SURGICAL AND BIOCHEMICAL ASPECTS OF PANCREATITIS*

BY

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The pancreas was known to Greek and Roman physicians, but it was not until 1642 that Wirsung described the main pancreatic duct, and a further two hundred years passed before Claude Bernard (1856) demonstrated ferments in the pancreatic juice and their role in digestion. Balser (1882) described necrosis of fat tissue in connexion with pancreatic inflammation, and in 1889 Fitz published his paper in which, for the first time, an effort was made to correlate the clinical findings and pathological changes in acute pancreatitis. Bayliss and Starling (1902) showed that a humoral mechanism existed for the control of external pancreatic secretion, and Mellanby (1925) showed that the external secretion of the pancreas was under dual hormonal and nervous control—secretin controlling the volume and bicarbonate content of the juice, the vagus nerve its enzyme content. Harper and Raper (1943), following experimental work on cats, prepared extracts of the mucosa of small intestine which, after intravenous injection, increase the output of enzymes from cat's pancreas without having any secretin activity. The active substance producing this effect has been named pancreozymin and it has no effect on the volume of juice secreted.

Clinical application has lagged behind these advances in understanding of the physiology of the pancreas; the deep situation of the gland in the abdomen and its close proximity to other organs have made accurate early clinical diagnosis of pancreatitis impossible. Pancreatic function is difficult to assess because the pancreas has no known excretory function and its external secretion is passed into the deeply situated duodenum. Measurement and analysis of pancreatic juice obtained after duodenal intubation has proved tedious in practice and is liable to gross technical errors. Faecal analysis has also proved unreliable except in the late stages of chronic pancreatic disease, and this is mainly because the enzymes of pancreatic and intestinal juice complement each other. In the absence of pancreatic juice 90% of the carbohydrate in the diet is absorbed: pancreatic proteolytic enzymes can be partially replaced by gastric pepsin and intestinal erepsin. The faeces contain more fat after pancreatectomy, but most of it may be "split fat," and this is attributed to the lipolytic action of bacteria in the colon.

Investigation of the digestive ferments—amylase and lipase—in blood and urine has been more helpful to clinicians; blood has been found to be more convenient and reliable than urine. Dozzi and Bockus (1946) found that in normal persons wide variations in the amount of amylase were present in 10-ml. specimens of urine taken from the same individual over a 24-hour period, and that these variations do not depend on diet. Although it has been known for a century that normal blood possesses starch-splitting properties, the role of the ferment diastase is still not understood, and it is not known if the diastase present in normal blood is contributed by the pancreas or is a by-product of tissue metabolism. The

lipolytic property of normal blood has been recognized only during the past fifteen years; Dozzi and Bockus believe that the serum lipase is all of pancreatic origin, and they have observed progressive lowering of serum lipase levels in a number of cases of pancreatic carcinoma. The serum diastase activity is measured by the iodometric method of Somogyi (1938); and Wapshaw (1948) stated that the normal indices obtained by this method ranged from 70 to 200 units of diastase per millilitre of serum. The lipolytic activity is measured by allowing the serum to act on an olive-oil emulsion for 24 hours: the fatty acids set free are neutralized by an N/20 solution of sodium hydroxide. Wapshaw, after investigating 76 subjects, found the range of normal serum lipase levels to be 0 to 1.5 ml. of N/20 NaOH per ml. of serum.

The value of serum enzyme determinations in acute pancreatitis is now fairly well established, and Elman (1937) thinks these tests have shown that acute oedematous pancreatitis (acute transient pancreatitis) is more common than was formerly realized. Wapshaw found that the diastase and lipase tests were equally satisfactory but that their clinical application was limited to the initial stages of the disease. Sauchez-Ubeda and Rousselot (1951) studied the serum enzymatic responses after stimulation of external pancreatic secretion with secretin and methacholine, and they demonstrated a consistently higher response of serum diastase in patients with certain stages of pancreatic disease than in normal subjects. These authors suggested that in the presence of pancreatitis obstruction of the outflow of juice would lead to a state of secretion retention within the gland and a greater absorption of the ferments into the general circulation. Wapshaw (1953), while investigating the influence of morphine on the pancreas in 84 normal subjects, found that the serum enzyme concentrations were significantly raised in 39% of the series, and here again it was suggested that morphine, by its excitant action on the sphincter of Oddi and neighbouring muscle, produced a state of secretion retention within the pancreas. He found that carbachol alone did not materially affect serum enzyme concentration, but it appeared to intensify the effect of morphine.

