Gut, 1963, 4, 193

A clinical study of chronic pancreatitis

OLIVER FITZGERALD, PATRICK FITZGERALD, JAMES FENNELLY[1], JOSEPH P. McMULLIN, AND SYLVESTER J. BOLAND

From St. Vincent's Hospital and the Departments of Medicine and Therapeutics and of Surgery, University College, Dublin

EDITORIAL SYNOPSIS A series of 53 cases of chronic pancreatic disease is described and attention drawn to the frequency with which symptoms are persistent rather than intermittent. A plea is made for the use of the term 'progressive' rather than 'relapsing' in describing many of these cases. Alcohol was an unimportant factor in the aetiology. The possibility of achieving an accurate and early diagnosis using the serum secretin/pancreozymin test is emphasized. The frequent relief of symptoms and the prevention of progress of the disease by surgery, especially sphincterotomy, is recorded.

While pancreatitis has been recognized for over a century as a cause of gastro-intestinal disturbance, much of the literature has dealt with acute rather than with chronic pancreatic disease. Reports on the latter have been published by Comfort, Gambill, and Baggenstoss (1946), by Gambill, Comfort, and Baggenstoss (1948), and by Janowitz and Dreiling (1958) but there is still disagreement as to the usual aetiology, presentation, pathogenesis, and treatment. It has been generally thought that in chronic pancreatitis the patient typically suffers from recurrent episodes of upper abdominal pain with intervals of complete freedom and that there is evidence of one or more of the major signs of pancreatic disease, such as a raised fasting level of serum amylase or lipase, steatorrhoea, pancreatic calcification, or diabetes. Cases of this nature should present little diagnostic difficulty to-day, but there are, we believe, many cases in which the pain and digestive disturbance may not be so confidently ascribed to pancreatic dysfunction. This paper in the main endeavours to elucidate the clinical aspects of such cases and to stress the value of evocative enzyme testing. It is agreed that earlier evocative tests 'provided little relevant information not obtainable by other methods' (Joske, 1955) but this evaluation has to be radically altered now. In 1943 Harper and Raper produced a purified pancreozymin which greatly increased the enzyme content of pancreatic juice as distinct from the increase in volume evoked by secretin. Both substances are currently combined in the evocative secretin/pancreozymin (S/P) test (Howat, 1952; Burton, Hammond, Harper, Howat, Scott, and Varley, 1960).

In this paper we propose to describe our experience with 53 cases of chronic pancreatitis, laying particular stress on the possibility and importance of early diagnosis of the condition, that is, when minimal damage to the acinar and islet tissues has been caused. At this stage treatment is most effective in the management of symptoms and in the prevention of further pancreatic destruction.

In so far as early, developing, mild, or atypical cases have been missed, mainly through lack of specific tests, the frequency of chronic pancreatitis has, we believe, been much underestimated. The 53 cases of our series have been encountered in eight years, 1952-1960. As they are drawn from a small population we feel that the condition must be a relatively common cause of upper abdominal discomfort.

METHODS OF INVESTIGATION

The deep situation of the gland and its closeness to other organs makes confident early clinical or radiological diagnosis of pancreatitis difficult (McCollum, 1955). Laboratory and radiological investigations, which may be divided into non-specific and specific tests, must be relied upon. This differentiation cannot be water-tight but it is of practical value.

NON-SPECIFIC LABORATORY TESTS We used four.

1 *Glucose tolerance test* A glucose tolerance test was usually carried out, using 1 g. glucose per kilogram body weight.

2 *Fat balance studies* Up to two years ago we carried

[1]Now at the Medical Center, Jersey City, New Jersey.

out fat balance studies on patients on a 50-g. fat diet. Since then patients have been on free-choice ward diets and we have used three-day collection periods.

3 *Vitamin A absorption tests* See below.

4 *Triolein ^{131}I and oleic acid ^{131}I studies.* See below.

SPECIFIC LABORATORY TESTS

1 *Serum secretin/pancreozymin (S/P) test* In the diagnosis of early cases of chronic pancreatitis the serum enzyme response to stimulation with secretin and pancreozymin is, in our experience, the most helpful test of all. Fasting amylase and lipase levels are often normal in quiescent phases of the disease. We used the method originally described by Howat (1952) and more recently elaborated on by Burton *et al.* (1960) with minor modifications as regards time. Serum specimens were assayed for amylase and lipase according to the methods of Myers, Free, and Rosinski (1944) and of Cherry and Crandall (1932) respectively. The development of pain over the pancreatic area following the injection of pancreozymin was noted, as it possibly indicated pancreatic obstruction. The patient was asked to compare any pain which might occur with that of his original complaint.

To avoid the development of thrombophlebitis, the pancreozymin must be diluted to 20 ml. and must be injected slowly. In our experience of about 300 tests the worst reaction to the injection has been occasional moderately severe abdominal pain with vomiting. This pain always passed away within 20 minutes.

We always avoided carrying out these tests on patients immediately after a suspected acute phase of pancreatitis; in many cases such tests would in any case be unnecessary as the patients would have shown increased enzyme levels in the absence of stimulation. Repeated tests in the same patient never gave rise to any reaction suggestive of hypersensitivity to the reagents.

In 26 of 34 hospital patients with non-pancreatic disease the fasting serum amylase varied between 0·56 and 2·1 mg./ml. reducing sugar (31 to 115 units), and in the other eight cases, which had higher amylase levels, portal hypertension, cholecystitis (2), biliary cirrhosis, hepatitis, coronary thrombosis (2), amyloidosis (1) were found. Bogoch, Roth, and Bockus (1954) reported raised serum amylase levels in acute gall bladder disease, perforated duodenal ulcer, uraemia, post-cholangiography, and after administration of morphine-like narcotics and parasympathomimetic drugs.

In 24 (93%) of our 26 normal control cases fasting amylase figures were from 0·57 to 1·16 mg./ml. (31 to 64 units). According to Howat's (1952) series, the normal fasting amylase figures varied from 0·3 to 1·35 mg. reducing sugar/ml. serum (16 to 74 units). In 27 normal controls the serum lipase range was 0·2 to 1·3 N/20 Na OH, of which the significance will be referred to later.

Secretin/pancreozymin test In normal cases serum amylase activity rose from the fasting level of 0·5 to 1·9 mg./ml. (28 to 105 units), mean 1·3 mg./ml. (72 units), to a peak post-stimulatory level, varying from 0·6 to 2·6 mg./ml. (38 to 137 units), mean 1·5 mg./ml. (84 units). In two normal cases higher figures were found, but repetition of the tests gave lower figures. The mean rise in serum amylase activity was 0·2 mg./ml. (11 units) in the non-pancreatic cases. This is in agreement with the results of Sun and Shay (1960) and of Burton *et al.* (1960).

2 *Vitamin A tests* Vitamin A post-absorption curves are useful in the diagnosis of errors of absorption. The contrast between post-absorption curves of vitamin A acetate and alcohol is helpful in deciding on the presence of maldigestion, as the alcoholic form of the vitamin does not require any further breakdown which the acetate needs before absorption. The fasting serum vitamin A level normally varies between 100 and 300 i.u. % and rises to over 800 i.u. % at peak absorption time (three to five hours) after ingestion of 250,000 i.u. % in the case of both acetate and alcohol preparations of vitamin A (FitzGerald, Fennelly, and Hingerty, 1961, 1962).

3 *Triolein ^{131}I and oleic acid ^{131}I test* This test has been used following a method similar to that used by Fennelly, FitzGerald, and Healy (1959). Triolein requires to be digested by pancreatic lipase before absorption. Hence, in conditions of pancreatic deficiency, it is poorly absorbed compared with oleic acid. We have relied upon serum levels following a test dose of the ^{131}I tagged fat rather than urinary or faecal excretion.

NON-SPECIFIC RADIOLOGY Non-specific radiology, such as a barium meal or cholecystography, will often have been performed in the preliminary investigation of such cases. They rarely yield information directly helpful in the establishment of a diagnosis of pancreatitis. One should, however, remember that the presence of pathology in associated organs does not rule out the possibility of chronic pancreatitis.

SPECIFIC RADIOLOGY Before the administration of barium or of radio-opaque dyes an antero-posterior radiograph of the abdomen is necessary to recognize the presence of pancreatic calcification. It is essential to demonstrate that the calcification is actually in the gland itself, if necessary by a lateral film.

Pancreatography Per-operative pancreatography by the method of Doubilet, Poppel, and Mulholland (1955) is occasionally useful. We have used 5 to 7 ml. of 22% Uropac, and this should be injected slowly and gently. It is important to use minimal pressure, otherwise acute pancreatitis may be precipitated. Occasionally distal pancreatography through the sectioned pancreatic tail may be necessary. The information derived from these pancreatograms has been of limited value in this series, possibly due to the fact that the clinical material was, generally speaking, early.

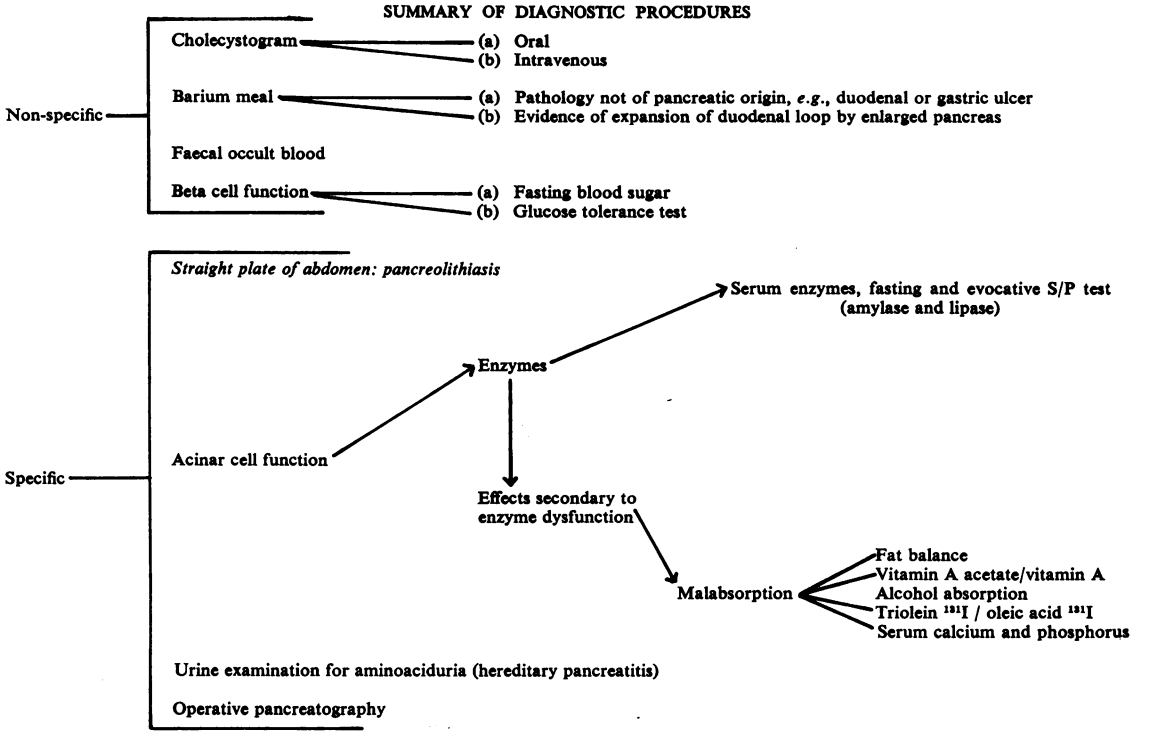
Our methods of investigation are summarized in Table I.

CASE MATERIAL

The 53 cases are divided into the following groups depending on their clinical presentation. This separation is essentially clinical. We think a recognition that this disorder may present in different patterns both in relation to the actual clinical story and also to its development

TABLE I

SUMMARY OF DIAGNOSTIC PROCEDURES



in the individual may be important diagnostically. We do not imply, of course, that the different groups described below are necessarily different aetiologically or pathologically. We would emphasize that chronic pancreatic disorders are common, do not present anything like a unified picture, and that they can often be diagnosed with reasonable certitude.

GROUP I Chronic, persistent pain suggestive of chronic progressive pancreatitis (cases 1 to 22).

GROUP II Classical recurring abdominal pain typical of chronic relapsing pancreatitis (cases 23 to 42).

GROUP III Cases presenting as a malabsorption state (cases 43 to 44).

GROUP IV Cases presenting after a gastro-duodenal operation with persistent or more recent symptoms now recognizable as pancreatic in origin (cases 45 to 48).

GROUP V Patients presenting initially with symptoms of coronary disease: (*a*) with proved coronary disease appearing with pancreatic disease (cases 49 to 51); and (*b*) pancreatic disease simulating coronary disease (cases 52 and 53). Cases 7, 9, and 36 had coronary disease in the presence of pancreatic disease, but the coronary disease was obviously quite a separate entity.

We propose to discuss each group separately, noting the most significant case details. A summary of findings in the 53 cases is found in Tables II and III.

GROUP I: CHRONIC, PERSISTENT PAIN

CASE 4 A man aged 44 years in 1958 complained of continuous left upper abdominal back pain with vomiting and loss of weight. The presenting symptoms were a recrudescence of symptoms which had lasted for some months over two previous years. At that time barium meal examination and cholecystography had disclosed no abnormality. The attack had then gradually subsided. He was tender over the pancreatic area, particularly to the left. The S/P test was positive. Glucose tolerance, a barium meal, and cholecystography were normal. Hydrochloric acid was present in normal amounts in the gastric contents. Microscopic examination of the stool showed an excess of undigested muscle fibres.

At operation the pancreas was enlarged and fibrotic. After sphincterotomy the patient's symptoms were considerable relieved.

This case is typical of chronic progressive pancreatitis, in which a fairly persistent though moderate pain associated with local tenderness and a positive S/P test were the only criteria on which the diagnosis rested pre-operatively. The whole syndrome is less dramatic than that found in chronic relapsing pancreatitis.

