PAPERS AND ORIGINALS

Simultaneous Combined Pancreatic Test

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Summary

A simultaneous combined pancreatic test can be performed in one morning with only one intubation of the duodenum. The test includes the measurement of exocrine pancreatic secretion of bicarbonate, enzymes, and radioactive selenium, pancreatic scanning, hypotonic duodenography, and cytology of the duodenal aspirate. In the first 70 patients it was found that a single secretion test was of only limited value in detecting pancreatic disease; cytology was the most reliable and scanning the least reliable single test; and that the combined test provided near-complete discrimination between patients with no pancreatic disease, with chronic pancreatitis, and with carcinoma of the pancreas.

Introduction

None of the many methods available for investigating patients for pancreatic disease are satisfactory. Not only is it difficult to distinguish between different diseases of the pancreas but it is often impossible to state whether the pancreas is normal or abnormal. To try to improve the accuracy of diagnosis three different pancreatic tests have been made simultaneously (Bourke *et al.*, 1972; Youngs *et al.*, 1973). We have combined in one morning, with only one intubation of the duodenum and

with no side effects, five established tests: exocrine pancreatic secretion of bicarbonate, enzymes, and radioactive selenium, isotopic scanning, hypotonic duodenography, and cytology. We describe the procedure of this combined test and the results in a consecutive series of 70 patients with suspected pancreatic disease.

Patients and Methods

The patient fasted overnight and the duodenum was intubated under fluoroscopic control with a double-lumen Dreiling tube, the tip being positioned at the duodenojejunal flexure. The stomach was aspirated continuously with a pump and the aspirate discarded. The duodenum was aspirated continuously with a separate pump for three hours in 12 collection periods of 15 minutes duration.

After basal aspiration for 30 minutes secretin GIH 0.25 U/kg/hr, and pancreozymin GIH 16 U/kg/hr (Crick-Harper-Raper) were infused intravenously in 0.9% saline for 90 minutes. This combined hormone infusion evokes near-maximal output of bicarbonate and enzymes (Wormsley, 1969). A single intravenous injection of ^{75}Se -selenomethionine 3 $\mu\text{Ci/kg}$ (Radiochemical Centre, Amersham) was given at the same time. This labelled amino-acid is probably incorporated into all the pancreatic enzymes, so that the selenium count in the duodenal aspirate is an index of total enzyme output (Youngs *et al.*, 1971). The pancreas was scanned simultaneously using a Nuclear Chicago PHO/gamma camera.

At the end of these tests hypotonic duodenography was carried out using intravenous propantheline 30 mg and x-ray pictures taken by a standard double-contrast technique (Raia and Kreel, 1966; Stage and Banks, 1969). The duodenal aspirates were analysed for volume, bicarbonate concentration, and tryptic activity by the methods of Gutierrez and Baron (1972). The ^{75}Se -selenomethionine count was measured with a scintillation counter.

Papanicolaou-stained smears of aliquots of the hormone-stimulated aspirate were examined for malignant cells. The cytologist did not know the results of the four earlier tests. Cytology studies were not made in the first six patients. Of the 70 patients studied between July 1971 and January 1973 67 fell into the following four groups.

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No Pancreatic Disease.—The 48 patients in this group had been referred with the possible diagnosis of pancreatic disease and have subsequently been presumed, either because of their clinical course or the findings at laparotomy, to have a normal pancreas. Of the 48, 14 were found (12 at laparotomy, two at necropsy) to have no pancreatic disease. Five patients had stones in the common bile duct and two had carcinoma in the hepatic ducts. The other 34 patients had not developed any evidence of pancreatic disease at the time of follow-up which was more than two years in nine patients, more than one year in 23 patients, and more than six months in the other two patients. One patient with no clinical evidence of pancreatic disease had diffuse pancreatic calcification on a routine chest x-ray examination. For obvious reasons no normal control subjects were studied.

Acute Pancreatitis.—Three patients with classical attacks were tested four weeks afterwards.

Chronic Pancreatitis.—Of eight patients in this group only two had radiological evidence of calcification in the region of the pancreas. In one the duodenal aspirate contained cells which were suggestive of malignancy, but at laparotomy and after a one-year follow-up there was no evidence of carcinoma. Four men had pancreatic pain associated with alcoholic bouts; one woman had diabetes and recurrent abdominal pain; and another woman had abdominal pain and malabsorption but the jejunal mucosa was normal on biopsy.