Present Series

In my practice pancreatitis has been established in 28 patients during the past six years; they have been subdivided into cases of acute haemorrhagic pancreatitis (15 cases), acute transient pancreatitis (11 cases), and chronic atrophic pancreatitis (2 cases). This clinical classification has been found useful and convenient. The diagnosis of acute haemorrhagic pancreatitis was confirmed by laparotomy or by post-mortem examination in every case, and in 6 of the 15 patients the disease was fatal. During the same period 491 cases of acute appendicitis with 4 deaths and 128 cases of acute perforation of gastric or duodenal ulcer with 8 deaths were seen in patients over 14 years of age.

A history of severe abdominal pain of sudden onset, felt at first across the upper abdomen and accompanied by nausea and vomiting, was obtained in every case. Abdominal tenderness was also present in all instances, and in early cases was most pronounced in the right hypochondrium and epigastrium. These features were not, however, considered sufficient for firm clinical diagnosis, and many of the clinical findings regarded as characteristic of acute pancreatitis were absent. The pain was referred to the back in only two instances and cyanosis was noted only once. Tenderness in the right loin was present in two patients, but left loin tenderness was not noted. One patient was jaundiced on admission to hospital, and in two there was glycosuria.

*Read before the North of England Surgical Society on May 6.

The 11 patients with acute transient pancreatitis all gave a history of recurrent attacks of abdominal pain associated with nausea and vomiting. In some the history suggested recurrent attacks of biliary colic, while in others it was more suggestive of gastro-duodenal disease. Four of these patients had been jaundiced on one or more occasions, but glycosuria was not present in any of them. In five patients gross thickening and induration of the pancreas was confirmed at laparotomy, and in the remaining six the diagnosis was made only after a cholecystogram and barium-meal x-ray examination had failed to reveal any abnormality. In 6 of the 11 cases it was necessary to obtain a cardiologist's opinion in order to exclude heart disease.

A diagnosis of chronic atrophic pancreatitis was made in two elderly female patients. Both complained of lassitude, flatulent dyspepsia, and frequent pale bulky stools. Glycosuria was not present in either patient, and a cholecystogram and barium-meal x-ray examination did not reveal any abnormality. In one, 65% of the fat in the stool was "split fat"; in the other, 85%. Neither had been relieved by a low-fat diet, but administration of pancreatin resulted in marked clinical improvement in each case.

In order to assess the value to the clinician of the amylase and lipase levels in blood and urine, and the serum enzymatic response to pancreatic stimulants in cases of pancreatitis, the following investigations were carried out. The serum amylase and lipase levels were measured in 25 normal fasting subjects. The lowest amylase reading obtained was 88 units and the highest 229 units, and the lipase levels varied between 0.01 and 1.5 ml. of N/20 NaOH. It has been decided that for this hospital laboratory the range of normal indices for amylase is 80 to 230 units per ml. of serum, and for lipase 0.01 to 1.5 ml. of N/20 NaOH per ml. of serum.

In the same 25 normal subjects the serum enzymatic response to various pancreatic stimulants was investigated by measuring the serum amylase and lipase levels before and one hour after administering the stimulants. Morphine, when it was used, was given in $\frac{1}{4}$ -gr. (16-mg.) doses subcutaneously and 10 minutes earlier than the other stimulants—that is 70 minutes before the second specimen of blood was taken from a vein. Methacholine, 25 mg. intramuscularly, was used to stimulate vagal secretion from the pancreas. Secretin was given in doses of 40 units intramuscularly and pancreozymin in doses of 100 units intravenously. Five subjects had pancreozymin alone, five secretin alone, three methacholine alone, seven methacholine and secretin, and five morphine and pancreozymin. No significant rise in serum amylase or lipase levels was obtained in any of these experiments.

