Hospital Topics

Pancreatic Scanning as a Diagnostic Tool in the District General Hospital

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Summary

The results of 200 radioisotope pancreatic scans in a general hospital show that 32 scans were recorded as "false positives," though these included 13 patients with diabetes mellitus and nine who had had truncal vagotomy. There were no "false negatives." Scanning is a useful diagnostic tool and a distinct advance on other tests more usually available for testing pancreatic function.

Introduction

Recent advances have led to the development of reasonably satisfactory ways of examining all the organs of the gastrointestinal tract, except the pancreas. Diagnosis of its disorders still presents problems to the specialist unit and the general hospital. Some techniques such as hypotonic duodenography and endoscopic retrograde pancreatography (E.R.P.) have led to improvements in diagnosis, but they are by no means generally available, and are not suitable for use as screening tests. Most general hospitals have to rely on the glucose tolerance test, barium meal, faecal fat output, serum amylase, and laparotomy to diagnose pancreatic disease.

Blau and Manske were the first to report successful pancreatic scanning in humans, using Se-75 selenomethionine (a precursor amino acid labelled with a gamma-emitting radio-nuclide). Though many authors¹⁻¹⁷ have suggested that scanning is a useful way of investigating the pancreas, others¹⁸⁻¹⁹ have refuted this, and the topic is still controversial. One advantage of scanning is that it is a non-invasive procedure which provides knowledge of both the structure and function of the organ.^{11 20-22} Furthermore, it can be performed by a technician on outpatients and the actual specialist time spent in reporting the scan is very small. These factors make it potentially suitable for use as a screening test, but, to date, there has been no report of its use from a general hospital. We decided, therefore, to analyse our experiences, to assess its feasibility in screening, and to comment on its success compared with other tests more commonly used. Of particular concern was the number of "false-positive" and "false-negative" scans that might be produced, since these have been a major source of difficulty with some groups.

Method

Scanning is performed with a twin-headed Selo Tracerlab Superscanner, which has electronic subtraction facilities. Digital

and analogue printout channels are available, and are displayed as photomaps and colour scans. The information can also be stored on magnetic tape and replayed, using different settings, in an attempt to enhance the image. The collimators used are F.C.8L, which have a nominal focal length, in air, of 15 cm, permitting the organ to be "focused" in almost every case. Imaging is also performed with a Nuclear Enterprises Gamma Camera, so that sequential dynamic studies are possible, in addition to routine imaging.

Various techniques of scanning have been employed: anterior scan alone, with subsequent ^{99m}Tc technetium sulphur colloid hepatic scan, simultaneous subtraction pancreatic and hepatic scans, and simultaneous anterior and either posterior or summed view scans followed by subtraction scans. The technique used at present is to administer 250 μ Ci of Se-75 selenomethionine intravenously and perform an anterior scan. Then 200 μ Ci of Au-198 gold colloid are given and simultaneous subtraction pancreatic and anterior view hepatic scans are obtained. This procedure takes about one-and-a-half hours and can be performed by a technician. The scans are reported "blind" by three observers and then the findings correlated with any clinical data that may be available. The subtraction image is used to locate the pancreatic position and the final report is usually made on the anterior scan, since its density may be compared with that of the liver, giving a guide as to the amount of isotope taken up by the pancreas. Specialists are involved only in reporting on the scans. All the cases have been followed up for 12-36 months to assess whether pancreatic lesions were present.

Results

In four cases there was complete hepatic overlap of the pancreatic image, making reporting impossible. These were early cases in the series, before additional subtraction scanning was routinely performed. The remaining 196 scans were categorized as follows: normal (111); localized patchy areas (11); generalized poor and patchy uptake (47); "cold areas" (15); pancreas not delineated (8); others (4).