Carcinoma.—This was confirmed at laparotomy in all the eight patients in this group. Five presented with obstructive jaundice and three with epigastric pain and weight loss.

Of the remaining three patients, one had a hormone-producing pancreatic tumour (Elias *et al.*, 1972) and two had inadequate follow-up data.

Results

The results in these 67 patients were examined with a view to assessing, firstly, the usefulness of an individual secretion test in distinguishing between groups of patients with different pancreatic diseases; secondly, the reliability of each single test; and, thirdly, the usefulness of the combined test.

USEFULNESS OF SINGLE SECRETION TEST

There was no significant difference between the means of the plateau bicarbonate output (expressed as the sum of the two highest consecutive bicarbonate outputs after hormonal stimu-

FIG. 1—Plateau bicarbonate output (mEq/hr) after intravenous infusion of secretin 0.25 U/kg/hr and pancreozymin 16 U/kg/hr. Each point represents one patient and the horizontal lines show the means in patients with no pancreatic disease ($32 \pm \text{S.D. } 1.6$), with acute pancreatitis (27 ± 7), with chronic pancreatitis (15 ± 5), and with carcinoma of the pancreas (15 ± 7).

FIG. 2—Plateau tryptic output (U/hr). Symbols as in fig. 1.

FIG. 3—Maximum ^{75}Se concentration, percentage count/100 ml aspirate. Symbols as in fig. 1.

lation multiplied by two) in each of the four groups of patients studied, but four patients with chronic pancreatitis and five patients with carcinoma secreted less bicarbonate than any of the patients with no pancreatic disease (fig. 1). The plateau tryptic output in each of the four groups (fig. 2) was similar to the plateau bicarbonate output. The highest ^{75}Se concentration (fig. 3) showed a similarly wide distribution, but there was a significant difference ($P < 0.05$) between patients with no pancreatic disease and those with chronic pancreatitis.

Thus few of the patients with pancreatic disease had a diagnostically lower secretion of alkali or enzymes than the patients with no pancreatic disease.

RELIABILITY OF EACH SINGLE TEST

For ease of comparison the measure of the correctness of each of the tests is expressed as a percentage relating the observed to the

expected result. Thus cytology correctly forecast six out of the seven pancreatic carcinomas examined and 53 of the 54 non-carcinomas. In 61 examinations the cytological report was correct in 59 cases, giving a ratio between the observed and expected results of 97%. At the other extreme the pancreatic scan was correct in only 65% of cases (fig. 4). The results of the other eight tests showed intermediate correlations between the observed and expected results, using the normal values for bicarbonate, trypsin, and selenium in the studies of Wormsley (1969) and Youngs *et al.* (1971).

In this small series, therefore, a pancreatic scan was of little help whereas cytological examination for carcinoma was very helpful.

FIG. 4—Percentage correctness of each of 10 tests.

USEFULNESS OF COMBINED TEST

One point was allotted for a normal result in each of the 10 tests. Thus if a patient had normal results in all the 10 tests he was given a score of 10. All but one of the patients without pancreatic disease and all those recovering from acute pancreatitis had six or more normal results (fig. 5). Patients with chronic pancreatitis had five or fewer normal results, and those with carcinoma had a complete range of normal and abnormal results. In contrast to the other groups, however, this last group almost always had malignant cells in the duodenal aspirate.

FIG. 5—Value of simultaneous combined test. Each closed circle represents the total score (out of 10) for each patient.

Thus the combined test almost completely discriminated between patients without pancreatic disease, those with chronic pancreatitis, and those with carcinoma of the pancreas.

Discussion

Reports on the value of individual tests in pancreatic disease are conflicting. Dreiling (1971) stated that measurements of volume,

bicarbonate concentration, and enzyme output after stimulation with a single intravenous injection of 1 U/kg of secretin (Boots) in over 5,000 tests provided a diagnostic accuracy of just under 90%. The experience of other workers (Bank *et al.*, 1963; Wormsley, 1968), admittedly from fewer tests, has been different.

In the present series a single secretion test was of only limited diagnostic value. Half of our patients with no pancreatic disease had plateau bicarbonate outputs below 30 mEq/hr, an output regarded by Wormsley (1969) as the lower limit of the normal pancreas. Wormsley (1970) suggested that patients with outputs below 30 mEq/hr in response to his combined infusion of secretin 0.25 U/kg/hr and pancreozymin 16 U/kg/hr should be retested with a near-maximum dose of secretin 2 U/kg/hr alone to determine whether the pancreas is merely insensitive to the lower dose of stimulant or incapable of stimulation even by the higher dose. We have not retested patients with no pancreatic disease or those with pancreatitis, nor are we convinced that a maximum dose of stimulant will necessarily provide greater diagnostic discrimination than a submaximum dose (Gutierrez and Baron, 1972).