TABLE II

DETAILS OF 53 CASES OF CHRONIC PANCREATITIS

Case. No.	Age and Sex	Symptoms	Past History	S/P Test	Glucose Tolerance Test	Fat Balance	Vitamin A Acetate
Group I							
1	47 M	Left upper quadrant, pain		4·2	Diabetic	Not done	Not done
2	57 M	Right upper quadrant, pain	Cholecystectomy 1956	1957, 2·7-3·9 1959, 2·7-3·3	Normal	Normal	+[1]
3	68 F	Left upper quadrant and chest pain, weight loss		1958, 3·0-3·3 (post-sphincterotomy) 1959, 1·4-2·0	Normal	Normal	+ Normal
4	44 M	Left upper quadrant, pain, flatulence		1958, 1·3-2·9	Normal	Normal	Not done
5	40 F	Left upper quadrant, pain, flatulence		1958, 1·3-2·9	Normal	Normal	Not done
6	19 F	Left upper quadrant, umbilical, right lower quadrant and right subcostal pain	Appendix	1958, 3·6-4·2 and post-operatively 2·6-3·8 1959, 1·4-3·0	Normal Normal	Normal	Not done
7	70 F	Right upper quadrant, pain	Cholecystectomy 1950	1958, 2·8	Normal		Not done
8	35 F	Left upper quadrant, pain, jaundice	Persistent left upper quadrant pain	1957, 3·2-3·5	Normal	Normal	Not done
9	52 F	Left upper quadrant, pain, flatulence	Coronary disease	1958, 2·0-2·6	Normal	+[2]	Not done
10	30 F	Right and left upper quadrant, pain	Cholecystectomy 1956, dyspepsia	1958, 2·5	Normal	Normal	Not done
11	44 M	Pain, vomiting, constipation		1958, 4·7	Normal		Not done
12	74 F	Epigastric pain		2·2-4·5	Normal	Normal	Not done
13	55 F	Right upper quadrant, pain, flatulence	Gall bladder operation, calculi 1950	1·8-3·8	Normal	Normal	Not done
14	69 F	Central abdominal pain	Gall bladder operation 1955				Not done
15	33 M	Epigastric pain, flatulence, jaundice	Haemolytic anaemia (splenectomy)	1958, 2·9-3·2	Normal	Normal	Not done
16	20 M	Right upper quadrant pain, jaundice					Not done
17	40 M	Abdominal pain			Normal	Normal	Not done
18	50 F	Right upper quadrant, pain		1957, 2·5-4·2	Normal	Normal	Not done
19	54 F	Left upper quadrant pain, weight loss	Gall bladder operation, diverticulitis	1959, 1·6-3·8	Normal	Normal	Not done
20	40 F	Left upper quadrant, pain for many years	Cholecystegastrostomy, 1958	1961, 1·6-3·6	Hypoglycaemic	+	
21	56 F	Right upper quadrant, pain and heartburn		1960, 2·2-3·5			Not done
22	45 F	Pain, weakness	Hypoglycaemia	1959 2·0-3·0	Hypoglycaemic	Normal	Not done
Group II							
23	62 F	Epigastric pain ++ after fats	—		Normal	+	Not done
24	50 F	Left upper quadrant, pain, vomiting, flatulence	—	3·2-4·5	Normal	Normal	Normal
25	27 F	Recurrent acute left and right upper quadrant, pain, vomiting, shock, constipation, weight loss	Partial gastrectomy and gall bladder operation 1957	1957, 1·4-3·2 3·0-4·0 2·6-3·3 1958, post-gastrectomy 2·5-2·9, 4·7-4·0 1959, post-sphincterotomy 1·7-1·6, 2·5-4·4 1960, 0·7-1·0	Normal Post-gastrectomy	Not done Normal	Not done Not done
26	37 F	Left upper quadrant, pain, jaundice, constipation	Gall bladder operation 1943	1952, 5·8 5·85 Lipase, 12·0 ml.	Normal	Not done	+
27	60 F	Acute epigastric pain, jaundice	Gall bladder operation 1955	1960, 2·3-3·2	Normal	+	Not done
28	50 M	Epigastric pain	Alcoholism	1959, 3·0-4·5	Not done	—	Not done
29	43 F	Right upper quadrant, pain flatulence, jaundice		1955, 1·6-2·9 1958, 2·8-3·3 1959, 2·2-4·7	Normal — Normal	Normal	Normal

[1] + = for acetate and alcohol respectively indicate maldigestion.
[2] + = abnormal, indicating malabsorption.
Figures given for S/P test = fasting and peak post-stimulatory level of serum amylase (mg./100 ml.)

TABLE II—*continued*

DETAILS OF 53 CASES OF CHRONIC PANCREATITIS

Absorption Test / *Alcohol*	*Radiograph*	*Treatment*	*Result*	*Remarks*
Not done	Calcification	Medical	Good, improved but not free of symptoms	
+	Barium meal normal	Medical	No real improvement	
+ Normal	Poor gall bladder function	1959 sphincterotomy, gall bladder operation	Very good, no symptoms remaining	Improved S/P and vitamin A after operation
Not done	Calcification, barium meal, and gall bladder normal	1958 sphincterotomy	Very good, no symptoms remaining	Pancreas fibrotic, calculus
Not done	Barium meal and gall bladder normal	1958 sphincterotomy	Very good, no symptoms remaining	Pancreas fibrotic, stormy post-operative period
Not done	Barium meal and gall bladder normal	1958 sphincterotomy	Good, improved but not free of symptoms	Pancreas indurated, weight loss
Not done	—	Medical	Died	Died of coronary disease
Not done	Biliary calculi	1957 sphincterotomy, gall bladder operation	Good, improved but not free of symptoms	Possible case of familial pancreatitis History of repeated abortions
Not done	Gall bladder and barium meal normal	Medical	Died	Hyperlipaemia, died of coronary disease
Not done	Intravenous cholangiogram normal	Sphincterotomy	Very good, no symptoms remaining	Post-partum pancreatitis
Not done	Barium meal and gall bladder normal, flocculation of barium	1958 sphincterotomy	Very good, no symptoms remaining	Hard, granular pancreas at operation
Not done	Barium meal and gall bladder normal, colonic diverticulitis	Medical	Good, improved but not free of symptoms	Upper abdominal pain referred left
Not done		Medical	Good, improved but not free of symptoms	
Not done		Medical	No real improvement	Pancreatitis noted at cholecystectomy Sphincterotomy not done
Not done	Gall bladder normal	Sphincterotomy	No real improvement	Depressed
Not done	Biliary calculi	Sphincterotomy, gall bladder operation	Good, improved but not free of symptoms	
Not done		1958 sphincterotomy	Good, improved but not free of symptoms	Discomfort for years
Not done		Medical	Good, improved but not free of symptoms	
Not done	Dilated common bile duct	Medical	Good, improved but not free of symptoms	Previous cholecystectomy, appendicectomy
	Small active duodenal ulcer	Sphincterotomy and pancreatectomy 1961	No real improvement	Had pale, bulky stools before cholecysto-gastrostomy
Not done	Gall bladder and barium meal normal	Medical	Poor	
Not done	Pancreatic calcification, gall bladder and barium meal normal	Medical	Good, improved but not free of symptoms	Chronic persistent pain partly controlled with medical measures
Not done	Calcification	Medical	Poor	
Normal	Calcification later, 1960 gastric ulcer	1957 sphincterotomy, removal of pancreatic stone	Good, improved but not free of symptoms	Perigastric abscess and stone in pancreatic duct
	1957 duodenal ulcer			Improved S/P after partial gastrectomy, then deterioration and back to normal after sphincterotomy
Not done		Sphincterotomy 1958	Good, improved but not free of symptoms	
Normal	Dilated common bile duct no calculi	1954 sphincterotomy	Very good, no symptoms remaining	Many years discomfort and pain, premenstrual attacks. Note high serum lipase level. Gluten-free diet
Not done	1960, dilated common bile duct, barium meal normal	Sphincterotomy + partial pancreatectomy 1960	Poor	Typical relapsing pancreatitis, partial pancreatectomy
Not done	N.A.D.	Medical	Poor	Treatment unsatisfactory because of alcoholism
Normal	Barium meal normal	1958 sphincterotomy	Very good, no symptoms remaining	Hypothyroid

TABLE II—*continued*

DETAILS OF 53 CASES OF CHRONIC PANCREATITIS

Case No.	*Age and Sex*	*Symptoms*	*Past History*	*S/P Test*	*Glucose Tolerance Test*	*Fat Balance*	*Vitamin A*
							Acetate
Group II—continued							
30	40 M	Left and right upper quadrant, pain and jaundice		1958, 3·0-4·3 post-sphincterotomy 1958, 1·6-3·4 1958, 1·4-1·8 1959, 0·7-1·8	Normal	—	+ post-sphincterotomy Normal
31	23 F	Epigastric pain, vomiting, constipation	Partial gastrectomy 1956	1957, 0·8-2·1 1958, 1·7-2·7 1959, 2·4-3·7 post-sphincterotomy F. 1·2	Not done	Normal +	1957, normal 1959, +
32	52 F	Left upper quadrant, pain, infrascapular pain	Gall bladder operation 1946	1958, 3·4-3·6 post-sphincterotomy 1958, 1·4-2·5	Possible diabetes	Normal	Not done
33	40 F	Left upper quadrant, pain		1958, 1·7-2·4 1959, 3·2-3·9 post sphincterotomy 1960, 2·1-3·6	Normal	Normal	Not done
34	47 F	Left upper quadrant and scapular pain		1958, 3·3-3·7	Diabetes	Normal	Normal
35	44 F	Left upper quadrant, pain	Gall bladder operation 1954	1958, 2·3-4·0 1959, 3·0-3·3	Normal	Normal	Not done
36	58 M	Pain, jaundice	Gall bladder operation 1945 and coronary disease	0·7-3·6	Normal	Normal	Not done
37	50 F	Right upper quadrant, pain, jaundice	Gall bladder operation 1958	1·8-3·0	Normal	Normal	Normal
38	11 M	R.I.F., pain, jaundice		1960, 2·6-4·2	Normal	Normal	Not done
39	51 F	Pain, flatulence, jaundice		1959, 3·3-4·2	Not done	+	
40	50 F	Pain, flatulence		1960, 3·0-5·0	Not done		
41	50 F	Right upper quadrant, pain, vomiting	Gall bladder operation 1953	1957, 1·9-3·8 1958, 3·1-7·0 post-sphincterotomy 1958, 3·1-4·6 1959, 4·4-4·8	Normal Normal	Normal	Normal Normal
42	68 F	Epigastric pain nocturnal	Gall bladder operation 1945	1959, 3·8-4·4	1957, Normal 1959, Normal	Normal	Normal
Group III							
43	65 F	Left and right upper quadrant, pain, steatorrhoea		1956, 2·0-3·8	Not done	+	Not done
44	42 M	Diarrhoea, no pain	Injury, gluten enteropathy	0·8-3·2	Normal	+	+ + +
Group IV							
45	55 M	Left upper quadrant and left axilla, pain	Partial gastrectomy 1950 for duodenal ulcer	1956, 1·7-3·7 1958, 3·0-3·9	Post-gastrectomy diabetic	 +	Normal +
46	48 M	Left upper quadrant, pain	1934, gastro-enterostomy, 1945 partial gastrectomy, 1949 vagotomy	1956, 4·7	Diabetic	+	Not done
47	53 M	Diarrhoea, back pain (once)	Partial gastrectomy 1954 for duodenal ulcer	1954, 3·0 1955, 3·0 1957, 3·4	Post-gastrectomy Post-gastrectomy	1956 + 1959 +	+ +
48	42 M	Back, chest, and right shoulder pain	Partial gastrectomy 1952 for duodenal ulcer	1958, 3·0-3·4	Post-gastrectomy	Normal	Normal
Group V							
49	44 F	Epigastric pain, flatulence, constipation	Post-partum coronary disease	1958, 2·3-5·0 1959, 2·5-3·1 1960, 0·8-1·3	Normal	Normal	Normal
50	43 M	Left upper quadrant, pain, diarrhoea, glycosuria	Gall bladder operation 1953, coronary disease	1955, 2·5-3·1 1956, 3·5	Normal	+	Not done
51	43 M	Left upper quadrant and right and left arm, pain	Coronary disease	1957, 2·4-2·7 1957, 4·0	Normal	Normal	Not done
52	59 M	Epigastric, chest, and left arm pain		1958, 2·8-3·6	Normal, 1956 Diabetic, 1958	+ +	Normal +
53	50 M	Chest pain, right upper quadrant pain, constipation		4·0-4·8	Normal	+	Normal

[1] + = for acetate and alcohol respectively indicate maldigestion.
[2] + = abnormal, indicating malabsorption.
Figures given for S/P test = fasting and peak post-stimulatory level of serum amylase (mg./100 ml.)