Seven of the nine patients who recovered from acute haemorrhagic pancreatitis were similarly investigated: the fasting serum amylase and lipase levels were within normal limits in every case, and no significant rise followed the administration of methacholine and secretin. The five patients suffering from recurrent pancreatitis, in whom the presence of gross thickening and induration of the pancreas had been confirmed at laparotomy, were given morphine, secretin, and pancreozymin, but again no significant rise in serum enzyme levels was obtained.

The results of investigations in the three patients with acute haemorrhagic pancreatitis encountered during 1954 are shown in Table I.

Forty-one patients with acute abdominal conditions in whom the diagnosis was later confirmed by laparotomy had blood withdrawn for serum amylase and lipase estimation immediately after admission to hospital, and the output of urinary diastase during the first 24 hours in hospital was measured. The results are summarized as follows.

In acute appendicitis (14 cases), acute cholecystitis (5 cases), acute perforation of diverticulum of pelvic colon (3 cases), acute obstruction with gangrene of small bowel (4 cases), and acute obstruction of large bowel (1 case) the serum amylase and lipase levels were within normal limits.

TABLE I

Clinical Data	Time of Observation	Serum Diastase per ml. Serum	Serum Lipase (ml. N/20 NaOH per ml. Serum)	Excretion of Urinary Diastase during 1st 24 Hours in Hospital
Male, aged 62. Jaundice and vague epigastric discomfort for a week before onset of acute abdominal pain. Laparotomy on day of admission: blood- and bile-stained fluid in peritoneal cavity and fairly widespread fat necrosis. No stones in G.B. or C.B.D. Cholecystectomy and choledochostomy performed. Patient recovered	8 hrs.	2,400	—	202,917 units
	8th day	533	2.95	
	4 mths. after recovery	200	0.31	
Female, aged 56. Progressive improvement after admission until afternoon of 13th day, when severe pain and nausea returned. Laparotomy on 20th day: moderate bile-stained effusion and fairly widespread fat necrosis. Numerous small calculi in G.B. None in C.B.D. Cholecystectomy and choledochostomy performed. Recovered	24 hrs.	1,060	3.55	4,150 units
	13th day, at 3.30 p.m.	123	1.15	
	13th day, at 11.30 p.m.	266	5.8	
	3 mths. after recovery	106	0.02	
Female, aged 77. Observed during attack 15 months previously, when laparotomy revealed widespread fat necrosis, no gross abnormality of biliary tract; abdomen was closed after confirming diagnosis. Present attack milder, and acute symptoms subsided after seven days. Recovered	4 hrs.	1,600	—	16,492 units
	18 "	800	3.05	
	3 mths. after recovery	145	1.0	

In four patients with calculi in the common bile duct and jaundice the serum amylase levels were 200, 229, 356, and 228 units per ml. of serum. The serum lipase levels were normal.

In one patient with perforated ulcer of the lesser curve of the stomach, close to the pylorus, the serum diastase level was 266 units per ml. of serum. The serum lipase was normal. In nine patients with perforated ulcers of the anterior wall of the first part of duodenum, high serum amylase readings were obtained in five instances—namely, 236, 400, 267, 533, and 530 units per ml. of serum. The serum lipase readings were normal in eight of these patients, but in one instance a reading of 2.4 ml. of N/20 NaOH per ml. of serum was obtained.

The output of urinary diastase during the first 24 hours in hospital in these 41 patients varied within very wide limits, but it may be said that the highest figures were obtained in cases of perforated duodenal ulcer. The results are summarized in Table II.