Other workers have suggested that near-maximum stimulation of the pancreas is a disadvantage in pancreatic scanning (Sodee, 1964). Except for two recovering from recent acute pancreatitis, all of the patients with an abnormal pancreas had a technically unsatisfactory or abnormal scan. However, only 18 of the 33 patients with a normal pancreas had a normal scan. Other workers (McCarthy *et al.*, 1969; McCready and Cottrill, 1971; McCarthy *et al.*, 1972; Agnew *et al.*, 1973) have pointed out that non-pancreatic conditions could cause abnormalities in scanning, including postgastrectomy/vagotomy, peptic ulceration, metastatic disease, cirrhosis, and diabetes mellitus. Many patients with a normal pancreas studied in this series had one of the above conditions. Thus while a normal scan argues strongly against the presence of pancreatic disease, an abnormal scan may be misleading (McCarthy *et al.*, 1969; McCarthy and Brown, 1969; McCarthy *et al.*, 1972; Braganza *et al.*, 1973; Youngs *et al.*, 1973).

Pancreatic cytology for carcinoma has been stated to have an accuracy of between 37% (Rankin and Brown, 1964) and 90% (Asnaes and Johansen, 1970). The tests were carried out on different patients and at different centres. In the present study we tried to evaluate individually the results from a large number of pancreatic tests done simultaneously in the same patient in the same centre under standard conditions of near-maximum stimulation. Cytological examination for carcinoma was the most accurate and pancreatic scanning the least accurate of the tests. The cytologist, however, was asked only to distinguish between malignant and non-malignant cells, whereas the radiologist had to differentiate a normal appearance on scanning or duodenography from changes consistent with pancreatitis or carcinoma.

The value of using a combination of tests was therefore assessed. Bourke *et al.* (1972) found that a triple combination gave quicker and better diagnostic results in 75 jaundiced patients. In the present study the group with suspected pancreatic disease included both jaundiced and non-jaundiced patients. Those in the group with no pancreatic disease mostly had abdominal pain as their predominant symptom, but they were judged to have no pancreatic disease if the pain had disappeared on follow-up or another cause for it was found. This group, therefore, probably included patients with minor but possibly clinical irrelevant abnormalities of pancreatic structure and function. The one patient with the low score had abdominal pain at the time of the test but no other evidence of pancreatic disease, and has remained symptom-free since. The patients with chronic pancreatitis had gross disease and in all patients with carcinoma the diagnosis was confirmed at laparotomy. In this small series, and especially in cases of advanced disease, the combined test provided better discrimination between the groups of patients studied than single tests used alone. To measure the cost-effectiveness of the combined test was more

difficult, since it did not obviate the need for laparotomy. Of the 12 patients with jaundice on whom the test was carried out five had stones in the common bile duct, two had carcinoma of the hepatic duct, and five had carcinoma of the head of the pancreas. Cytological examination predicted the presence or absence of carcinoma with considerable accuracy.

The triple test of Youngs *et al.* (1973) failed to diagnose carcinoma in one-third of the patients by the two intubation tests, and the abnormal pancreatic scans were not in themselves diagnostic of carcinoma. In the present study the additional information obtained from duodenography and cytology resulted in a correct diagnosis of carcinoma in all but one patient. A preoperative diagnosis of carcinoma of the pancreas allows suitable adjustment of preoperative preparation and also obviates the need for biopsy of a pancreatic mass, which may be misleading and dangerous. With increasing experience we hope that the accuracy of preoperative diagnosis will be improved further.

