THE CANADIAN MEDICAL ASSOCIATION JOURNAL
LE JOURNAL DE L'ASSOCIATION MÉDICALE CANADIENNE

Volume 98 • Number 4 • January 27, 1968

Clinical Correlations with Pancreatic Function Tests

N. B. HERSHFIELD, M.D., F.R.C.P.[C],*
J. F. LIND, M.D., F.R.C.S.[C] and J. A. HILDES, M.D., F.R.C.P.[C],
Winnipeg, Man.

THE secretin test of pancreatic function was introduced by Lagerlöf.[1] The diagnostic value of the original test and of its various modifications is still not clearly established.[2, 3] The addition of pancreozymin stimulation to the original procedure was considered by Sun and Shay[4] and Burton *et al.*[5] to be of value, although Dreiling and Janowitz[2] do not consider it adds to the diagnostic accuracy. Sun and Shay,[4] and Burton *et al.*[6] and Fitzgerald[7] suggested that analysis of serum lipase and amylase after secretin and pancreozymin injection was useful in uncovering disease causing pancreatic duct obstruction. Recently Raskin *et al.*[8] reported that the search for tumour cells in the centrifuged duodenal juice was extremely useful in the detection of pancreatic, hepatobiliary and gastric carcinomas.

In the present report we have reviewed our experience over a four-year period of 160 secretin-pancreozymin tests, with serum enzyme and cytology studies, and have related the results to the subsequent clinical course of the patients, and to the findings at operation or autopsy.

Methods

A double-lumen gastroduodenal tube was passed through the mouth and positioned under radiographic control. The "gastric" portion of the tube was positioned in the antrum of the stomach with the distal tip of the "duodenal" portion at the ligament of Treitz. Intradermal tests of sensitivity to secretin and pancreozymin, one in each forearm, were performed. A slow intravenous drip of normal saline was established for withdrawal of blood samples and for injection of the pancreatic stimulants. Blood was drawn for fasting amylase and lipase estimation; and duodenal juice was collected for 30 minutes. Secretin, 1 unit per kg. body weight, was injected intravenously over 3 to 5 minutes and four collections of juice for 20 minutes each were made. At the end of 80 minutes blood was again withdrawn for estimation of amylase and lipase; 90 units of pancreozymin was then administered intravenously, and a further 30-minute collection of juice was obtained. Forty minutes after the injection of pancreozymin, blood was again drawn for amylase and lipase determination. The duodenal juice and blood were kept on ice until analyzed; an aliquot of the juice was centrifuged, and the sediment was fixed with alcohol and sent to the pathology department for routine cytology.

Bicarbonate was estimated by the Van Slyke method,[9] amylase in blood and duodenal juice by the Somogyi method,[10] and pH on a Beckman pH meter. Bilirubin was estimated by the van den Bergh method[9] and lipase in the serum was estimated by the method of Cherry and Crandall.[11]

Twenty normal male subjects aged 20 to 65 years were studied, as well as 160 patients in whom there were clinical grounds for suspecting pancreatic dysfunction. These patients ranged in age from 17 to 85 years and the sex distribution was almost equal.

Results and Discussion

Duodenal Juice Volume, Amylase and Maximal Bicarbonate Concentration

The ranges of values for the duodenal juice found in the 20 control subjects are shown in

From the Clinical Investigation Unit, Winnipeg General Hospital, and the Departments of Surgery and Medicine, University of Manitoba, Winnipeg, Manitoba.
*Present address: Calgary Associate Clinic, Calgary, Alberta.
Reprint requests to: Dr. J. A. Hildes, Clinical Investigation Unit, Winnipeg General Hospital, Winnipeg, Manitoba.

Table I. Although the ranges were quite broad for most of the parameters, the results were fairly evenly distributed throughout these ranges. Therefore, the lower limit of the range rather than the mean was considered appropriate as the differentiating point between normal and abnormal. None of the control subjects showed significant skin reactions to the stimulants. It was common in the control group as well as in the patient group to have some mild abdominal discomfort after the injection of pancreozymin. However, no serious side effects occurred in either group.