NORMAL SCANS

Of the 111 normal scans 22 were confirmed at operation to have a normal pancreas. Among this group 22 patients had diabetes mellitus, nine intra-abdominal malignancy of another organ, and 14 abdominal pain, which was subsequently shown not to be pancreatic in origin. None of the cases have been found, on follow-up, to have any clinically significant exocrine pancreatic disease—i.e., there were no "false-negatives."

LOCALIZED PATCHY AREAS

Eleven scans were assessed as presenting localized patchy areas, and four had operative confirmation of the pancreatic status (see table I).

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TABLE I—*Abnormal Scans localized Patchy Area*

Condition	No. of Patients
Post acute pancreatitis	4
Diabetes mellitus	2
Irritable bowel syndrome	2
Relapsing pancreatitis	1
Pseudocyst	1
Carcinoma pancreas	1
Total	11

GENERALIZED POOR AND PATCHY UPTAKE

Forty-seven scans were assessed as presenting a generalized poor and patchy uptake, and in twenty-four there was operative confirmation of the pancreatic status (see table II).

TABLE II—*Abnormal Scans Generalized Poor and Patchy Uptake*

Condition	No. of Patients
Acute pancreatitis	7
Relapsing pancreatitis	2
Chronic pancreatitis	8
Carcinoma pancreas	3
Carcinoma invading pancreas	2
Diabetes mellitus	8
Post truncal vagotomy	10
Miscellaneous	7
Total	47

"COLD AREAS"

We categorized 15 scans into "cold areas", and in 12 there was operative confirmation of the pancreatic status (see table III).

TABLE III—*Abnormal Scans "Cold Areas"*

Condition	No. of Patients
Carcinoma pancreas	7
Diabetes mellitus	2
Local pancreatitis 2° to D.U.	2
Partial pancreatectomy	2
Carcinoma ampulla	1
Gall stone biliary obstruction and local pancreatitis	1
Total	15

PANCREAS NOT DELINEATED

In eight scans the pancreas was not delineated. This occurs when the pancreas does not concentrate adequate amounts of the radiopharmaceutical. Five had operative confirmation of the pancreatic status. Seven patients had pancreatic carcinoma and one diabetes mellitus.

OTHERS

There were four miscellaneous cases. In one the pancreas was largely obscured by uptake in a retroperitoneal reticulum cell sarcoma. A Zollinger-Ellison syndrome tumour was identified as a "hot-spot" in an otherwise normal scan, and a third case—of coeliac disease—scanned both before and after the institution of a gluten-free diet, showed a very high gut uptake, almost obliterating the pancreatic image.

Pathology

CARCINOMA PANCREAS

Eighteen cases of primary pancreatic carcinoma were scanned, and in 13 there was operative confirmation. All the scans in this group were assessed as being abnormal (poor and patchy uptake (3), locally patchy (1), "cold areas" (7), undelineated (7). No patient with primary pancreatic carcinoma had a normal scan—i.e., there were no "false-negatives" in this group.

PANCREATITIS

Pancreatitis was divided into acute and postacute pancreatitis, relapsing pancreatitis, and chronic pancreatitis. Sixteen patients with acute, or postacute, pancreatitis were scanned, and it was found that the appearance of the scan depended on the length of time after the acute attack. In the first week all scans were abnormal, showing a very poor isotope uptake. Nevertheless, by the end of the second week after the attack, most had reverted to normal. All cases scanned more than one month after the acute attack were assessed as having normal scans. This improvement parallels the recovery of exocrine function as judged by pancreatic function studies.^{21 23 24} Five patients had relapsing pancreatitis. In one the scan was normal, two presented a localized patchy appearance and the remaining two a generally poor and patchy uptake. Three of the cases with abnormal scans were subjected to laparotomy and in all the organ was abnormal. Eight patients with chronic pancreatitis were scanned, and all presented a poor and patchy uptake. Two patients who had had partial pancreatectomies had filling defects on the scan equivalent to the excised area. Three patients with localized areas of pancreatitis, two secondary to penetrating duodenal ulcers, and one secondary to an impacted gall stone all showed filling defects.