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References

- Agnew, J. E., Youngs, G. R., and Bouchier, I. A. D. (1973). *British Journal of Radiology*, **46**, 83.
- Asnaes, S., and Johansen, A. (1970). *Acta Pathologica et Microbiologica Scandinavica*, Suppl. No. 212, p. 11.
- Bank, S., Marks, I. N., Moshal, G. F., Efron, G., and Silber, R. (1963). *South African Medical Journal*, **37**, 1061.
- Bourke, J. B., Swann, J. C., Brown, C. L., and Ritchie, H. D. (1972). *Lancet*, **1**, 605.
- Braganza, J., Critchley, M., Howat, H. T., Testa, H. J., and Torrance, H. B. (1973). *Gut*, **14**, 383.
- Dreiling, D. A. (1971). In *The Exocrine Pancreas*, ed. I. T. Beck and D. G. Sinclair, Chap. 12, p. 154. London, Churchill.
- Elias, E., *et al.* (1972). *Lancet*, **2**, 791.
- Gutierrez, L. V., and Baron, J. H. (1972). *Gut*, **13**, 721.
- McCarthy, D. M., and Brown, P. (1969). *Gut*, **10**, 913.
- McCarthy, D. M., Brown, P., Melmed, R. N., Agnew, J. E., and Bouchier, I. A. D. (1972). *Gut*, **13**, 75.
- McCarthy, D. M., Kreel, L., Agnew, J. E., and Bouchier, I. A. D. (1969). *Gut*, **10**, 665.
- McCready, V. R., and Cottrill, M. F. (1971). *British Journal of Radiology*, **44**, 870.
- Raia, S., and Kreel, L. (1966). *Gut*, **7**, 420.
- Rankin, G. V., and Brown, C. H. (1964). *Cleveland Clinical Quarterly*, **31**, 119.
- Sodee, D. B. (1964). *Medical Radioisotope Scanning*. 2nd Athens Symposium. Stage, P., and Banke, L. (1969). *Gut*, **10**, 428.
- Wormsley, K. G. (1968). *Gastroenterology*, **54**, 197.
- Wormsley, K. G. (1969). *Scandinavian Journal of Gastroenterology*, **4**, 623.
- Wormsley, K. G. (1970). *Proceedings of the Royal Society of Medicine*, **63**, 431.
- Youngs, G. R., Agnew, J. E., Levin, G. E., and Bouchier, I. A. D. (1971). *British Medical Journal*, **2**, 252.
- Youngs, G. R., Agnew, J. E., Levin, G. E., and Bouchier, I. A. D. (1973). *Quarterly Journal of Medicine*, **42**, 597.

Response of Leucocyte Adenyl Cyclase to Isoprenaline and Effect of Alpha-blocking Drugs in Extrinsic Bronchial Asthma

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Summary

The finding by several workers that biochemical responses to catecholamines are diminished in asthmatic patients during periods of active asthma as compared to normal subjects has led to the recognition of the beta-adrenergic blockade phenomenon, a common accompaniment of extrinsic bronchial asthma. Using an intact cell method to measure leucocyte adenyl cyclase activity, we have been able to show that there is a noticeably reduced responsiveness of this enzyme system (which is now identified with beta-receptor function) to isoprenaline in the leucocytes of patients suffering from acute bronchial asthma, but that asthmatic patients in remission could not be distinguished from normal persons in this respect. Evidently the defective beta-receptor function may be associated with overactivity of the alpha-receptors in acute bronchial asthma, since the responsiveness to isoprenaline stimulation could be restored towards normal by concomitant treatment of the leucocytes of these patients with alpha-receptor blocking drugs such as phentolamine or thymoxamine. Ouabain, though

somewhat less potent, also enhanced responsiveness to isoprenaline stimulation. The relation of these results to the clinical observation of adrenaline resistance in active asthma suggests that alpha-receptor blocking drugs may be of value in restoring the sensitivity of beta-receptors to sympathomimetic amines.

Introduction

Patients suffering from extrinsic bronchial asthma have a greater tolerance to adrenaline than normal persons. This resistance or "adrenaline fastness" is most pronounced in patients in status asthmaticus. Resistance to adrenaline can be produced in laboratory animals with agents such as *Bordetella pertussis* vaccine, whose actions are now known to include beta-receptor blocking activity. From clinical observations and experimental investigation of these findings Szentivanyi (1968) suggested an autonomic neural imbalance with decreased beta-adrenergic responsiveness to explain the atopic state in bronchial asthma. The association of the beta-adrenergic receptor function with adenyl cyclase activity by Robison *et al.* (1967) paved the way for a more fundamental investigation of the nature of the refractoriness to catecholamines in patients with bronchial asthma. The report by Scott (1970) of adenyl cyclase activity in broken cell preparations from human leucocytes prompted other investigators (Bourne and Melmon, 1971) to examine the adenyl cyclase system in intact leucocytes and its responsiveness to stimulation by adrenergic agonists and antagonists. Smith and Parker (1970) first reported that the peripheral-blood leucocytes of some asthmatic patients had a reduced adenyl cyclase responsiveness to catecholamines compared to that in normal

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