survival and offers excellent palliation. However, the increase in life expectancy must be weighed against the very substantial operative mortality of the procedure.
usually 15-20%. Shapiro tabulated the results of 17 studies of the use of Whipple’s procedure in the treatment of adenocarcinoma of the head of the pancreas, published since 1962, and found a mean operative mortality of 21% from 496 operations, with a five year survival rate of 4%. In the same paper, Shapiro was unable to show a significant improvement in length or quality of survival when pancreaticoduodenectomy was compared with simple bypass.

Conclusion

The increasing incidence of pancreatic cancer is an important problem facing gastroenterologists and oncologists, as current diagnostic techniques rarely permit diagnosis sufficiently early to enable surgical, cytotoxic, or radiotherapeutic measures to effect cure. The present report has sought to outline the 'state of play' at present, in the hope that the topic will thereby receive more much-needed attention.

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References

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**Carcinoms. Langenbeck's Archiv für Chirurgie, 339, 259-266.**


**Kasugai, T. (1975). Recent advances in endoscopic retrograde cholangiopancreatography. Digestion, 13, 76-99.**


(ERBC) of the biliary and pancreatic ducts. Scandinavian Journal of Gastroenterology, 10, 829-831.