TABLE I.—RANGES OF VALUES OF TESTS IN 20 NORMAL SUBJECTS AGED 20 - 65 YEARS

	Duodenal juice
Volume after stimulation	1.7 - 3.7 c.c. per kg.
pH	8.0 - 9.0
Amylase	4000 - 12,000 units per kg.
Maximal bicarbonate	67.5 - 88.5 mEq. per litre

Tests were attempted in 160 patients. They were abandoned in 15: five would not accept the tube; in four the tube failed to pass the pylorus after 2½-3 hours; five had positive pancreozymin skin tests; and one had a positive secretin skin test. In the remaining 145 patients in whom the test was completed, 75 tests were designated abnormal in that at least one of the three major components of the juice (volume, bicarbonate and amylase concentration) fell below the range of our normal subjects (Table II).

TABLE II.—RESULTS OF TESTS ON DUODENAL JUICE IN 145 PATIENTS AFTER PANCREATIC STIMULATION

No. of patients	*Volume*	*Bicarbonate*	*Amylase*
70	Normal	Normal	Normal
32	Low	Low	Low
11	Normal	Low	Low
12	Normal	Low	Normal
17	Normal	Normal	Low
1	Low	Normal	Low
2	Low	Low	Normal

Tests Showing Normal Values—70 Patients (Table III)

Of the 70 patients with all three of the above-mentioned values in the normal range, 20 had subsequent laparotomy and in all but one the pancreas was found to be normal. In the one exception there was a small insulinoma of the body of the gland. Four additional patients died of unrelated causes and were found to have no pancreatic disease at autopsy. A further 25 of these patients have been followed up from one to three years with no subsequent clinical evidence of pancreatic disease. Twenty-one patients have not been adequately followed up to determine the presence or absence of pancreatic disease. Therefore, in all of the 48 patients for whom we have data the test correlated very well with the clinical findings.

TABLE III.—SUBSEQUENT FINDINGS IN 70 PATIENTS WHOSE DUODENAL JUICE FOLLOWING PANCREATIC STIMULATION WAS WITHIN NORMAL RANGE IN VOLUME, BICARBONATE AND AMYLASE

Pancreas normal at laparotomy	20
Pancreas normal at autopsy	4
Asymptomatic at follow-up	25
No follow-up	21

Tests Showing Three Abnormal Values—32 Patients (Table IV)

Sixteen of the 20 patients with chronic pancreatitis were diagnosed by the typical gross findings at laparotomy or autopsy, although surgical biopsy of the gland was performed in only two. Each of the other four patients had a long and typical history associated with radiographic evidence of pancreatic calcification; two of them also had steatorrhea and diabetes.

The four patients with carcinoma of the pancreas were diagnosed at laparotomy. In two, the neoplasm was localized to the head of the gland and in the remaining two it was more extensive. Two patients, who had had partial gastrectomies, were investigated because of severe malnutrition; in one, the diagnosis of chronic pancreatitis was made at laparotomy and in the other, at autopsy. The third patient with a partial gastrectomy was lost to follow-up.

There were two cases of hyperparathyroidism confirmed at operation (with removal of the adenomas). One patient was later found to have chronic pancreatitis localized to the head of the gland, causing obstructive jaundice. The other patient has not as yet had an abdominal exploration.

Six patients listed as having no known disease have recovered and have no apparent clinical disease of the pancreas or of the upper gastrointestinal tract. Four of them were operated upon and no abnormalities were found. These

TABLE IV.—SUBSEQUENT FINDINGS IN 32 PATIENTS WHOSE DUODENAL JUICE FOLLOWING PANCREATIC STIMULATION WAS BELOW NORMAL RANGE IN VOLUME, BICARBONATE AND AMYLASE

Patients with proved pancreatic disease		24
Chronic pancreatitis	20*	
Carcinoma	4	
Others		8
Partial gastrectomy	1	
Hyperparathyroidism	1	
With no known disease	6**	

*Two of these had had gastrectomies and one had hyperparathyroidism.

**Two of these were lost to follow-up and so it is not known whether they had any disease.

are considered as false positives. Two patients have been lost to follow-up. Therefore, four of the 32 tests have been considered to have given false-positive results as far as supplying evidence of extensive pancreatic dysfunction is concerned. Despite this the finding of abnormal values for these three measurements is considered good evidence of pancreatic disease.

Tests Showing Abnormal Amylase and Bicarbonate—11 Patients (Table V)

The diagnoses were established at laparotomy in six of these patients and at autopsy in three. The patient with intestinal lymphangiectasia subsequently died; an autopsy was not performed. The patient with hemochromatosis was diagnosed by clinical features and liver biopsy. Therefore, in only one of 11 patients with this pattern of abnormality of the test was the test misleading.