POST GASTRIC SURGERY

Thirteen patients who had had gastric surgery were scanned; 11 had had a truncal vagotomy and drainage procedure, and nine of these presented a poor and patchy isotope uptake, though the remaining two were normal. Function studies were performed on four of the cases with abnormal scans, but, in all, the exocrine function was shown to be normal. Two patients who had Bilroth 1 gastrectomies were scanned. In one the scan was normal and in the other it was rather patchy.

DIABETES MELLITUS

Thirty-three cases of diabetes mellitus were scanned. There was a wide variation in the scan findings (normal (20), generally patchy (8), locally patchy (2), "cold areas" (2), undelineated (1)). No correlation was found between the scan findings and the duration or severity of the illness; Lundh tests performed on two of the cases with abnormal scans showed normal duodenal enzyme activity.

Discussion

It is rather surprising that, as a decade has elapsed since the first report on pancreatic scanning, its general suitability as a diagnostic tool remains controversial. This is apparently the first report from a general hospital about its use, and about its comparison with the more readily available techniques for investigating the pancreas. The scans that compose this series were the first 200 performed, and the operators of the equipment were such as would be found in any other similar unit. Certain conclusions may be drawn from this series and suggest the technique might be considered for use in other service units. Nevertheless, before studying these in detail, various methods available for investigating the pancreas will be reviewed.

The following are procedures which are currently available for investigating the pancreas:

X-ray examination: plain abdominal film, barium meal, hypotonic duodenogram, angiography, retroperitoneal air insufflation, E.R.C.P.

Routine blood tests: Hb E.S.R., amylase, bilirubin, alkaline phosphatase, G.T.T.

Five-day faecal fats.

Lundh test.

Secretin-pancreozymin test.

Scan.

Laparotomy/necropsy.

It is difficult to draw firm conclusions about the value of many of these procedures, though some commentaries are available. K reel²⁵ stated that there are abnormalities in the second part of the duodenum on barium meal in 20% of cases of carcinoma of the head of the pancreas, though if pancreatic cancer is suspected, and hypotonic duodenography performed, then 75% of the carcinomas will be detected. Nevertheless, it is not the experience of most radiologists that this degree of accuracy is obtainable. K reel also concluded that good results are obtainable from arteriography and retroperitoneal gas insufflation, though no figures are quoted. Indeed, figures for the success of these two latter techniques would be almost valueless, since they are so specialized that there must almost be clinical certainty before they are requested.

Progress is being made in some specialized centres with endoscopic retrograde pancreatography. Even so, it is difficult to interpret results since clinical suspicion must be high before requesting the examination. Probably, in experienced hands, almost all carcinomas can be detected and information about duct abnormalities in relapsing pancreatitis, that can guide the surgeon, is obtainable. Nevertheless, both E.R.P. and the specialized radiologic techniques, though highly successful in experienced hands, can hardly be regarded as screening tests, and, furthermore, are not widely available at present.

If more conventional investigations are performed, then the diagnostic yield is very poor. The serum amylase is only raised during an acute attack of pancreatitis or occasionally after a meal in carcinoma. Abnormalities in glucose tolerance are so common that the test is rarely of use alone in differential diagnosis, and by the time that abnormalities in faecal fats, bilirubin and alkaline phosphatase occur in carcinoma, it is probably too late to treat the patient. The cost of a week in hospital, plus the routine investigations discussed, is of the order of £200, and even then the results may be of doubtful value.

Tests of pancreatic function are useful in diagnosing both carcinoma and chronic pancreatitis, since there are always gross abnormalities in the latter, and often in the former.^{23 24 26} The tests available are the Lundh test, and several modifications of the secretin-pancreozymin test. It is claimed that secretin-pancreozymin test is the more sensitive of the two and is therefore more likely to detect an early cancer.²⁷ Certainly it does have the advantage that it can be combined with pancreatic cytology.²⁸ Again, these tests are difficult and time consuming to perform in the general hospital and cannot be considered to be reliable unless being performed regularly by an experienced team.