TABLE II—*continued*

DETAILS OF 53 CASES OF CHRONIC PANCREATITIS

Absorption Test	*Radiograph*	*Treatment*	*Result*	*Remarks*
Alcohol				
Group II—continued				
Normal post-sphincterotomy	No biliary calculi	1958 Sphincterotomy + gall bladder	Very good, no symptoms remaining	Lipase figures also abnormal, jaundice in absence of gall bladder calculi, calcification of pancreas visible only at operation. No evidence of cholelithiasis
Not done				
Normal	1956, gastric ulcer	1959 Sphincterotomy	Very good, no symptoms remaining	Polyp removed from pancreatic duct at operation. Poor triolein ^{131}I and normal oleic acid ^{131}I absorption
Not done	Barium meal normal	1958 Sphincterotomy and partial pancreatectomy	Very good, no symptoms remaining	Chronic recurrent pain since about time of gall bladder operation. Tender on palpation. Developed pancreatic pain during S/P test
Not done		1959 Sphincterotomy	Good, improved but not free of symptoms	
Normal	Normal gall bladder	Medical	Good, improved but not free of symptoms	
Not done	Normal barium meal and cholangiogram	Sphincterotomy 1959	Good, improved but not free of symptoms	All tests normal except S/P test Pancreatic obstruction at operation
Not done	Biliary calculi	Medical	Good, improved but not free of symptoms	Jaundice with biliary calculi at operation
Normal	Dilated common bile duct	Sphincterotomy 1959	Good, improved but not free of symptoms	Hyperlipaemia: enlarged head of pancreas
Not done	Gall bladder and barium meal normal	Medical	Good, improved but not free of symptoms	Family history of dyspepsia
	Non-functioning gall bladder	Pyloroplasty + gall bladder operation and sphincterotomy, 1960	Very good, no symptoms remaining	Jaundice without biliary calculi
Normal	Barium meal and gall bladder normal	Sphincterotomy 1960	Good, improved but not free of symptoms	Inflammation of pancreas at operation
Normal	Barium meal normal	Sphincterotomy 1958	Good, improved but not free of symptoms	Cholecystectomy had little effect on chronic abdominal pain
Normal	Dilated common bile duct	Medical	Good, improved but not free of symptoms	
Not done	Normal	Medical	Good, improved but not free of symptoms	Fatty diarrhoea was main complaint
+	Calcification	Medical	Good, improved but not free of symptoms	Poor triolein ^{131}I and normal oleic acid ^{131}I absorption
Normal				Moderately heavy beer drinker up to 1950
Normal	Dumping type of stoma	Medical	Poor	
Not done	Stomal ulcer	Sphincterotomy 1956	Good, improved but not free of symptoms	No relief of pain until sphincterotomy was completed
Normal +	Post-gastrectomy	Medical	Poor	Alcoholic abnormal triolein ^{131}I and normal oleic acid ^{131}I absorption
Normal	Gastro-jejunal ulcer	Medical	Poor	Chronic discomfort for many years; for surgery later
Normal	Barium meal and gall bladder normal	Medical	Very good, no symptoms remaining	Hyperlipaemia and hypercholesterolaemia; lipase 1·6 to 2·3 ml.
Not done	Barium meal normal	Medical	Died	Died following a coronary episode
Not done	Gall bladder normal, hypertrophy of gastric mucosa	Medical	Good, improved but not free of symptoms	
Normal +	Gastric ulcer, gall bladder normal, calcification pancreas	Surgery (see case report)	Died	Father of case 31 took alcohol to relieve pain. Died after operation
Normal	Gall bladder and barium meal normal	Medical	Good, improved but not free of symptoms	Coronary disease suspected but not proved

CASE 5 A woman aged 40 years was first seen in 1958 when she complained of upper abdominal pain, mainly to the left, with associated flatulence and nausea, which had been present for many years. She had vomited on a few occasions only. She had gradually come to subsist on a bland, low-fat diet. No diarrhoea was present, nor was it a prominent feature of her history. She had been investigated on many occasions elsewhere, but no precise diagnosis had been arrived at. A barium meal examination and cholecystography were both normal. Her symptoms were not especially suggestive of pancreatitis but she was tender on palpation over the pancreas and to the left. The S/P test was abnormal (rise 1·3 to 2·9). A glucose tolerance test was normal.

At operation the pancreas was indurated and nodular. A sphincterotomy and biopsy were carried out. The patient had a stormy post-operative course, developing pulmonary atelectasis and jaundice. However, she eventually did well and is now in normal health. She says that she can eat normally and has put on weight and she does not suffer from any pain. The biopsy at operation revealed fibrosed pancreatic tissue.

The contrast of the pre-operative symptoms with the present freedom from all discomfort is striking. We might draw attention to the post-operative morbidity seen in this case, a none too rare occurence after sphincterotomy, particularly in the early cases of this series.

GROUP II: TYPICAL RECURRING PAIN

CASE 25 A woman, aged 27 years, was first seen in 1956, complaining of vomiting and of epigastric pain radiating to the left scapular area. The pain was aggravated by fried food and was accompanied by diarrhoea. A barium meal confirmed the presence of a duodenal ulcer with possible pancreatitis. The S/P test was positive (1·5 mg. fasting to 3·2 mg. at maximum). In July 1957 a partial gastrectomy and cholecystectomy was performed with exploration of the common bile duct, a T tube being left in place for 10 days. After this operation she felt well until November 1957, when she developed an attack of acute pancreatitis, complaining of excruciating pain and intractable constipation. She recovered on treatment with smooth muscle relaxants and steroid therapy. The S/P test a few weeks later was strongly positive (peak 4·0 mg./ml.), and the glucose tolerance test showed a typical post-gastrectomy curve. After this episode the patient suffered from recurrent episodes of severe abdominal pain. In Frebruary 1958 the S/P test was strongly positive (peak serum amylase again 4.0 mg./ml.). Moreover, following the pancreozymin, she developed moderately severe abdominal pain and vomiting which, however, disappeared in 30 minutes. A sphincterotomy was performed and a definite improvement symptomatically followed. The S/P test returned to normal (peak 1·7 mg./ml. serum amylase). However, just one year later she again complained of intermittent abdominal pain spreading to the left and into the back, with vomiting and diarrhoea, occurring in acute attacks which alternated with constipation in the intervals of freedom from pain. The S/P test supported the suggestion that obstruction in the pancreas had recurred (peak 4·0 mg./ml.). A further operation was then contemplated, possibly a partial pancreatectomy, but a further S/P test some months later revealed a return to normal, the peak being 1·0 mg./ml., a lower level than had been noted for some four and a half years. The patient is now nearly free of symptoms and no further surgery is intended. The results of the tests are shown in Figure 1.

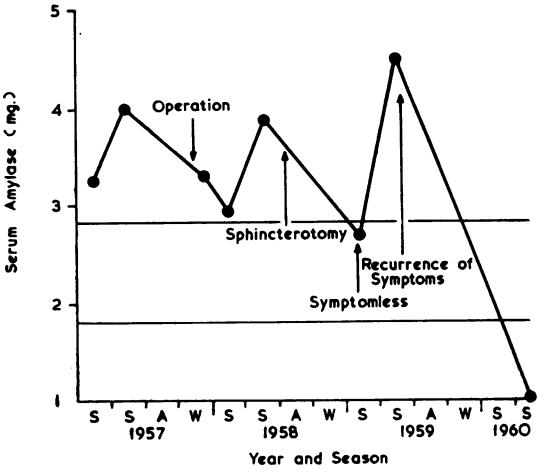


FIG. 1. *Case 25, group II. Peak serum amylase responses in repeated S/P tests and their relationship to symptoms and response to therapy.*

This case presented as a typical example of chronic relapsing pancreatitis. Results of repeated S/P tests have correlated very well with symptoms and pathology. The persistence of symptoms after sphincterotomy suggests chronic acinar inflammation or an intraductal obstruction away from the sphincter of Oddi, either alone or associated with recurrence of sphincteric obstruction.

CASE 31 A woman, aged 25 years, is a daughter of case 52, and was already complaining of severe symptoms. At the age of 19 years she had a partial gastrectomy for a penetrating gastric ulcer. Afterwards she experienced some relief of her pre-operative symptoms which had consisted of colicky pain in the left hypochondrium. These pains bore no relation to meals and were worse at night time. When examined in relation to a possible pancreatic disorder in 1954 the S/P test showed a low normal fasting level, rising to a figure within the normal limits; this was not considered diagnostic at the time, though there actually was a rise of 1·3 mg./ml. The vitamin A and other tests were quite normal. The patient was of a nervous disposition, was upset due to family disturbances, and had recurrent migraine. She was tentatively thought to be psychoneurotic. The pain

did not respond to a low-fat diet or to smooth muscle relaxants. In 1958 the S/P test was more suggestive of abnormality but still was not definitely abnormal; the fasting level was higher though the rise in serum amylase (1·3 mg./ml.) was still the same. However, during the test she complained of severe pain over the pancreatic area. Vitamin A absorption was normal for both forms, but the faeces showed 27% of fat/g. dry weight on a 50 g./day fat diet. The pain was now related to meals. Constipation was present in the interval between the major attacks which changed to diarrhoea during the acute attack. In 1959 the S/P test was definitely abnormal (2·4 mg./ml. to 3·7 mg./ml.). Vitamin A acetate and triolein ^{131}I absorption tests were abnormal but vitamin A alcohol and oleic acid ^{131}I were normally absorbed, indicating pancreatic maldigestion. The fasting amylase was now abnormal, indicating chronic pancreatic obstruction. Urinary chromatography revealed an excess of lysine on two occasions.

At operation a highly vascular adenomatous polyp was found obstructing the ampulla of Vater, accompanied by stenosis of the sphincter of Oddi, and a nodular head of the pancreas. Sphincterotomy and excision of the polyp was carried out. Post-operative progress was complicated, but after a few weeks the pain improved; three months after the operation she had gained 20 lb. in weight and the fasting serum amylase level was normal.

In Fig. 2 are shown the changes in various tests in this patient. The striking feature is the similarity of the S/P curve from the time it was first performed.

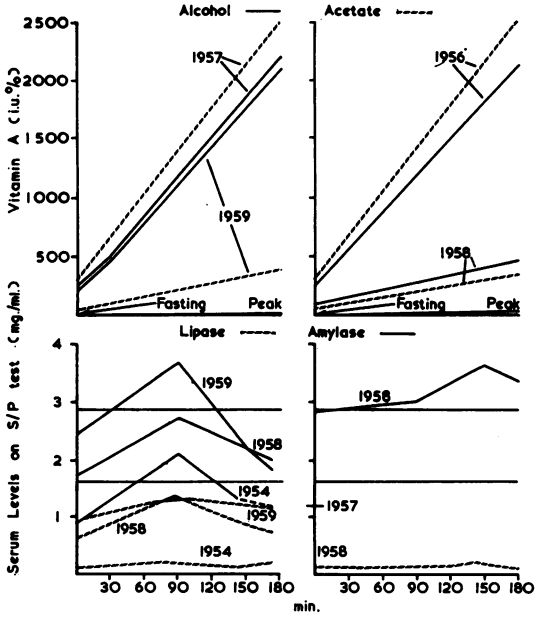


FIG. 2. *Salient biochemical data for case 31 (group II) and her father, case 52 (group V).*

The rise in serum amylase (1·3 mg./ml.) was the same in 1958 as when the test was first performed. Increased resistance at the sphincter of Oddi had been noted by Gross and Comfort (1957) in cases of hereditary pancreatitis. It should be observed that despite considerable temporary benefit following sphincterotomy, this has not been maintained, and further surgery, probably a partial pancreatectomy, is under consideration.

This patient is one of the most interesting cases of our series. Aetiologically she could be described first as a case of familial pancreatitis, both in the light of her father's history and of the presence of lysinuria (Comfort and Steinberg, 1952; Gross and Comfort, 1957; Gross, Comfort, and Ulrich, 1957). Secondly, she might (erroneously) have been classified as a case of post-operative pancreatitis. In fact, she suffered from definite obstruction at the sphincter. She illustrates the difficulties of diagnosis in a young, thin, rather nervous woman when even the S/P test was apparently normal for some time, though the sharp post-stimulatory rise was probably significant. Her pancreatic function deteriorated. Finally, she illustrates the immediate hazards of surgery, its temporary value, and the risk of recurrence.

GROUP III.
MALABSORPTION DUE TO PAINLESS PANCREATITIS

CASE 44 A man, aged 42 years, was first seen in February 1953, referred from a rural area with a history of diarrhoea for six months and occasional bowel looseness off and on for over three years. There was no complaint of pain or tenderness, or none ever admitted to, despite frequent enquiries. He had never observed any pus, blood, or mucus in the stool. However, he had suffered from peri-anal soreness for some time, and had occasionally noticed a little blood after defaecation. The feet, ankles, and lower legs had been swollen for some time before admission. He had lost a considerable amount of weight (over 70 lb.), being 114 lb. in 1953.

He showed evidence of cachexia and there was some peripheral oedema. The cardiovascular and respiratory systems were clinically normal (blood pressure 112/74 mm. Hg). The abdomen was somewhat distended, but there was no evidence of free fluid. The liver was enlarged about 2 in. below the costal margin. The spleen was not enlarged. The faeces showed an excess of neutral fat and meat fibre on microscopic examination; there was no unusual micro-organism on culture. Gastric acid studies showed normal levels. A barium meal using a proprietary suspension showed no abnormality of pattern, and the presence of pancreatic calcification was not observed. There was a high (26%) bromsulphalein retention at 45 minutes after a dose of 5 mg./kg. Total serum protein was low (4·0/g.) with the A/G ratio normal (later at times it was inverted). He was put on methionine and choline in March 1953, but with little response.