TABLE V.—SUBSEQUENT FINDINGS IN 11 PATIENTS WHOSE DUODENAL JUICE FOLLOWING PANCREATIC STIMULATION WAS BELOW NORMAL RANGE IN BICARBONATE AND AMYLASE

Carcinoma of the pancreas	4
Chronic pancreatitis	3
Carcinoma of lower end of bile duct	1
Intestinal lymphangiectasia	1
Hemochromatosis	1
False positive	1

Tests Showing Abnormal Bicarbonate Only—12 Patients (Table VI)

The majority of these had had a previous partial gastrectomy and were referred for investigation of vague abdominal pain; none had clinical or laboratory evidence of malabsorption. It is difficult to interpret the significance of this single finding since tube placement is difficult and prevention of gastric juice mixing with the duodenal juice is impossible. Such mixing results in neutralization of juice bicarbonate. Therefore pancreatic function may have been normal in these patients.

The two patients with sprue may fall into the small percentage of such cases reported to have associated pancreatic dysfunction reported by Dreiling, Janowitz and Perrier[3] and more recently by Creamer and Pink.[12] The latter authors consider this complication of sprue to have a poor prognosis. Our two patients have responded well to therapy.

TABLE VI.—FINDINGS IN 12 PATIENTS WHOSE DUODENAL JUICE FOLLOWING PANCREATIC STIMULATION WAS BELOW NORMAL RANGE IN BICARBONATE ONLY

Partial gastrectomy	8
Sprue	2
Recurrent pancreatitis	1
No lesion at operation	1

In this group with only an abnormally low bicarbonate concentration, there may have been only one patient with pancreatic dysfunction—a patient with recurrent pancreatitis. Therefore, this single abnormal measurement is not considered a good indicator of pancreatic disease. This is not in keeping with the findings of Dreiling, Janowitz and Perrier,[3] who consider that the reduction of bicarbonate concentration is the most sensitive sign of early pancreatic dysfunction.

Tests Showing Abnormal Amylase Only—17 Patients

Six of these patients have been lost to follow-up; of the remaining 11, only two had lesions which may have interfered with secretion of pancreatic juice; both had an obstruction at the lower end of the common bile duct, one due to stone and one to carcinoma. Of the remaining patients, two had extensive liver involvement with hepatomas, one each had mesenteric vascular insufficiency, gastric ulcer and no disease at laparotomy; four patients had no laparotomy, and have remained well. Therefore, this single deficit is not considered a reliable indicator of pancreatic disease.

Tests Showing Other Combinations of Results

Only one patient had marked reduction in volume and amylase with normal bicarbonate concentration. This patient was found to have chronic pancreatitis at laparotomy. Two patients had reduction in volume and bicarbonate, but unfortunately we have no follow-up information on them.

Duodenal Juice Bilirubin Response to Pancreozymin

All of the 20 control subjects and all but 24 of the 145 patients tested had at least a five-fold increase of bilirubin concentration in the duodenal juice after pancreozymin. Most responses were much higher than this. Patients with no response are shown in Table VII.

All but one patient had sufficient biliary tract disease to explain the results. In the single exception, the gallbladder could not be visualized after dye was administered orally. At laparotomy, however, no disease of the gallbladder or biliary tract was found.

The measurement of bilirubin in duodenal juice after stimulation, however, is a useful confirmatory test of biliary function.

TABLE VII.—DIAGNOSES IN PATIENTS WITH NO BILIRUBIN RESPONSE TO PANCREOZYMIN

Cholelithiasis and cholecystitis	11
Complete biliary obstruction	5
Previous cholecystectomy	6
Choledochoduodenal fistula	1
False positive	1

The Serum Enzyme Response to Secretin and Pancreozymin

Many authors have advocated the use of the serum enzyme tests after pancreatic stimulation as an indicator of pancreatic disease.[4, 6, 7] Our experience with the test in 20 controls and in 25 of the 145 patients is shown in Tables VIII and IX respectively. The test was normal in the remaining 105 patients.

TABLE VIII.—RANGE OF SERUM ENZYME RESPONSES TO SECRETION AND PANCREOZYMIN IN 20 NORMAL SUBJECTS AGED 20 TO 65 YEARS

	Amylase units/100 ml.	*Lipase units/100 ml.*
Fasting	57 - 113	0.5 - 1.1
Post secretin	97 - 291	0.9 - 1.5
Post pancreozymin	97 - 291	0.9 - 1.5

Table IX shows the type of patient in whom a rise in enzymes might be expected. It is obvious that in the majority of our patients no such rise occurred. We therefore believe that this test is of no value.