VALUE OF SCANNING

In the light of these comments it is possible to assess the value of pancreatic scanning as shown in this series. Firstly, no cases whose scans were assessed as being normal were subsequently shown to have any significant exocrine pancreatic disease. This is valuable information for the clinician, since frequently pancreatic disease is a possibility in the differential diagnosis, but has largely to be ignored because no technique which has an acceptable diagnostic accuracy is available to study the pancreas, even if only to eliminate it as the site of disease. Furthermore, as there were no "false-negatives" in this series, and very few in other reports,^{1 11 22} it could be argued that a normal pancreatic scan is of greater diagnostic value than a normal barium meal, barium enema or cholecystogram, since "false-negatives" are well known with these investigations. It is certainly true that a normal scan is of greater diagnostic value than normal results in other techniques which are more usually available for assessing the pancreas. Other factors which make the test useful are that it causes no unpleasantness to the patient, since all he is required to do is lie still. We think, therefore, that a normal pancreatic scan is a useful advance in diagnosis, and is suitable for out-patients.

If abnormal scans are considered, then useful information is also obtained. In the case of primary pancreatic carcinoma, all

our scans were abnormal. No patient subsequently shown to have a pancreatic carcinoma had a normal scan. While it is true that scanning did not allow any curative operations for pancreatic cancer to be performed, this in no way invalidates the procedure, since we think that it is just as illogical to operate for suspected pancreatic cancer without first performing a scan, as to operate for suspected gastric cancer without performing a barium meal. Possibly if the scan were used more widely as a screening tool for vague abdominal symptoms, rather than waiting until the patient has obstructive jaundice, curative operations for pancreatic cancer might be possible. The pathological basis for this statement is that most neoplasms arise in the head of the organ, causing early duct obstruction, and thus disrupt the acinar cell function and therefore isotope uptake. A report from the Royal Free Group²⁹ showed that scanning in the usual conservative way did not improve survival in pancreatic carcinoma.

The pancreatic scan is also of value in the diagnosis of malabsorption since a normal scan means that the malabsorption does not result from pancreatic insufficiency. In this series none of the patients with pancreatic insufficiency had normal scans, all demonstrating a poor and patchy uptake of isotope. This is an expected finding, since the pancreas has to compete with other organs for the radiopharmaceutical. Similarly, in the differential diagnosis of obstructive jaundice, scanning is of value, because, if the pancreas appears normal, then it is possible to predict with some certainty that a pancreatic neoplasm is not responsible. There are no specific abnormalities indicating a particular pathological process. Nevertheless, "cold areas" are more likely to represent neoplasms than any other lesion.

FALSE POSITIVES

Pancreatic scanning has been much criticised on the premise that an unacceptable number of "false-positives" are produced. This means that the scan is abnormal when the exocrine pancreas is normal, and figures as high as 30%²¹ have been quoted. Some of these "false-positives" can be accounted for by the collimators being out of focus owing to the patients' obesity or ascites. If both anterior and subtraction scans are performed the number of false positives can be minimized, and the image is generally easier to assess,¹ though poor "setting-up" may distort the subtraction scan.

In this series there were 32 "false-positive" scans. Of the 11 cases who had had truncal vagotomies nine had abnormal scans, all demonstrating a poor and patchy uptake of isotope. Lundh tests were performed on three of these and secretin/pancreozymin test on one. They all demonstrated normal exocrine function. At present, the explanation for this phenomenon is obscure.

Of the 33 patients with diabetes mellitus scanned 13 had abnormal scans. Though abnormal exocrine pancreatic function is reported in diabetes mellitus,³⁰⁻³² there is no reason to think that these 13 were all abnormal, particularly since two had normal Lundh tests.