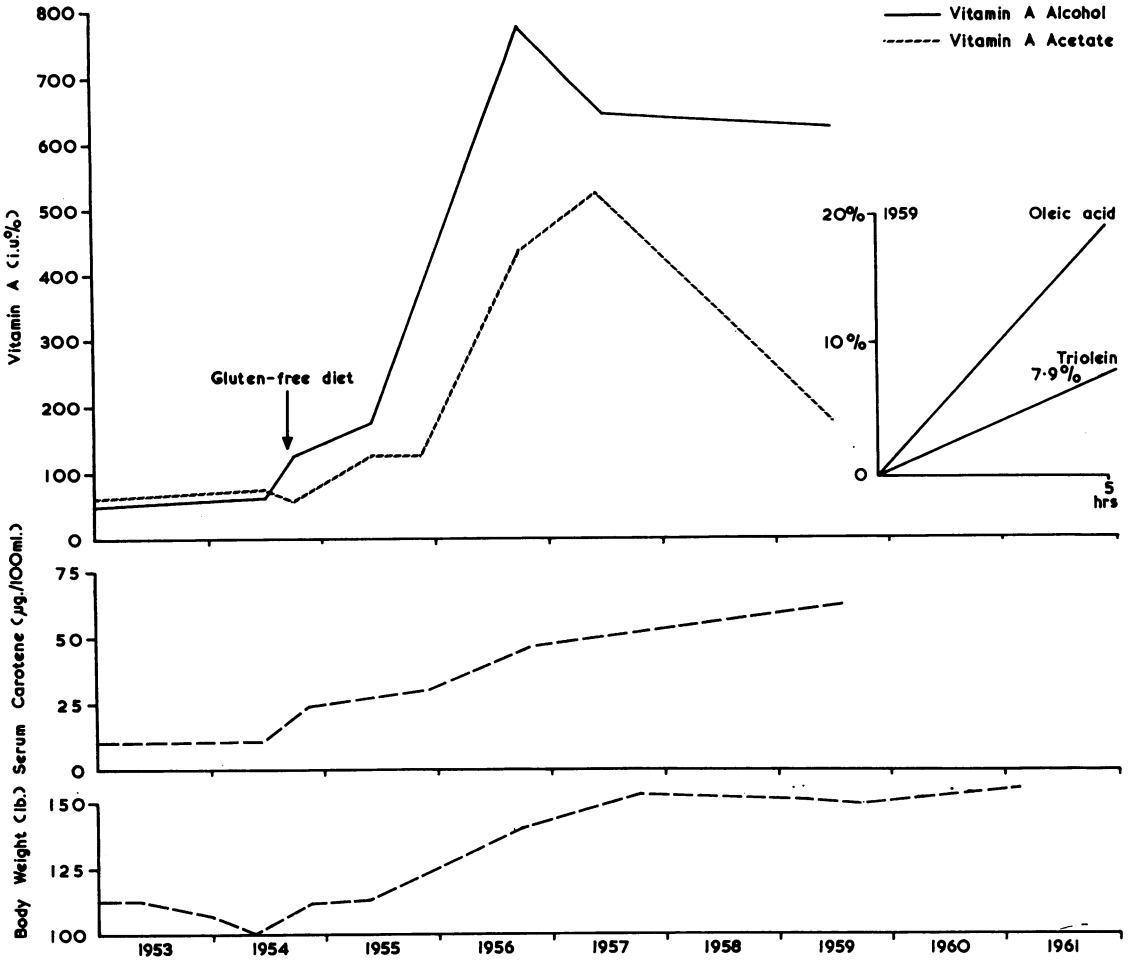


FIG. 3. *Case 44, group III. Weight response, serum carotene levels, serum vitamin A acetate, and alcohol curves from 1953 to 1959. The serum triolein-^{131}I and oleic acid-^{131}I curves were estimated in 1959 only.*

Apart from the diarrhoea and chronic cough he was reasonably well until his return in November, 1953. The legs still swelled during the day but the liver was not enlarged and there was no free peritoneal fluid. A barium meal using flocculable barium showed considerable flocculation. Pancreatic calcification was also noted. (Review of earlier films showed that it had been present at least one year before.) A number of investigations were carried out, including duodenal intubation which showed a low level of amylase, lipase, and trypsin with little change after carbachol. Serum lipase and amylase were both within the low normal range. He was put on pancreatin in November 1953 and on a low-fat diet in December 1953. Afterwards he showed improvement in digesting and absorbing fat. He complained occasionally of muscle cramps and intermittently Chvostek's sign was positive, but the reinforced Trousseau's sign was always negative. The serum calcium level in December 1953 was 8·5 mg. %, serum phosphatase 3·9 mg. %, and alkaline phosphatase was 9 K.-A. units. In January 1954 he was given 50,000 units calciferol for seven days by intramuscular injection for mild hypocalcaemia. He complained of nausea after two days, and the drug was discontinued. A vitamin A absorption test was carried out showing no rise in the curve after administration of 250,000 units of both acetate and alcohol preparations. He felt well on pancreatin and went home on 12 February 1954. In June 1954 he was put on a gluten-free diet, and from this time there was a dramatic improvement in his condition, his symptoms cleared up, the serum carotene, vitamin A absorption, fat balance, weight (plus 50 lb.) all improved; however, vitamin A acetate was still poorly absorbed in contrast to vitamin A alcohol, and there was a large amount of unsplit fat in the faeces. Starch tolerance curves were low compared to that of glucose (starch up to 110 mg. %; glucose 160 mg. %). In

1959 triolein ^{131}I absorption was found to be poor in relation to that of oleic acid ^{131}I. The improvement in his condition is shown graphically in Figure 3.

This case is unusual in that it appears to be a gluten-enteropathy in combination with a painless pancreatitis, presenting as an absorption defect. It is faintly possible that the calcification might have been initiated following a back injury in an air raid in 1943. Recurrent respiratory infection suggested muco-viscidosis as a possible diagnosis but specific sweat tests for muco-viscidosis were negative. Pancreatic calcification would be unusual in muco-viscidosis. He has been on a gluten-free diet for five or six years, and is most anxious to continue it. In 1959 we persuaded him to discontinue the diet temporarily, but ordinary food upset him with associated bowel discomfort and marked flatulence. Jejunal biopsy in 1960 and 1961, using the Crosby capsule, showed partial villous atrophy, a picture suggestive of adult coeliac disease.

GROUP IV: CASES PRESENTING AFTER A GASTRO-INTESTINAL OPERATION

CASE 45 A man aged 55, presented in 1955 with severe left upper abdominal pain. This patient had a haematemesis due to a gastric ulcer in 1947, and in 1950 had a Polya gastrectomy. Until 1945 he used to drink six glasses of beer daily. In 1955 he complained of left upper abdominal pain spreading to the left and coming on after meals. He said that the operation in 1950 had not notably improved his symptoms, but he now had less trouble with heartburn and flatulence than in the past. The pain was now more to the left than he had felt pre-operatively. A barium meal showed the usual post-operative appearance. Fasting serum amylase was 3·6 mg./ml. He lost much weight, being 106 lb. in 1956 and 93 lb. in 1958. There was no bowel disturbance. The S/P test was strongly positive in 1956 (1·7 to 4·3). The vitamin A acetate and alcohol tests were both within normal limits (Table V). Stool fat analysis at that time was reported as 10·5 g. excreted in three days. A barium meal showed a dumping type of stoma but no evidence of gastro-jejunal ulceration. A cholecystogram was normal, a glucose tolerance curve, 114 mg.% fasting, 297 (30 min.), 366 (60 min.) 211 (90 min.), and 98 (120 min.). He was treated with Panar granules and antispasmodics. In 1958 he still complained of left upper abdominal pain which frequently woke him at night. It was often related to meals. He was quite tender over the pancreas. His weight was 93 lb. He was now considered to be a diabetic and was treated with tolbutamide. An S/P test was again abnormal (3·0 to 3·9). Vitamin A acetate was poorly absorbed in relation to vitamin A alcohol, indicating pancreatic maldigestion. We decided to attempt to control him medically with diet, replacement therapy (Panar, Armour), antispasmodics (Piptal), and diabetic control with tolbutamide. This was fairly successful. He continued to take alcohol, but in moderation. He has had less discomfort recently though an S/P test in 1960 was still abnormal (2·0 to 4·4). His weight is now 101 lb.

It is difficult to say with certainty when the pancreatitis began, but it appears that the typical left-sided pain only declared itself after the gastrectomy. Over the years he showed considerable deterioration, notably the development of definite diabetes and evidence of pancreatic exocrine insufficiency. These may eventually become even more of a problem. For all that, he is reasonably well on a suitable low-fat diet combined with an antacid and tolbutamide. Surgery does not seem to be indicated at the moment though it would probably have been carried out if complaints of pain had been more vocal rather than the gradual development of diabetes mellitus and mild pancreatogenous maldigestion.

CASE 47 A man, aged 53, presented in 1952 suffering from violent epigastric pain and vomiting. He had a history of many years of epigastric discomfort. In 1921 he had been on hunger strike for over two weeks. He had been a heavy drinker for some years and was an alcoholic. In 1954 after severe melaena he had a Polya gastrectomy for a duodenal ulcer which was penetrating the pancreas. After this operation he progressed quite well, but two weeks later he developed severe diarrhoea and pain in the lower right back. At operation patches of fatty necrosis were noted in the omentum; the pancreas was indurated and inflamed. The diarrhoea continued and this was considered to be due to pancreatic deficiency (fasting serum amylase 3·0 mg./ml.). The faeces showed an excess of unsplit fat. Vitamin A acetate was poorly absorbed in relation to vitamin A alcohol. In 1959 triolein ^{131}I absorption was poor, but oleic acid ^{131}I was normally absorbed. These tests suggested the presence of exocrine pancreatic insufficiency. Because of complaints of weakness and palpitations two hours post-prandially, a glucose tolerance test was carried out with concurrent serum potassium studies. Results were normal. Owing to alcoholism this patient was not recommended for further surgery but medical treatment has been used.

It seems likely that pancreatitis in this case resulted from a partial gastrectomy in which a penetrating duodenal ulcer was dissected off an adherent pancreas (case previously reported by Morrin and Dunkin, 1956).

GROUP V: SIMULATING CORONARY DISEASE

CASE 52 A man, aged 59 years, was first seen in April 1950, complaining of severe abdominal pain referred to the precordium, the left side of the chest, and the left arm. He vomited when the pain was severe and this usually relieved it. Work led to pain but rest eased it. This pain had been recurring since 1939. Diarrhoea was present on and off for a few years. In 1945 he had been treated

for angina pectoris, though no conclusive evidence was ever seen by us to support the diagnosis. In 1949 a barium meal had disclosed a small gastric ulcer. When first seen by us in 1950 he had lost 20 lb. weight. No masses were palpable on abdominal examination.

A cholecystogram was normal, but diffuse calcification of the pancreas was noted. A glucose tolerance test was normal (90, 150, 166, and 100 mg. %); an E.C.G. was normal (peak vitamin A acetate was 3,500 i.u. % and vitamin A alcohol up to 3,000 i.u. %. Antacids and a low-fat diet, while each initially was successful in relieving pain, lost their effect. Right and left splanchnicectomies were carried out in 1956 with little permanent relief of symptoms. In 1958 he complained of persistent, intractable epigastric pain and vomiting, with watery diarrhoea. He had lost much weight and appeared emaciated. A fat balance test showed 46% fat/g. dry weight (excretion of 68·4 g. fat in three days). A glucose tolerance test was mildly diabetic (110, 160, 185, and 185 mg. %). Both vitamin A acetate and vitamin A alcohol were poorly absorbed. The enzyme curves through the years are shown in Figure 2. Fasting amylase in 1954 was 4·1 mg./ml., in 1956 1·2 mg./ml., and in 1958 it was 2 mg./ml. The S/P test was positive (2·8, 3·0, 3·6, and 2·6 mg./ml. amylase). A radiograph showed that the calcification in the pancreas had become more extensive since the first examination. A mass was palpated over the pancreatic area. At operation a penetrating gastric ulcer was found, the pancreas was enlarged, cystic and calcareous, and a pancreaticoduodenectomy was performed. He progressed well for two weeks but then diabetes became uncontrollable, he developed a large pelvic abscess and cardiac failure, and died.

A daughter of this patient is case 31 and this is our second case of familial pancreatitis. In this patient the spread of pain from the abdomen to the chest and left arm had suggested myocardial ischaemia, but no E.C.G. evidence was provided to prove it. Calcification was noted over the entire gland. The deterioration in vitamin A absorption and change in glucose tolerance test was followed over four years. Lysine studies were not done although lysine was present in the daughter's urine.

ANALYSIS OF CASES

AGE AND SEX In Table III is shown the distribution of patients as regards sex and age. Females were more frequent sufferers, forming 62·4% of the cases as against 37·6% of males. This is in agreement with the figures of Olmos, Enriquez, Salazar, Hermansen, and Biel (1958) of Chile, who reported a female excess of 60%, but contrasts with those found in North America by Comfort *et al.* (1946) and by Gambill *et al.* (1948) who reported a male preponderance of 6·2/1·0 and 2·4/1·0 in cases without and with gall-bladder disease respectively. A series of 100 cases of acute pancreatitis in England showed a female excess of 2·45/1 (Pollock, 1959).

TABLE III

SEX, AGE, AND LENGTH OF SYMPTOMS IN 53 CASES OF CHRONIC PANCREATIC DISEASE

Sex	*Age Group (yr.)*	*Mean Age (yr.)*	*Length of Symptoms and Mean Length*
Male 20 (37·6%)	11-59	45·3	3 months to 12 years (3½ years)
Female 33 (62·4%)	19-74	49·4	3 months to 12 years (5 years)

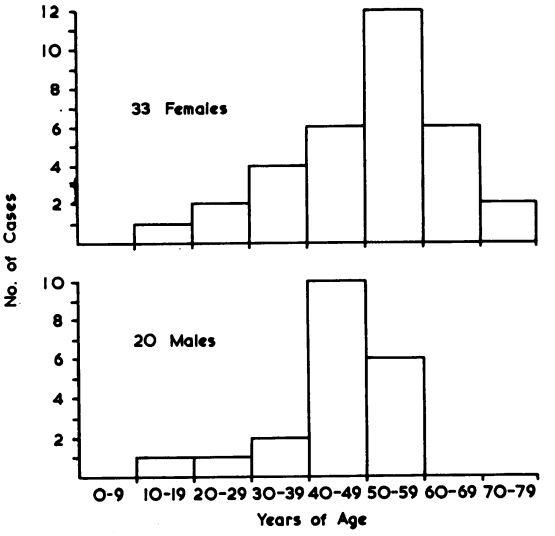


FIG. 4. *Sex and age incidence of 53 cases of chronic pancreatitis.*

Another feature clearly illustrated in Fig. 4 is the wide scatter through the life cycle in women from 19 to 74 years and in men from 11 to 59 years. In North America the ages ranged from 10 to 75 years, and Pollock's youngest patient was 6 years old. The mean age of onset of symptoms in our series was 47·8 years, which was almost 10 years older than that in other series. A mean age of onset of 41·1 years was reported by Gambill *et al.* (1948), and in the series of Olmos *et al.* (1958) it was between 30 and 40 years of age.

PRESENTING FEATURES In Table IV are shown the major features noted in this series. The general pattern of symptoms is definite enough, though lacking specificity.

PAIN AND TENDERNESS Pain was the presenting symptom in 96·2% of cases. Exceptions were cases 42 and 47. It varied from severe, gripping, colicky or knife-like, to less acute, *viz.*, dull, boring, aching, or

TABLE IV

IMPORTANT FEATURES OF 53 CASES OF CHRONIC PANCREATIC DISEASE

Clinical Features	*Total (53)*	*Male (20)*	*Female (33)*
Pain	51 (96·2%)	19 (95%)	32 (97%)
Dyspepsia	32 (60·4%)	14 (70%)	18 (60%)
Gall bladder disease (past and present)	22 (41·5%)	5 (25%)	17 (53%)
Steatorrhoea	13 (25%)	6 (30%)	7 (21%)
Peptic ulcer (past or present)	10 (19%)	5 (25%)	5 (15%)
Icterus (past and present)	11 (21%)	5 (25%)	6 (18%)
Coronary disease	6 (11%)	3 (15%)	3 (9%)
Diabetes	4 (7·6%)	4 (20%)	
Calcification	6 (11%)	3 (15%)	3 (9%)
Alcohol	4 (7·6%)	3 (15%)	3 (3%)

gnawing. In the majority of cases the pain was not very severe. Fatty foods, fries, alcohol, exercise, and emotion were noted as precipitating factors. Two patients (cases 31 and 34) noted relief after the ingestion of alcohol. The pain bore no particular relation to meals; in 14% of these cases the patients were disturbed between midnight and 3·0 a.m. by the pain. The periodicity was variable. The acute pain was often accompanied by vomiting.