TABLE IX.—SERUM ENZYME RESULTS AFTER PANCREATIC STIMULATION

	No rise	*Rise*
Chronic pancreatitis	13	3
Carcinoma of pancreas	8	1

Routine Cytology

In none of the 11 patients with carcinoma of the pancreas, liver or biliary tract were tumour cells reported on routine cytological examination. In a number of these the cells seen had disintegrated. Raskin *et al.*[8] carried out cytological examination immediately and had much better results. We conclude that our technique of cytological examination was probably unsatisfactory.

Summary Pancreatic function tests with measurement of gastric juice volume, amylase and maximal bicarbonate concentrations were performed on 145 patients suspected of having pancreatic dysfunction. In 70 the tests were normal; adequate follow-up was possible in 48 of these patients and the results were confirmed in these.

The tests were a useful indicator of pancreatic disease in those patients showing more than one abnormal result in the three tests. Patients with only one abnormal value had little evidence of pancreatic disease, and it is concluded that one abnormal value is a poor criterion for detection of dysfunction.

The bilirubin response to pancreozymin has proved to be a valuable indicator of biliary tract disease.

Serum enzyme response to stimulation was of no value in diagnosing disease of the pancreas.

Routine cytological examination was not successful in demonstrating tumour cells in patients in whom carcinoma of the pancreas or contiguous organs was subsequently proved.

Résumé Des tests de la fonction pancréatique avec mesure du volume du suc gastrique, de l'amylase et des concentrations maximum de bicarbonate ont été pratiqués chez 145 malades soupçonnés d'avoir un trouble fonctionnel du pancréas. Les épreuves ont été normales chez 70 d'entre eux; il a été possible d'en suivre convenablement 48 et les résultats ont été confirmés chez ceux-ci.

Les épreuves ont constitué un indice utile de pathologie pancréatique chez ceux des malades qui présentaient plus d'un test anormal sur les trois. Les malades n'ayant qu'un seul test anormal ne présentaient que peu de signes de dysfonctionnement pancréatique et les auteurs en concluent qu'une seule valeur anormale représente un critère médiocre pour déceler le trouble fonctionnel.

La réaction de la bilirubine au pancréozymine s'est montrée come indication précieuse d'une maladie du tractus biliaire.

La réaction à la stimulation de l'enzyme sérique n'a eu aucune valeur pour diagnostiquer la maladie du pancréas.

Les examens cytologiques périodiques n'ont pas permis de mettre en évidence la présence de cellules tumorales chez des malades dont le cancer du pancréas ou des organes contigus a cependant été confirmé subséquemment.

REFERENCES

1. LAGERLÖF, H. O.: *Acta Med. Scand.*, Suppl. **128**: 1, 1942.
2. DREILING, D. A. AND JANOWITZ, H. D.: The measurement of pancreatic secretory function. *In*: Ciba Foundation symposium on the exocrine pancreas: normal and abnormal functions, edited by A. V. S. de Reuck and M. P. Cameron, J. & A. Churchill Ltd., London, 1962, p. 225.
3. DREILING, D. A., JANOWITZ, H. D. AND PERRIER, C. V.: Pancreatic inflammatory disease, a physiologic approach, Hoeber Medical Division, Harper & Row, Publishers Inc., New York, 1964.
4. SUN, D. C. H. AND SHAY, A.: *Gastroenterology*, **38**: 570, 1960.
5. BURTON, P. *et al.*: *Gut*, **1**: 111, 1960.
6. BURTON, P. *et al.*: *Ibid.*, **1**: 125, 1960.
7. FITZGERALD, O.: *Postgrad. Med. J.*, **43**: 1, 1967.
8. RASKIN, H. F. *et al.*: *Gastroenterology*, **34**: 996, 1958.
9. MACDONALD, R. P.: Bilirubin (modified Malloy and Evelyn). *In*: Standard methods of clinical chemistry, vol. 5, edited by S. Meites, Academic Press Inc., New York, 1965, p. 65.
10. SOMOGYI, M.: *J. Biol. Chem.*, **125**: 399, 1938.
11. CHERRY, I. S. AND CRANDALL, L. A., JR.: *Amer. J. Physiol.*, **100**: 266, 1932.
12. CREAMER, B. AND PINK, I. J.: *Lancet*, **1**: 304, 1967.