The value of scanning patients who have diabetes mellitus or who have had truncal vagotomies is not established and there may be little point in doing so. Nevertheless, this is not entirely true, since a patient with glucose intolerance who has a normal scan may confidently be said not to have a neoplasm of the pancreas. The remaining 10 cases are difficult to explain, though the three patients with alcoholic cirrhosis may have had undetected pancreatic disease. Out-of-focus collimators owing to obesity were responsible for at least two others and a further case with gall stone biliary obstruction may also have had the pancreatic duct compromised.

Conclusion

In this report we have presented the experiences of pancreatic scanning in a typical new general hospital. It is the first such report to come from a service unit rather than a research unit. Analysis of our results show that the technique is applicable to

the general hospital and gives results which are definitely superior to other techniques more usually available for investigating the pancreas. We think that it is suitable for use as a screening test, possibly leading to more advanced pancreatic investigations, when these seem appropriate. Useful information can be gained which excludes the pancreas from further inquiry if the scan is normal, and help provided in the differential diagnosis of malabsorption and jaundice. "False-positive" scans were not a great source of difficulty, but abnormalities may be expected in diabetes mellitus and after truncal vagotomy.

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Today's Treatment

Blood and Neoplastic Diseases

A Rational Approach to the Chemotherapy of Human Malignant Disease—I

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This article is concerned only with the rationale behind the chemotherapy of patients with advanced malignancy. I will concentrate largely on those drugs which come under the heading of cytotoxic agents or antimetabolites.

Type of Drugs

The initial choice of a drug for treating malignancy depends on its efficacy and toxicity in experimental tumours in animals. Unfortunately, there can be no foolproof method of screening these agents and undoubtedly many drugs which could have been useful in man have been missed. Nevertheless, some useful chemotherapeutic agents have been found using these methods (table I). The experimental animal chosen, the type of tumour, and the way in which the drug is administered are of paramount importance.

TABLE I—Therapeutic indices of Different Antitumour Agents*

Experimental Tumour	Agent	Therapeutic Index
Gardner lymphosarcoma	Asparaginase	7,500
Gardner lymphosarcoma	Cyclophosphamide	0-20
PC6 (plasma cell tumour)	Melphalan	†280
YOSHIDA ascites tumour	Cyclophosphamide	200
Walker tumour	Cpd 1954	70

*T. Connors, personal communication

†The highest recorded therapeutic index for a cytotoxic antitumour agent

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L-asparaginase was discovered in this way and has the highest therapeutic index of any agent in any experimental tumour system. Though L-asparaginase is effective against acute lymphoblastic leukaemia (A.L.L.) and some other lymphoid malignancies, its use has been disappointing in man in relation to its promise from experimental work. Certainly many drugs which are curative in animals may have little effect in man, and for this reason a clinical trial is an important second step. After this, comparative trials may be set up to assess the value of different single agents. Any clinical evaluation of a new drug involves three steps: firstly, pharmacological evaluation to establish toxicity (antitumour activity not required); secondly, measurement of clinical activity against several tumours; and thirdly, comparative studies to establish its role in the treatment of a tumour. This involves comparison with the best standard treatment and the evaluation of combined treatments.

Some of the more important agents which have proved to be of value in human cancer are classified in table II. The mech-

TABLE II—Chemotherapeutic Agents in Common Use

Mechanism	Class	Examples
Interfere with DNA synthesis	Pyrimidine analogues Purine analogues Folate antagonists Hydroxyurea	Cytosine Arabinoside 5-Fluorouracil 6-Mercaptopurine 6-Thioguanine Methotrexate
Interfere with mitotic spindle formation	Vinca alkaloids	Vincristine vinblastine
Alkylate and cross link strands of DNA at any stage of cell cycle	Alkylating Agents	Mustine hydrochloride Cyclophosphamide Busulphan Chlorambucil Danorubicin Duoxymycin (Adriamycin)
Bind with DNA and interfere with replication	Antibiotics	Adriamycin (Cerubidin) BCNU CCNU Me CCNU
Action on transfer RNA	Actinomycin D	
Action unknown	Nitrosoureas Procarbazine	