TABLE II.—Output of Urinary Diastase

Diagnosis	Urinary Diastase Excretion		
	Highest (Units)	Lowest (Units)	Average in 24 Hrs. (Units)
Acute appendicitis (14 cases) ..	59,000	2,871	13,224
Acute cholecystitis (5 cases) ..	44,000	5,280	15,192
Acute perforation of diverticulum of pelvic colon (3 cases) ..	43,000	2,720	19,888
Acute intestinal obstruction (5 cases) ..	32,000	7,000	20,066
Calculi in C.B.D. and jaundice (4 cases) ..	12,820	1,745	7,264
Acute perforation of peptic ulcer (10 cases) ..	120,744	2,500	62,226

Summary and Comments

The major advances in the understanding of the mechanism of control of external pancreatic secretion are reviewed and the difficulties encountered in applying this knowledge to clinical practice discussed.

A personal experience of 28 cases of pancreatitis is summarized in order to illustrate the diagnostic difficulties encountered. The relative incidence and impor-

tance of acute haemorrhagic pancreatitis with two common acute abdominal conditions are noted.

The serum amylase and lipase levels were measured in 25 normal subjects and in 12 patients with past or present pancreatic disease. No significant serum enzyme response was obtained after pancreatic stimulation with morphine, methacholine, secretin, or pancreozymin in any of the individuals investigated, and the suggestion that the response obtained with these substances may be of value as an indication of the presence of pancreatitis was not confirmed.

The serum amylase and lipase levels were investigated in three cases of acute haemorrhagic pancreatitis and in certain other acute abdominal conditions; the highest readings were obtained in acute pancreatitis, but a two-fold or threefold increase was found to be fairly common in cases of perforated duodenal and juxtapyloric ulcers, and high levels were recorded in patients with calculi in the common bile duct.

The excretion of urinary diastase during the first twenty-four hours in hospital was measured in three cases of acute pancreatitis and in 41 other patients with acute abdominal disease: wide variations were recorded, and this investigation is not considered useful or reliable.

REFERENCES

- Balser, W. (1882). *Virchows Arch. path. Anat.*, **90**, 520.
 Bayliss, W. M., and Starling, E. H. (1902). *J. Physiol. (Lond.)*, **28**, 325.
 Bernard, Claude (1856). *Mémoire sur le Pancréas*, Paris.
 Dozzi, D. L., and Bockus, H. L. (1946). In H. L. Bockus's *Gastro-Enterology*, vol. 3. Philadelphia.
 Elman, R. (1937). *Ann. Surg.*, **105**, 379.
 Fitz, R. H. (1889). *Boston med. surg. J.*, **120**, 181.
 Harper, A. A., and Raper, H. S. (1943). *J. Physiol. (Lond.)*, **102**, 115.
 Mellanby, J. (1925). *Ibid.*, **60**, 85.
 Sauchez-Ubeda, R., and Rousselot, L. M. (1951). *Surg. Gynec. Obstet.*, **93**, 283.
 Somogyi, M. (1938). *J. biol. Chem.*, **125**, 399.
 Wapshaw, H. (1948). *British Medical Journal*, **2**, 68.
 — (1953). *Ibid.*, **1**, 373.

PRIMARY MYXOEDEMA APPARENTLY DATING FROM POST-PARTUM SHOCK

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Hypopituitarism is an important sequel of severe post-partum haemorrhage (Sheehan and Murdoch, 1938), and may lead to secondary hypothyroidism. Primary (idiopathic) myxoedema may also first become evident during the post-partum period. Frank myxoedema is seldom an early feature of hypopituitarism; yet when the onset of myxoedema appears to have been preceded by post-partum shock it is natural to suspect that the primary lesion may lie within the pituitary gland.

In practice it may be hard, on purely clinical grounds, to distinguish between primary and secondary myxoedema. We propose, therefore, to draw attention to four patients whose disabilities, though dating from a post-partum haemorrhage or shock, were nevertheless found to be due to primary and irreversible thyroid failure, and were fully corrected by thyroid hormone alone. In these patients the diagnosis was established

most clearly by a careful assessment of anterior pituitary function and by radio-iodine tests after thyrotrophin (T.S.H.) injections. The validity of this last test we will attempt to evaluate by analysing the results obtained from its use in other patients.