The varying sites of pain are shown in Table V. We have always looked upon pain going obliquely to the left lower dorsal region as suspicious. There was no strong correlation between the primary site of pain and the macroscopic pathology discovered at operation, though pain to the right was usually associated with pathology in the head of the pancreas or concurrent gall bladder disease. One patient complained of right iliac fossa pain, but as no operation was carried out we were unable to confirm the presence of pathology in the uncinate process, as suggested by Beckman in such cases. Myocardial disease had been diagnosed elsewhere on clinical grounds in case 52, though no abnormal E.C.G. findings were found to substantiate that diagnosis. Some patients mentioned relief on leaning forward or lying face downwards in bed.

It was unusual to find a patient complaining of recurring acute abdominal pain with intervals of complete freedom. The more usual presentation was of an upper abdominal pain, varying from mild to severe in character and lasting some days, being unrelieved by antacids or antispasmodics. Right upper quandrant pain has been very hard to distinguish from that of gall-bladder disease: in this series 17 patients has cholecystectomies in an attempt to treat dyspeptic symptoms. Many cases in this series presented with chronic persistent pain, not typical of chronic relapsing pancreatitis. The association of flatulence with pain had in the past often led to suspicion of gall-bladder disease primarily.

It is impossible in this discussion to separate pain from tenderness. Typically tenderness was elicited in the upper abdomen along a line beginning inside the right border of the rectus abdominis at a level just above the umbilicus and passing obliquely upwards to the left at an angle of about 45°. This tenderness could be associated with considerable guarding, though little rigidity, but tenderness in milder cases could only be elicited on relatively deep palpation.

DYSPEPSIA AND INTOLERANCE TO FATS While pain was the presenting feature in 96·2% of cases it was noted that dyspepsia with intolerance to fats had often been present for many years before the onset of pain (cases 14, 26, and 27). Five cases in group 7 of the series of Comfort *et al.* (1946) had dyspepsia and flatulence for many years before the onset of more acute symptoms of pancreatitis. Fried foods are frequently mentioned as an aggravating factor. In our series dyspepsia was present in 60·4% of cases.

BOWEL FUNCTION Constipation was present in 11 (21%) of our cases, and diarrhoea in nine (17%). Gambill *et al.* (1948) noted that of 27 patients, four had constipation and six had suffered from diarrhoea, the diarrhoea being so severe as to overshadow all other symptoms. Some of these patients (cases 11, 25, 31, and 41) noted that constipation was present in the quiescent phase but changed to diarrhoea during the acute attacks. In 13 cases of pancreolithiasis described by Hepp and Moreaux (1958) constipation rather than diarrhoea was the prominent feature.

LOSS OF WEIGHT This was a constant finding, and there were a variety of causes: malabsorption due to pancreatic deficiency and resulting from diarrhoea; loss of appetite because the pain was aggravated by food; and loss of sleep due to nocturnal pain (cases 3, 6, 25, 27, and 31).

TABLE V

SITES OF PAIN IN 53 CASES OF CHRONIC PANCREATITIS

Primary Site						*Sites of Radiation*					
Right Upper Quadrant	*Left Upper Quadrant*	*Mid Epi-gastrium*	*Right Iliac Fossa*	*Chest*	*Back*	*Back*	*Infra-scapular Area*	*Chest*	*Chest and Left Arm*	*Chest and Right Arm*	*Transverse Abdominal*
16	12	15	1	3	7	6	3	3	1	2	3

Note that some patients had more than one primary site or radiation of pain.

JAUNDICE Jaundice was present at some stage in 11 cases: associated with biliary calculi (case 8, 16, 36) in three; not associated with biliary calculi (radiologically or at operation) (in seven cases, 26, 27, 29, 30, 37, 38, 29); coincidentally one patient (case 15) had haemolytic jaundice. Those jaundiced patients without biliary calculi were generally found at operation to have inflammation of the head of the pancreas. The cholecystogram in cases 26 and 27 revealed dilatation of the common duct suggesting some obstruction at the head of the pancreas.

CORONARY DISEASE Coronary disease was present in six cases (11%), and in three of these there was evidence of hyperlipaemia. Three of the four fatal cases in this series died of myocardial infarction (cases 7, 9, and 50).

ALCOHOLISM Alcoholism was present in only four cases (7·6%), three of them being males (cases 28, 47, and 52). This figure is much lower than that reported in northern American states, where alcohol is blamed as a principal aetiological factor. This will be further discussed later.

DEPRESSION A number of patients in this series exhibited considerable depression, so great indeed that it was only when careful study had demonstrated a definite pancreatic disease that an endogenous depression was finally ruled out. Some patients noted relief of depression after surgery.

INVESTIGATIONS

FASTING ENZYMES In patients with chronic pancreatitis in Howat's (1952) series the figures were generally higher than in his normal controls; however, of 70 tests, 25 (36%) gave a level of 2·1 mg./ml. (115 units) or less. In our experience, in the early stages of relapsing pancreatitis the figures in the quiescent phase may be quite normal, though as the more chronic phase is reached an abnormal fasting level is frequently found (cases 5, 13, 35, 31, 36, 37, 46, and 52). We feel that while a normal fasting level does not exclude the diagnosis of chronic pancreatitis, amylase levels above 2·1 mg./ml. (115 units), in the absence of the diseases mentioned above, are suggestive of pancreatic disease.

There was greater overlap of serum lipase figures in normal and pancreatic patients. One patient only (case 26) showed unusually high levels, *viz.*, 12·0, 10·0, 10·8 ml. N/20 NaOH in an acute episode. Forty-nine of 55 (89%) of the levels found in our patients with chronic pancreatitis were 1·3 or less, *i.e.*, within normal levels. From these figures it appears that fasting serum lipase levels are of less value in the diagnosis of pancreatic disease than fasting serum amylase. Normal figures from McCollum (1955) were 0·01 to 1·5 ml. N/20 NaOH per millilitre serum.

Secretin/pancreozymin test Sixty-nine tests were carried out on 40 patients with pancreatitis. Serum amylase rose from fasting levels of 0·7 to 4·4 mg./ml. (40 to 242 units) with a mean of 2·53 mg./ml. (157 units) to 2·5 to 8·2 mg./ml. (137 to 451 units) with a mean of 3·41 mg./ml. (188 units), median 3/3 mg./ml. (182 units). Twenty-five (30%) had normal fasting levels: in untreated cases 92·1% showed peak serum amylase levels of 2·9 mg./ml. (159 units) or over at some stage during the test. Of the 7·9% who failed to reach these levels three were patients who had early symptoms whose tests later became positive (cases 3, 33, 51) and two were cases proved at operation to have pancreatic disease.

There was a difference between the rise in serum amylase level in those showing normal fasting levels and those with abnormal levels. In those with normal fasting amylase levels of 2·1 mg./ml. (116 units) or less serum enzyme values rose between 0·6 and 2·6 mg./ml. (33 to 143 units) with a mean rise of 1·6 mg./ml. (88 units), median 1·6, while those with fasting serum amylase levels over 2·1 mg./ml. (116 units) showed a rise between 0·3 and 2·3 mg./ml. (17 to 126 units) with a mean rise of 0·97 (53 units), median 0·8 mg./ml. (44 units). The mean rise for all patients was 1·3 mg./ml. (72 units), median 1·3 mg./ml. (72 units).

Results for serum lipase in the secretin/pancreozymin test were only occasionally of diagnostic value. In case 49, for example, fasting lipase, 1·6 ml., rose to 2·3 ml. N/20 Na OH following stimulation. More recent experience of cases not included in this series has demonstrated that lipase figures may be of similar value to those for amylase.

The following were the criteria we used for diagnosis of pancreatitis in relation to enzyme tests: high fasting amylase (over 2·1 mg./ml.) in the absence of other possible causes of such a finding as mentioned above; peak serum amylase 2·9 mg./ml. (159 units) or over at any time during the test; rise in serum enzymes of 1·3 mg./ml. (72 units) or greater (cases 5/and 31).

In the cases reported in this series we relied on the amylase figures.

ABSORPTION TESTS

PANCREATIC MALDIGESTION This was studied by means of fat balances and tests of vitamin A absorption.

Fat balance studies As only occasional cases presented with possible steatorrhoea, we relied on

the other tests. No diagnosis of pancreatic disease can be based solely on the presence of malabsorption of fat.

Vitamin A absorption This test was carried out on 19 of these patients (Table VI and Fig. 3). In nine the typical contrast was quite clear. The changing pattern in absorption with deterioration in clinical condition was shown by cases 31, 47, and 52, and the rise in absorption figures after surgery and ensuing return to good health was demonstrated in cases 3 and 30. Case 44 (Fig. 3) shows the change from the predominant steatorrhoea of a gluten enteropathy to that of the underlying pancreatic insufficiency after the introduction of a gluten-free diet. We have dealt with this in more detail elsewhere (FitzGerald *et al.*, 1962).

TRIOLEIN ^{131}I AND OLEIC ACID ^{131}I ABSORPTION Normally at peak absorption time (3 to 5 hours) 14% ± 2% of the ingested dose of triolein ^{131}I is found in the total blood volume and 8% of the ingested dose of oleic acid ^{131}I. In patients with pancreatic malabsorption this ratio was reversed as shown in Figure 3. This test was carried out on six patients with pancreatitis.

GLUCOSE TOLERANCE TEST The fasting blood sugar was less than 120 mg. % in 36 (90%) patients on whom this test was carried out. The glucose tolerance test was carried out in 45 cases and of these four (7·6%) proved to be diabetic (cases 1, 34, 45, and 46); three (cases 25, 47, and 48) had post-gastrectomy types of curves; two others had abnormal curves which were not typically diabetic. Cases 20 and 22, previously reported by Ryan (1957), had hypoglycaemic curves.

In Table VII are summarized the results obtained from laboratory tests in our series.

RADIOLOGY

In Table VIII are shown the results of radiological investigations in this group.

CALCIFICATION Radiological evidence of calcification of the pancreas was present in five (9%) of our cases, usually being widely spread through the gland. The progression of calcification was noted in cases 42 and 52. We have not noted the appearance of calcification, though we frequently sought for it. Comfort *et al.* (1946) described this development in

TABLE VI

VITAMIN A ABSORPTION IN PANCREATIC MALDIGESTION[1]

Case No.	*Vitamin A Acetate (i.u.%)*	*Vitamin A Alcohol (i.u.%)*	*Comment*
Mean rise in 15 normal subjects	1,800	1,500	
2	600	700	
3 Post-sphincterotomy	350	350	Dramatic clinical improvement after operation
	2,000	1,800	
26	750	1,150	
30 Post-sphincterotomy	458	956	Improvement after operation
	900	—	
31	3,100	2,270	Daughter of case 52
	290	2,161	
44 Gluten-free diet	50	60	Improved pattern after introduction of gluten-free diet after first test
	50	120	
	125	175	
	500	700	
45 (1956)	1,140	1,650	Deterioration with progression of disease
(1958)	580	1,450	
47 (1956)	450	900	Deterioration with progression of disease
(1959)	435	410	
52 (1956)	3,000	2,120	Much decreased absorption after 2 years
(1958)	299	360	

[1]Serum rise after administration of 250,000 units of vitamin A acetate or vitamin A alcohol.

TABLE VII

PROPORTION OF POSITIVE TESTS IN PATIENTS WITH CHRONIC PANCREATIC DISEASE

Test	*No. of Patients*	*No. Tested*	*No. Positive*	*No. Negative*
Secretin/pancreozymin test[1]	53	40 (69 tests)	38 (95%)	2 (5%)
Fat balance	53	44 (47 tests)	14 (32%)	30 (68%)
Vitamin A acetate and alcohol absorption	53	19 (27 tests)	9 (47%)	10 (53%)
Triolein ^{131}I and oleic acid ^{131}I absorption	53	6 (6 tests)	3 (50%)	3 (50%)
Glucose tolerance test	53	45 (57 tests)	11 (24%)	34 (76%)

[1]This does not include cases in which only fasting levels were determined.

TABLE VIII

RADIOLOGICAL FINDINGS IN 53 CASES OF CHRONIC PANCREATITIS

Results of Cholecystogram in 28 Cases[1]	*Male*	*Female*	*Total*	*Percentage*	*Results of Barium Meal in 24 Cases*[2]	*Male*	*Female*	*Total*
Normal gall bladder	5	8	13	46	Gastric ulcer	1	3	4
Normal common bile duct (post-cholecystectomy)	1	2	3	11	Duodenal ulcer	2	2	4
Dilated common bile duct (post-cholecystectomy)	0	5	5	18	Gastro-jejunal ulcer	2	–	2
Non-functioning gall bladder without or with calculi	1	3	4	14	Dumping stoma	1	–	1
	2	1	3	11	Flocculation	1	2	3
					Hypertrophic gastritis	–	1	1
					Visceroptosis	1	–	1
					Pancreatic calcification	3	3	6

[1]Cholecystograms were not carried out on seven females and two males who previously had had a cholecystectomy carried out.
[2]A number of cases had previously been operated upon for peptic ulcer.

two patients over periods of one to 19 years respectively. In that series 14 of 29 cases showed calcification—a surprisingly high level. Warren and Cattell (1959) found that 64 of 160 cases (40%) exhibited calcification. It is worth emphasizing that pancreatic calcification may not always be demonstrated on *x*-ray examination. We have seen a number of cases with pancreatic calcification visible at laparotomy, but this could not be demonstrated even when sought for again post-operatively. This is known to occur in association with placental calcification also.

CHOLECYSTOGRAPHY Thirty-five of the 53 cases (66%) had some gall bladder investigation carried out either previously or at the time of our investigation. Thirteen cases (24%) showed no abnormality. Seventeen (three men and 14 women, 33%) had had a cholecystectomy carried out previously, and five more (two men and three women 9%) had a cholecystectomy at the same time as pancreatic surgery, a total of 22 cases (42%). Eight of the previously operated 17 cases were re-investigated by choledochography and five of the eight exhibited a dilated common bile duct. Nine post-cholecystectomy cases were not re-investigated by choledochography, usually because the diagnosis of pancreatitis was unequivocal and did not require any support from such findings as a dilated common bile duct.

PEPTIC ULCER A history of previous or concurrent peptic ulceration was a feature of 10 (19%) of our cases. Four of the 10 were cases of gastric ulcer, three of these being in women; the remaining six cases included two of gastro-jejunal ulcer (both men) and four of duodenal ulcer (two men and two women). Twenty-three (14%) of the 160 cases of Warren and Cattell (1959) had a duodenal ulcer and four (2·5%) of 160 had a gastric ulcer. The overall ulcer rate was 17%.

The association between the two conditions may be complex, and we may mention an aetiological and a clinical relationship. It had been believed that chronic pancreatitis was always associated with the presence of gastric hydrochloric acid and presumably also with the potentiality for peptic ulceration. A theoretical relationship between gastric acidity and pancreatic disease, though obviously a frequent possibility, is certainly not always necessary and cases of pancreatitis associated with achlorhydria have been described (Gross and Hallenbeck, 1960). The clinical association is more complex. If ulcer and pancreatitis are both present, the ulcer only may be diagnosed and a poor response to therapy might be blamed upon the ulcer rather than upon the underlying pancreatitis. Finally, chronic pancreatitis (usually superimposed upon acute) may follow an operation for peptic ulcer. This occurred in four cases of our series.

TREATMENT

The medical treatment of this disorder has not, in our experience, been satisfactory. Twenty-six (48%) of the 53 cases reported were treated solely by a variety of medical measures. Some of the remaining 27 cases were so treated temporarily before operative measures were used. The length of medical treatment became more restricted in many of the later cases of this series as it was thought that surgery offered a more certain prospect of control of symptoms. It should be emphasized that the presence of other disorders might lead to the decision that surgery should be avoided and, therefore, the medically treated group in some ways might be considered to be the less promising. Cases usually considered by us to be unsuitable for surgery were alcoholics, psychologically disturbed patients, and patients in a state of advanced malnutrition. No hard and fast rule was adopted, as the possibility that surgery might abolish or lessen symptoms when severe and otherwise not controlled by medical means led to some members of each of these groups being operated upon. Medical measures rarely abolished symptoms

but generally speaking they caused an amelioration. Of the 26 cases, the results in one were described as very good, no symptoms remaining, 14 good, six fair, three poor, and two patients died, both of myocardial infarction.

The measures adopted were as follows. The diet was a low-fat, moderate-residue diet. The reduction, especially of oxidized fats in the form of fried foods, was emphasized as we considered that this might lessen intestinal smooth muscle spasm and so increase the patients' comfort. The reduction in foods likely to increase faecal bulk was designed to lessen bowel irritability and looseness as many of these patients had clinical evidence of a spastic colon syndrome. Though not particularly impressed with the value of these dietetic measures yet in some form or other such diets were frequently advised post-operatively. Apart from the diet referred to above, a gluten-free régime was used with great advantage in case 44 as detailed in the case report. It was, however, also used in a few other cases with only one other success in a patient (case 26), who showed borderline evidence of malabsorption, whose response to sphincterotomy was poor until this diet was used, and who eventually, either *post hoc* or *propter hoc*, became and has remained symptomless. We have not been able to persuade her to stop the diet, and therefore feel hesitant in drawing conclusions, but report the history.

Apart from diet, certain other measures were used. Replacement therapy with pancreatin (B.P.) or proprietary preparations such as Panar granules (Armour) or Enzypan (Norgine) appeared to be helpful when taken during a meal. The use of antacids was sometimes valuable especially if hyperchlorhydria or peptic ulceration was present.

The direct relief of pain formed one of the major problems. All ordinary anodynes of the opium family or derivatives were unsuitable due to their addictive properties, except under direct medical supervision in hospital and then nearly always as part of the treatment (referred to below) of an acute episode or immediately related to surgery. We have used two other groups of drugs for the relief of pain. First, anticholinergic drugs such as atropine, methyl scopolamine bromide (Pamine bromide), or isopropamide (Tyrimide) have often been used in the treatment of this disease on what we think are somewhat doubtful theoretical grounds. They appeared to be helpful if colospasm was prominent. However, they did occasionally help otherwise. We were more impressed with the more direct-acting, smooth muscle relaxants such as glyceryl trinitrate or pentaerythritol tetranitrate, and regularly used (and use) these in the medical treatment of this condition.

If the patient was a diabetic specific measures were adopted. In most cases the diabetes was not severe and therefore not requiring the permanent use of insulin. In our experience tolbutamide or chlorpropamide always appeared to control the diabetes adequately.

Finally, reference must be made to the problem of dealing with acute episodes of pancreatitis occurring in a patient already diagnosed as suffering from chronic pancreatitis. The problem arose on about 10 occasions The measures used were standard apart, perhaps, from a particular emphasis on the value of corticoids given in large doses for a matter of a few days parenterally as we felt that this might abort an attack if given early. They were successful in a number of cases. Combined with such a therapy was complete avoidance of all food by mouth, judicious intravenous fluids, with some care in glucose administration, the use of pethidine for relief of pain, combined with anticholinergics or trinitrin as referred to above. No patient died in an acute episode, all had attacks lasting less than a week, and nearly all were eventually operated upon.

SURGICAL TREATMENT In this series of 53 cases of various forms of pancreatic disease, 27 (52%) were operated upon. In most cases the indication for operation was upper abdominal pain of a type already discussed; in general, operation was reserved for those cases which did not respond to medical therapy, but with increasing experience surgery was offered to the majority.

The evocative S/P test was utilized in 21 of the 27 surgical cases. In no case in which the test was positive did we fail to find a definite pancreatic lesion, usually a sphincteric stenosis or other obstructive addition. In three cases suspected on clinical grounds of having a pancreatic lesion, but with normal S/P tests, no lesion could be demonstrated in the pancreas at the time of operation. This is reflected in the pathological findings (Tables IX and X), in the operations employed (Table X and XI), and in the group analysis (see case reports). In group I sphincterotomy was performed 11 times, that is in all cases operated on, either by itself (7), or with cholecystectomy, (3) or with partial pancreatectomy (1).

In group II, for a total of 14 cases operated on, nine simple sphincterotomies were performed, two sphincterotomies were combined with cholecystectomies, and one combined with removal of pancreatic calculi and drainage of pancreatic abscess plus two cases of distal hemi-pancreatectomy with sphincterotomy. We believe that in this group the failure fully to subside, or the partial recurrence of symptoms, may be associated with more severe damage to the pancreas.

TABLE IX

MACROSCOPIC FINDINGS AT OPERATION: S/P TEST FINDINGS

Case No.	*S/P Test*	*Pathology*
Group I		
3	Abnormal	Hard nodular pancreas plus tight sphincter
4	Abnormal	Diffuse pancreatic fibrosis plus tight sphincter
5	Abnormal	Fibrosis mainly in tail of pancreas plus tight sphincter
6	Abnormal	Diffuse pancreatic induration plus tight sphincter
8	Abnormal	Stenosis of sphincter of Oddi (cholelithiasis)
10	Not done	Stenosis of sphincter of Oddi (contorted cystic duct)
11	Not done	Diffuse pancreatic induration plus tight sphincter
15	Abnormal	Stenosis of sphincter of Oddi
16	Not done	Stones in gall bladder and common bile duct plus tight sphincter
17	Not done	Post-Billroth I for duodenal ulcer plus tight sphincter
20	Abnormal	Stenosis of sphincter of Oddi and distal pancreatitis
Group II		
24	Abnormal	Pancreatic fibrosis, fibrosis of duct, and epigastric abscess
25	Abnormal	Partial gastrectomy for duodenal ulcer, subsequent tight sphincter
26	Not done	Indurated pancreas, inflamed common bile duct, tight lower end of duct
27	Abnormal	Stenosis of sphincter of Oddi and distal pancreatitis
29	Abnormal	Tight sphincter of Oddi
30	Abnormal	Tight sphincter of Oddi, calcification of centre of pancreas
31	Abnormal	Polyp and stenosis of sphincter of Oddi
32	Abnormal	Stenosis of sphincter of Oddi plus partial obstruction of mid-segment of pancreatic duct
33	Abnormal	Tight sphincter of Oddi
35	Abnormal	Tight sphincter of Oddi
37	Abnormal	Chronic inflammation and thickening of head of pancreas
39	Abnormal	Induration, stenosis of duct of Santorini, congestion of sphincter of Oddi
40	Abnormal	Induration of head of pancreas, thickening of common bile duct
41	Abnormal	Fibrosis of sphincter of Oddi and tail of pancreas
Group IV		
46	Not done	Tightening of sphincter of Oddi and accessory duct
Group V		
52	Abnormal	Fatty patches in omentum and induration of pancreas

TABLE X

PATHOLOGICAL LESIONS ENCOUNTERED IN GROUPS I AND II AT OPERATION

Group	*Sphincteric Stenosis*	*Ampullary Polyp*	*Fibrosis of Pancreatic Duct*	*Ampullary Stones*	*Pancreatic Lithiasis or Calcification*	*Pancreatic Induration or Fibrosis*	*Gall Bladder or Common Bile Duct Inflammation or Stones*
I	11	–	–	1	1	5	4
II	14	1	1	–	2	5	3

TABLE XA

POST-OPERATIVE RESULTS IN ALL GROUPS

Group	*Total No.*	*No. Operated*	*Post-Operative Result*		
			Very Good	*Good*	*Poor*
I	22	11 (50%)	5	4	2
II	20	14 (70%)	6	7	1
III	2	0	–	–	–
IV	4	1 (25%)	–	1	–
V	5	1 (20%)	–	–	1 (died)
	53	27 (52%)	11	12	3 (+1)

TABLE XI

OPERATIONS USED IN GROUPS I AND II

Group	*Total Operations*	*Sphincterotomy Alone*	*Sphincterotomy*				
			+Chole-cystectomy	*+Pancreatico-lithotomy*	*+Choledocho-lithotomy*	*+Abscess Drainage*	*+Partial Pancreatectomy*
I	11	7	3	1	1[1]	–	1
II	14	9	2	1	–	1	2

[1]Cholecystectomy also performed.

No case of malabsorption (group III) was submitted to operation, and in this series only one case each of post-gastrectomy (group IV) and simulatory coronary disease (group V) was operated upon. The group IV case had well-marked sphincteric stenosis and achieved a good result from sphincterotomy. The patient with angina-like pain (case 52) had gross calcification and destruction of the pancreatic parenchyma, for which a pancreatico-duodenectomy was performed. The patient died subsequently.

It is, we believe, unnecessary in this paper to give a complete description of all the operative methods employed in the treatment of these cases. We will confine our remarks on technique to a short description of the basic operation of sphincterotomy (Doubilet and Mulholland, 1951). We consider our procedure to be in essence a meatotomy.

In the great majority of cases the ampulla has been the site of blockage as demonstrated by the failure to pass a 3 to 5 mm. sound easily through it. In these circumstances, the duodenum is mobilized and a small incision made in its anterior wall at the level of the ampulla. The probe, which is impacted in the tight ampullary orifice, is manipulated so as to herniate the ampulla through the opening in the duodenum. Four united fine sutures are inserted in the four quadrants of the ampulla, and an incision is made in the middle of the upper and outer quadrant (11 o'clock). This incision is usually about 1·0 cm. in length. The main pancreatic duct is then sought at its usual site of entry, that is, in the lower inner quadrant (5 o'clock). Its location may be facilitated by the intravenous injection of 10 units of secretin. The pancreatic duct is then cannulated with a fine soft polythene tube and a sample of pancreatic juice is collected. If there is any doubt as to the patency of the duct, a retrograde pancreatogram is now made (Doubilet, Poppel, and Mulholland, 1955). Once the pancreatic duct has been identified, it is safe to suture the edges of the incision in the sphincter. These are carefully sutured so as to ensure that the cut edge of the duodenal mucosa is coapted accurately to the cut edge of the common bile duct. The long limb of a T-tube is introduced into the distal part of the common bile duct and this limb is split so as to prevent post-operative occlusion of the pancreatic duct. The duodenum is then closed and the common bile duct sutured, and the operation concluded by drainage of the operative site through the right flank.

PROGNOSIS

Three of the four fatal cases of our series died of myocardial infarction. The remaining patient died following an attempt at a total pancreatectomy in a debilitated patient suffering from intractable pain due to pancreolithiasis. This apparent preponderance of myocardial disease may be in part due to the age group of the disease, and in part to the role which hyperlipaemia may play in the genesis of both disorders. We do feel, however, that pancreatic disease is, itself, an important cause of ill health. A recent survey of the cause of death in a classical series of this disorder emphasized that though many patients died of myocardial disease, a high percentage died from pancreatic disease itself or its complications (Gambill, Baggenstoss, and Priestley, 1960).

It is theoretically probable that measures, other than denervation, which relieves the obstruction underlying this chronic condition, must have some beneficial influence upon the basic pathology of the disease, and thus may improve the prognosis in regard to morbidity and mortality. This is our experience in regard to morbidity, and this viewpoint has been supported by Gambill *et al.* (1960).

DISCUSSION

Steatorrhoea, pancreatic calcification, or diabetes are, we believe, late manifestations of a disease which begins with upper abdominal symptoms, often similar to those of gall bladder disease (Tables IV and V), which are associated with an abnormal S/P response. This contention is supported by a recent North American survey of all the necropsy material in one hospital which showed an incidence of about 10% of significant chronic pancreatic changes (Braunstein, 1961). The pathological changes of chronic pancreatitis are unlikely to be present without giving rise to some symptoms.