Case 1 (E.I. 168467)

The patient, aged 33, was admitted with obvious myxoedema in 1947. Symptoms of anaemia dated from a miscarriage in 1944 which was accompanied by a severe uterine haemorrhage requiring blood transfusion. Menstruation then returned, and in November, 1946, the patient had a normal delivery, followed by amenorrhoea and symptoms of myxoedema. Lactation had occurred, but was inadequate.

Examination (August, 1947) showed obvious myxoedema, hypotension (B.P. 90/60), and moderate anaemia (Hb, 12.6 g./100 ml.; R.B.C., 3,300,000; M.C.V., 100 cubic microns; M.C.H.C., 37%). Tests of endocrine function showed: B.M.R., -49% (Boothby and Sandiford standards); plasma cholesterol, 400 mg. per 100 ml.; E.C.G., low voltage and flat T waves; urinary 17-ketosteroids, 1.9 mg./24 hours; water-excretion tests, 56 and 70% excretion of water dose in three hours*; insulin-tolerance test (0.1 unit/kg.), hypoglycaemic unresponsiveness (blood sugar at two hours = 65% of fasting level); urinary excretion of follicle-stimulating hormone (F.S.H.), between 4 and 8 mouse units in 24 hours.

At first, because pituitary failure was suspected, she was given testosterone (600-mg. implant). This did not correct the anaemia or E.C.G. voltage, but caused a slight improvement in her general condition. Later, both of these abnormalities, and also the hypoglycaemic unresponsiveness, were fully corrected by thyroid extract alone (180 mg. a day). Menstruation returned in December, 1947, infrequent at first, but giving way to menorrhagia when the dose of thyroid extract was reduced early in 1953. The urinary F.S.H. excretion had risen to over 48 m.u./24 hours by December, 1951, and to over 96 m.u. the following year. After raising the dose of thyroid extract to 360 mg. a day, the urinary F.S.H. excretion fell to between 24 and 48 m.u.; the menorrhagia took longer to subside. Otherwise the patient has remained well on thyroid treatment alone. Results of the radio-iodine tests (November, 1951) are shown in the Table.

Case 2 (C.C. 127563)

The patient, aged 20, ruptured her uterus and suffered a post-partum haemorrhage, due to uterine inversion, at the end of her first pregnancy, in 1949. She was given a blood transfusion, and lactation was suppressed by oestrogens. Five months later menstruation returned with menorrhagia and other signs of myxoedema.

On examination (November, 1951) there was obvious myxoedema and hypotension (B.P. 90/65). The breasts, sexual hair, and uterine size were normal. Tests of endocrine function showed: B.M.R., -28% (Boothby and Sandiford standards); plasma cholesterol, 374 mg. per 100 ml.; E.C.G., low voltage and flat T waves; urinary 17-ketosteroids, 4.4 and 4.3 mg./24 hours; water-excretion test, only 10% of water dose excreted in three hours (normal exceeds 70%); insulin-tolerance test (0.1 unit/kg.), normal; eosinophil responses to corticotrophin and adrenaline (Thorn test), normal; urinary F.S.H. excretion exceeded 48 m.u./24 hours. Endometrial biopsy showed a hyperplastic proliferative endometrium. Results of the radio-iodine tests (November, 1951) are shown in the Table.

The patient has remained well on treatment with thyroid hormone alone (thyroxine, 0.3 mg. a day), and has since had a normal delivery. The E.C.G. has reverted to normal, and she now excretes 88% of a water dose in three hours. The menorrhagia has responded to thyroxine, and the urinary F.S.H. excretion has fallen to between 5 and 50 m.u./24 hours.

*Normal excretion of water dose (20 ml./kg.) exceeds 70%.