The view has been advanced that many of these patients would be more properly described as cases of 'chronic progressive pancreatitis' (FitzGerald and FitzGerald, 1959). This differentiation is made on the basis that the patient's condition is less evidently a disease with relapses but a disturbance which very often appears as a comparatively minor disorder which over the years becomes more florid in its manifestations. The pain becomes more marked, and eventually complications such as diabetes and steatorrhoea appear. This all would appear to be much more adequately covered by the term 'chronic progressive pancreatitis' rather than 'chronic relapsing pancreatitis'. Once the patient has reached this late stage of the disorder he may often suffer from severe attacks of pain, superimposed on a background of a more moderate discomfort, and at this stage the advanced disease might often be called 'chronic relapsing pancreatitis'. Some support for the attitude that the disorder should be called

'chronic progressive pancreatitis' was recently advanced for similar reasons by Tumen (1960).

AETIOLOGY In our present state of knowledge it is not possible to make a clear distinction between the aetiological factors responsible for acute pancreatitis and those responsible for chronic pancreatitis. It is probable that some forms of chronic pancreatitis, such as post-operative pancreatitis, follow on an acute incident. This also may be true of alcholic pancreatitis, although here acute and chronic factors usually overlap. However, other forms of the disorder, such as that associated with sphincteric disturbance or cholecystic disease, are probably always less acute in their development although acute episodes may be superimposed upon a chronic disturbance of the gland.

GALL BLADDER DISEASE In this series, 33% of the patients who were operated upon had had a previous cholecystectomy. (Many of these antecedent operations were, we believe, incomplete in that the ampullary region and pancreas were not thoroughly inspected.) The presence of gall bladder disease is a common finding in chronic pancreatitis. The common entrance of the pancreatic duct and the common bile duct into the ampulla of Vater with resultant reflux (Opie, 1901, 1902) is not sufficient to explain the damage to the pancreas (Fisher, Fisher, and Selkar, 1953). The presence of uninfected bile at normal pressure in the pancreatic duct gives rise to little trouble (Rich and Duff, 1936; Mallet-Guy, Guillet, and Durand, 1948). But if there is spasm or stenosis of the sphincter of Oddi, where a common channel exists, the resultant rise in pressure, together with the presence of bile in the pancreatic duct, will produce degenerative changes in the pancreas (Archibald and Gibbons, 1921), and these changes will be accentuated if infection is present as well (Rich and Duff, 1936). The association of chronic pancreatitis and gall bladder disease, where a common channel exists, is therefore to be expected. In all of the cases in this series which have had a sphincterotomy, a common channel has been found.

The pathological process involved may well be an increase in the pressure in the pancreatic duct leading to degeneration of the ductal epithelium, which allows an extravasation of the bile and pancreatic juice into the parenchyma of the pancreas, thus leading to progressive destruction of the gland (Rich and Duff, 1936).

SPHINCTERIC DISORDERS Evidence of dysfunction of the sphincter, leading to hyper- or hypotonia, as described by Mallet-Guy, Jean Jean, and Feroldi (1945), was not clearly found, though per-operative pressure and cholangiographic studies were frequently conducted. More reliance was placed on the failure to pass a sound with a maximum diameter of 5 mm. In most abnormal cases a sound of 3·0 mm. diameter will not pass. This is in keeping with the recent observations of Grage, Lober, Imamoglu, and Wangensteen (1960). We would particularly emphasize that sphincteric stenosis is a common lesion in cases presenting with a positive S/P test; as Table IX demonstrates, it was found in the 19 cases in which the test was performed. This is not to say that stenosis is an invariable lesion, or that it always precedes other pathological entities, such as ampullary stones, pancreatic lithiasis, and pancreatic parenchymatous inflammation. Probably it does so in the majority of cases, but some lesions may start in the gland itself, sometimes in areas well removed from the sphincteric zone. It follows, therefore, that removal of the sphincteric obstruction, though usually of benefit, may not completely answer the patient's therapeutic problem (Tables X and XI). This would particularly apply in cases diagnosed late. At the same time obstruction of the common channel or of the main pancreatic duct orifice are evidently much the commonest causes of chronic pancreatitis, other factors, such as infection, trauma, ischaemia, allergy, and circulating enzymes being, as Hermann and Davis (1960) state, 'of significance in a minority of cases'.

ALCOHOLISM The proportion of patients who are alcoholics varies in different series. Since Opie in 1902 suggested a relation between pancreatitis and alcoholism this has been described by many: in 32% of the cases of Comfort *et al.* (1946); in 16 of Joske's (1955); in 90 Australian cases (18%); in 25% of the 27 cases of Gambill *et al.* (1948); in 39% of 60 cases of Olmos *et al.* (1958); and in 37 of 160 (23%) cases of Warren and Cattell (1959) were alcoholics. Weiner and Tennant (1938) found that 47% of chronic alcoholics had evidence of pancreatitis at necropsy.

In some of our patients (cases 12, 47, and 52) and those described in the literature by Gambill and co-workers (1948), the drinking habits increased because of pain. Drinking provoked attacks in four of the cases of Comfort *et al.* (1946). Two patients noted relief on taking alcohol (cases 34 and 41). Olmos *et al.* (1958) suggested that alcohol was the trigger which set off the acute symptoms. Cattell and Warren (1953) found that 60 ml. of ethyl alcohol when taken orally reduced by 50% the volume of pancreatic secretion but others hold the opposite view. Though alcoholism is seriously incriminated in a number of American cases our experience shows it to be a minor cause of pancreatitis.

POST-OPERATIVE CAUSES A striking number of patients have had various gastroduodenal operations before the diagnosis of pancreatitis was established. Five patients in this series had partial gastrectomies (cases 31, 45, 46, 47, and 48). One patient (case 46) during his illness had a gastroenterostomy, a partial gastrectomy, vagotomy, cholecystectomy, and finally, a sphincterotomy, this last being the only measure which resulted in any real improvement. According to Schmieden and Sebening (1928), chronic pancreatitis develops mainly after gastrectomy and splenectomy and operations on the biliary tract. Millbourn (1949) held that damage to Santorini's duct and the posterior pancreatico-duodenal artery are the most likely causes of pancreatic disturbance. Morrin and Dunkin (1956) described three cases of post-operative pancreatitis which occurred in patients, all of whom had deep penetrating peptic ulcers. They held that the mobilization necessary in these types of cases involving ligation of the posterior superior pancreatico-duodenal branch of the gastro-duodenal artery leads to pancreatic ischaemia, resulting in subsequent pancreatitis. From this it would appear that post-operative pancreatitis is most likely in those cases in which there is an ulcer which is deep and penetrating. Experience with pancreatic arteriography leads us to believe that simple ligature of this artery is in itself insufficient to precipitate post-operative pancreatitis (McMullin, unpublished data).

HYPERLIPAEMIA Six patients had hyperlipaemia as shown by raised fasting lipid or fasting cholesterol levels (cases 7, 9, 29, 49, 50, and 51). This type of case may have associated coronary insufficiency (cases 7, 9, 49, and 50). Burn (1951) found a close relation between coronary thrombosis and acute pancreatitis. Seventeen of Joske's (1955) cases exhibited primary vascular disease, with lipids above normal, *i.e.*, 560 mg. %. Speck (1864) was the first to note the association of pancreatitis with hyperlipaemia; cases were described by Thannhauser (1950) and by Collett and Kennedy (1948). Poulsen (1950) and Klatskin and Gordon (1952) were the first to define the genetic element in this type of case.

PREGNANCY The development of post-partum pancreatitis is well recognized. Eleven of the 90 cases of Joske (1955) were of this type. Schmitt (1818) first noted the relation of pregnancy and pancreatitis. Two of our patients developed pancreatitis one or two months post-partum (cases 10 and 49): the first of these had coronary insufficiency at the same time. She had hypercholesterolaemia (300 mg. %) over eight months after parturition, so this was possibly the cause of her attack. FitzGerald (1955) pointed out that a disturbance of pancreatic function may occur during pregnancy, and that a post-partum attack of acute pancreatitis was possibly a rebound phenomenon. We have a strong impression that pancreatitis itself may lead to repeated abortions in otherwise healthy women.

MALNUTRITION Other aetiological factors are malnutrition: alcoholism perhaps may be best classified under this heading. Case 47 was on hunger strike for a few weeks many years before the onset of his symptoms, and it is faintly possible that this may have been responsible for his subsequent pancreatic disturbance.

HEREDITY True familial pancreatitis (Comfort and Steinberg, 1952) is now an accepted entity, and was present in at least one family, but case 8 showed a curious other association which possibly may have hereditary features. This patient had undoubted pancreatitis, her mother had died of carcinoma of the pancreas, almost certainly superimposed upon old-standing pancreatic insufficiency, and the patient's nephew had died of mucoviscidosis at the age of less than 12 months.

TRAUMA A possible association between trauma and pancreatitis was seen in case 44. The possibility of such an association has long been recognized but never been proved. The difficulty, here, as in other fields of traumatic disease, is to prove that there is an association between trauma and the later development of a disease in the area which has actually been damaged at the time of the injury.

MISCELLANEOUS We have not seen any case of chronic pancreatitis associated with a definite virus or other infection. We have had no case associated with hyperparathyroidism (Cope, Culver, Mixter, and Nardi, 1957). Arteriosclerosis and auto-immune disease may be causative in some cases; it is difficult to be assured that any of our cases had resulted solely from either of these factors.

DIAGNOSIS

The serum enzyme response to secretin and pancreozymin has been most helpful in diagnosis. In only two of our cases did the serum amylase level fail to rise over 2·9 mg./ml. (160 units) following stimulation, giving a 95% accuracy for the test. This is much higher than the 50% of positive tests reported by Sun and Shay (1960), who used the pancreozymin before the secretin in the test. However, in that series of 18 cases the upper limit of normal post-stimulatory serum amylase was higher than the upper normal figures in our series and in that of

Burton *et al.* (1960). In our series the more dramatic rise in serum enzymes occurred in those cases in which the fasting amylase was within normal limits. In these cases it is possible that the chronic obstructive phase had not been reached nor had the parenchyma been seriously damaged.

The serum test is easier for the patient but we think that it may be better than the intubation test for recognition of the early phases of the disease, especially for cases of type B of the 'post-acute pancreatitis' group of Burton *et al.* (1960). In this group, as in the early cases of what we would call chronic pancreatitis (progressive or relapsing), there is insufficient acinar damage to reduce duodenal enzyme levels significantly, yet if obstruction be present serum levels may rise sharply following the injection of secretin and pancreozymin. It is possible to demonstrate abnormal S/P tests in patients who show no evidence of maldigestion by any test we have used. In practice, we have had many examples of abnormal serum tests in patients even with considerable pancreatic damage. The use of evocative tests should rarely be required for purely diagnostic purposes in cases of advanced disease, as the diagnosis can usually be easily made on simple clinical grounds.

We have been puzzled at the difference between our amylase and lipase figures and those reported by Burton *et al.* (1960). We are now satisfied that serum lipase results can be seriously depressed by use of a poorly emulsified substrate. However, our serum amylase figures are generally higher and more significant than those reported by authors who used a modification of the Somogyi (1938) method; we have used that of Myers *et al.* (1944).

We have been struck with the not infrequent complaint of upper abdominal pain following the secretion or, more usually, the pancreozymin injection. The pain at times is severe and at times is recognized by the patient as similar to the presenting pain. It is interesting that this pain is related much less to the rise in pressure in the duct system but rather more to the phase of active secretion by the acini, the typical response to pancreozymin.

Can false positive tests occur? We think that true false positive tests do not occur if the test is not used in the presence of conditions such as uraemia, abdominal emergencies, or amyloidosis. But it is important to emphasize that a positive test in a patient suffering even from a relatively chronic disease need not point toward the diagnosis of pancreatitis. The test can be positive in the presence of any disease involving the pancreas, notably intrinsic malignancy or even extrinsic disease, such as a penetrating peptic ulcer or an invasive gastric carcinoma. Full diagnosis must not depend on any test but upon a proper evaluation of the whole situation.

Follow-up S/P tests in six patients after sphincterotomy revealed a satisfactory improvement in the test after relief of the ductal obstruction. Case 25 at first showed symptomatic improvement after a partial gastrectomy and exploration of the common bile duct but regressed later, as evidenced by recurrent attacks of subacute pancreatitis and a strongly positive S/P test. Following sphincterotomy the test once again reverted to normal, only to become positive again after the episode of acute abdominal pain. This cleared quickly and the S/P test has once again returned to normal levels (Fig. 2).

STEATORRHOEA This occurs if there is much obstruction at the head of the pancreas (cases 3 and 31) or if there is gross destruction of acinar cells (cases 44 and 52). Some of our cases seem to disprove the view of Comfort *et al.* (1946) that pancreatic steatorrhoea is an irreversible process. The reversal has been shown in two of our patients (cases 3 and 31), who, following operation, improved definitely in this respect. (In case 3 the vitamin A test reverted to normal, and case 31 put on over 30 lb. in weight following operation.) Of the tests used in the diagnosis of pancreatic maldigestion, vitamin A acetate/vitamin A alcohol and triolein ^{131}I/oleic acid ^{131}I differential absorption tests are probably the most useful. With earlier diagnosis and treatment, a smaller number of patients with chronic pancreatitis may develop malabsorption.

DIABETES Only four patients in this series had clinical diabetes. Disturbance of islet function does not appear to follow closely on that of acinar function; obviously there is no strong association between the disorders of the exocrine and endocrine functions of the pancreas. We feel that there must be a higher proportion of diabetics in cases of advanced pancreatitis. The greater the incidence of diabetes in a series the higher the proportion of advanced cases.

There is a considerable variation in the incidence of diabetes in different series reported in the literature. Thus, Comfort *et al.* (1946) reported an incidence of seven in 29 cases (24·1%) without gall-bladder disease. They emphasized the possibility of a transitory appearance of a benign non-diabetic glycosuria during the acute phase of some patients. This point was also referred to in a similar series (Gambill *et al.*, 1948) of 27 cases with associated gall-bladder disease, in which, however, the incidence of diabetes in the combined group is 11 out of 56, or just 20%. The highest incidence reported was 50% (King, 1949). The criteria of diagnosis in King's

series appear to have been insufficiently severe. Other figures reported an incidence of 14% of diabetes in 100 cases of acute pancreatitis in the phase of resolution (Pollock, 1959); 38 of 60 cases (63%) had hyperglycaemia; and seven of 60 cases (11%) had permanent diabetes (Olmos *et al.*, 1958).

CALCIFICATION Calcium is deposited in three sites in the pancreas: in regions of fat necrosis, in pancreatic degenerative tissues, and in the pancreatic duct. According to Warren and Cattell (1959), fibrotic obstruction of the duct precedes and gives rise to stones in the ducts of Wirsung and Santorini. Intraductal calculi were found in case 53. Analysis showed its composition as predominantly $CaCO_3$. The relation of calcification to the parathyroid gland is not clear, and in our series there was no proven case of hyperparathyroidism. Olmos *et al.* (1958) noted low serum calcium values in 26 of 40 cases following an acute episode of pancreatitis. The pain in cases of calcareous pancreatitis is usually distributed towards the left side (cases 3, 5, and 14). Calcification has been noted in a high percentage of cases of painless and hereditary pancreatitis.

As has been mentioned earlier a negative radiological search for calcium may not be entirely conclusive. Pancreatic calcification may be visible only on laparotomy.

One of us (J.F.) is indebted to the Medical Research Council of Ireland for a training grant as is O.F. for a grant in aid. We are obliged to Professor E. J. Conway F.R.S. and to Professor E. F. McCarthy for laboratory space. Mr. D. O'Shea is to be thanked for ever-willing technical assistance. We are grateful to Messrs. Boots for supplies of secretin and pancreozymin in the early stages of the study and to Messrs. Roche Ltd. for supplies of vitamin A. Finally, we must thank many colleagues who gave us access to their cases.

REFERENCES

Archibald, E., and Gibbons, E. C. (1921). Further data concerning the experimental production of pancreatitis. *Ann. Surg.*, **74**, 426-433.

Beckman, T. M. (1936). Contributions au diagnostic des pancréatites chirurgicales. *Acta chir. scand.*, suppl., 44. Quoted by Lagerlöf, H. O., 1942, in *Pancreatic Function and Pancreatic Disease Studied by Means of Secretin*, p. 288. MacMillan, New York.

Bogoch, A., Roth, J. L. A., and Bockus, H. L. (1954). The effect of morphine on serum amylase and lipase. *Gastroenterology*, **26**, 697.

Braunstein, H. (1961). Tocopherol deficiency in adults with chronic pancreatitis. *Gastroenterology*, **40**, 224-231.

Burn, C. G. (1951). The association of acute pancreatitis with acute coronary thrombosis. *Amer. J. Path.*, **27**, 680-682.

Burton, P., Hammond, E. M., Harper, A. A., Howat, H. T., Scott, J. E., and Varley, H. (1960). Serum amylase and serum lipase levels in man after administration of secretin and pancreozymin. *Gut*, **1**, 125-139.

Cattell, R. B., and Warren, K. W. (1953). *Surgery of the Pancreas.* Saunders, Philadelphia.

Cherry, I. S., and Crandall, L. A. Jr. (1932). The specificity of pancreatic lipase; its appearance in the blood after pancreatic injury. *Amer. J. Physiol.*, **100**, 266-273.

Collett, R. W., and Kennedy, R. L. J. (1948). Chronic relapsing pancreatitis associated with hyperlipemia in an eight year old boy. *Proc. Mayo Clin.*, **23**, 158-162.

Comfort, M. W., Gambill, E. E., and Baggenstoss, A. H. (1946). Chronic relapsing pancreatitis. A study of 29 cases without associated disease of the biliary or gastrointestinal tract. *Gastroenterology*, **6**, 239-285 and 376-408.

——, and Steinberg, A. G. (1952). Pedigree of a family with hereditary chronic relapsing pancreatitis. *Ibid.*, **21**, 54-63.

Cope, O., Culver, P. J., Mixter, C. G. Jr., and Nardi, G. L. (1957). Pancreatitis, a diagnostic clue to hyperparathyroidism. *Ann Surg.*, **145**, 857-863.

Doubilet, H., and Mulholland, J. H. (1951). The results of sphincterotomy in pancreatitis. *J. Mt. Sinai Hosp.*, **17**, 458-462.

——, Poppel, M. H., and Mulholland, J. H. (1955). Pancreatography: technics, principles, and observations. *Radiology*, **64**, 325-339.

Fennelly, J. J., FitzGerald, O., and Healy, J. B. (1959). I^{131} Labelled triolein (glyceryltrioleate) and oleic acid ^{131} absorption studies as an index of small intestional function. *Irish J. med. Sci.*, No. **406**, 462-469.

Fisher, B., Fisher, E. R., and Selkar, R. (1953). Further observations on the role of bile in the pathogenesis of pancreatitis. *Surg. Forum*, **4**, 406-412.

FitzGerald, O. (1955). Pancreatitis following pregnancy. *Brit. med. J.*, **1**, 349.

——, Fennelly, J. J., and Hingerty, D. J. (1961). Serum studies in man after administration of vitamin A acetate and vitamin A alcohol. I. In normal subjects. *Gut*, **2**, 263-266.

——, ——, —— (1962). Serum studies in man after administration of vitamin A acetate and vitamin A alcohol. II. In subjects suffering from disturbances of absorption and digestion. *Ibid.*, **3**, 74-79.

——, and FitzGerald, P. (1959). Pancreatitis. *Brit. med. J.*, **1**, 1188.

Gambill, E. E., Comfort, M. W., and Baggenstoss, A. H. (1948). Chronic relapsing pancreatitis: An analysis of 27 cases associated with disease of the biliary tract. *Gastroenterology*, **11**, 1-33.

——, Baggenstoss, A. H., and Priestley, J. T. (1960). Fate of 56 patients first encountered in the years 1939 to 1943, inclusive. *Ibid.*, **39**, 404-413.

Grage, T. B., Lober, P. H., Imamoglu, K., and Wagensteen, O. H. (1960). Stenosis of the sphincter of Oddi. A clinicopathologic review of 50 cases. *Surgery*, **48**, 304-317.

Gross, J. B., and Comfort, M. W. (1957). Hereditary pancreatitis: report on two additional families. *Gastroenterology*, **32**, 829-854.

——,——, and Ulrich, J. A. (1957). Abnormalities of serum and urinary amino acids in hereditary and non-hereditary pancreatitis. *Trans. Ass. Amer. Phycns.*, **70**, 127-139.

——, and Hallenbeck, G. A. (1960). Chronic relapsing pancreatitis despite achlorhydria. Report of 5 cases and consideration of pathogenesis. *Gastroenterology*, **38**, 919-925.

Harper, A. A., and Raper, H. S. (1943). Pancreozymin, a stimulant of the secretion of pancreatic enzymes in extracts of the small intestine. *J. Physiol. (Lond.)*, **102**, 115-125.

Hepp, J. M., and Moreaux, J. (1958). Documents sur les pancréatites avec calcifications. *Arch Mel. Appor. dig.*, **47**, 1057-1072.

Hermann, R. E., and Davis, J. H. (1960). The role of incomplete pancreatic duct obstruction in the etiology of pancreatitis. *Surgery*, **48**, 318-329.

Howat, J. T. (1952). Pancreatitis. In *Modern Trends in Gastroenterology*, edited. by F. Avery Jones, p. 766-802. Butterworth, London.

Janowitz, H. D., and Dreiling, D. A. (1958). Is there pancreatic ductal obstruction in chronic pancreatitis? An analysis of the functional trans-sphincteric pancreatic and biliary flow in patients with and without pancreatic disease. World Congress of Gastroenterology. **2**, 1218-1222. Williams and Wilkins, Baltimore.

Joske, R. A. (1955). Aetiological factors in the pancreatitis syndrome. *Brit. med. J.*, **11**, 1477-1481.

King, S. E. (1949). The syndrome of chronic relapsing pancreatitis. The frequency of insular deficiency (pancreatic diabetes) in the fibrocalcific state. *Med. Clin. N. Amer.*, **33**, 883-897.

Klatskin, G., and Gordon, M. (1952). Relationship between relapsing pancreatitis and essential hyperlipemia. *Amer. J. Med.*, **12**, 3-23.

Langmade, C. F., and Edmondson, H. A. (1951). Acute pancreatitis during pregnancy and the post partum period: a report of 9 cases. *Surg. Gynec. Obstet.*, **92**, 43-52.

Mallet-Guy, P., Guillet, E., and Durand, L. (1948). Le reflux dans le canal de Wirsung au cours des cholangiographies; dystonies du canal de Wirsung. *Lyon Chir.*, **43**, 653-676.

——, Jean Jean, R., and Feroldi, J. (1945). Résultats éloignés de la splanchnicectomie unilatérale dans le traitement des pancreatites chroniques. *Ibid.*, **40**, 293-314.

Millbourn, E. (1949). On acute pancreatic affections following gastric resection for ulcer or cancer and the possibilities of avoiding them. *Acta chir. scand.*, **98**, 1-21.

Morrin, F. J., and Dunkin, L. (1956). Pancreatitis following subtotal gastrectomy. *Irish J. med. Sci.*, No. **363**, 106-114.

Myers, V. C., Free, A. H., and Rosinski, E. E. (1944). Studies on animal diastases. VI. The determination of diastase (amylase) in blood. *J. biol. Chem.*, **154**, 39-48.

McCollum, J. K. (1955). Surgical and biochemical aspects of pancreatitis. *Brit. med. J.*, **11**, 1482-1484.

McMullin, J. P. (1961). Pancreatic arteriography. Unpublished data.

Olmos, A., Enriquez, D., Salazar, J., Hermansen, I., and Biel, F. (1958). Chronic recurrent pancreatitis; study of sixty cases proved by laparatomy. World Congress of Gastroenterology, 1, 264-273. Williams and Wilkins, Baltimore.

Opie, E. L. (1901). The relationship of cholelithiasis to disease of the pancreas and to fat necrosis. *Amer. J. med. Sci.*, **121**, 27-43.

—— (1902). The causes and varieties of chronic interstitial pancreatitis. *Ibid.*, **123**, 845-868.

Pollock, A. V. (1959). Acute pancreatitis: analysis of 100 patients. *Brit. med. J.*, **1**, 6-14.

Poulsen, H. M. (1950). Familial lipemia. A new form of lipoidosis showing increase in neutral fats combined with attacks of acute pancreatitis. *Acta med. scand.*, **138**, 413-420.

Rich, A. R., and Duff, G. L. (1936). Experimental and pathological studies on the pathogenesis of acute haemorrhagic pancreatitis. *Bull. Johns Hopk. Hosp.*, **58**, 212-259.

Ryan, W. A. (1957). Chronic relapsing pancreatitis with hypoglycaemia. *J. Irish med. Ass.*, **41**, 187-190.

Schmitt, W. J. (1818). *Sammlung zweifelhafter Schwangerschaftsfaelle nebst einer kritischen Einleitung*, pp. 172-180. Wimmer, Vienna. Cited by Langmade, C. F., and Edmondson, H. A., 1951 (op. cit.).

Schmieden, V., and Sebening, W. (1928). Surgery of the pancreas with especial consideration of acute pancreatic necrosis. *Surg. Gynec. Obstet.*, **46**, 735-751.

Somogyi, M. (1938). Micromethods for the estimation of diastase. *J. biol. Chem.*, **125**, 399-414.

Speck, C. (1864). *Arch. d. Ver. f. wissensch. Heilk.*, **1**, 232-238. Cited by Thannhauser, S. J., 1950, p. 301 (op. cit.).

Sun, D. C. H., and Shay, H. (1960). Pancreozymin-secretin test. The combined study of serum enzymes and duodenal contents in the diagnosis of pancreatic disease. *Gastroenterology*, **38**, 570-581.

Thannhauser, S. J. (1950). *Lipidoses: Diseases of the Cellular Lipid Metabolism.*, 2nd ed. Oxford University Press, New York.

Tumen, H. J. (1960). Discussion of paper by Gambill, Baggenstoss, and Priestley. *Gastroenterology*, **39**, 411-412.

Warren, K. W., and Cattell, R. B. (1959). Medical progress: pancreatic surgery. *New Engl. J. Med.*, **261**, 280-288, 333-340.

Weiner, H. A., and Tennant, R. (1938). A statistical study of acute hemorrhagic pancreatitis (hemorrhagic necrosis of pancreas). *Amer. J. med. Sci.*, **196**, 167-176.

The June 1963 Issue

THE JUNE 1963 ISSUE CONTAINS THE FOLLOWING PAPERS

The aetiology and management of ascites in patients with hepatic cirrhosis: A review SHEILA SHERLOCK and STANLEY SHALDON

The serum pepsinogen level with special reference to the histology of the gastric mucosa O. A. A. BOCK, G. ARAPAKIS, L. J. WITTS, and W. C. D. RICHARDS

The relationship between acid secretion after augmented histamine stimulation and the histology of the gastric mucosa O. A. A. BOCK, W. C. D. RICHARDS, and L. J. WITTS

The clinical and metabolic significance of jejunal diverticula W. T. COOKE, E. V. COX, D. J. FONE, M. J. MEYNELL, and R. GADDIE

Intussusception in adults complicating specific inflammatory diseases of the intestine PETER GOODALL

Studies of basal and peak acid output with an augmented histamine test J. H. BARON

Primary lymphoid neoplasms of the stomach H. A. ELLIS and R. LANNIGAN

Tumour-forming gastritis J. C. HAWKSLEY

Hypoalbuminaemia due to protein loss from gastric carcinoma PAUL TURNER, G. S. C. SOWRY, and P. M. O'DONNELL

The management of primary adenocarcinoma of the vermiform appendix K. T. HESKETH

Bacteriological and histological studies of the small intestine of rats treated with mecamylamine J. M. S. DIXON and J. W. PAULLEY

Function of the pylorus and pyloric antrum in gastric emptying A. K. ARMITAGE and A. C. B. DEAN

The relation of sensation in the anal canal to the functional anal sphincter: a possible factor in anal continence H. L. DUTHIE and R. C. BENNETT

Ulcerative colitis in the United States Army in 1944 *Follow-up with particular reference to mortality in cases and controls* M. DEAN NEFZGER and E. D. ACHESON

Methods and techniques

The application of the Holter valve to the treatment of resistant ascites ADAM N. SMITH

Copies are still available and may be obtained from the PUBLISHING MANAGER, BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, W.C.I., *price* 18s. 6d.