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Chronic pancreatitis: a cause of cholestasis[1]

J. SCOTT, J. A. SUMMERFIELD, E. ELIAS, R. DICK, AND SHEILA SHERLOCK

From the Departments of Medicine and Radiology, Royal Free Hospital, London

SUMMARY The bile ducts were visualised using endoscopic retrograde cholangiopancreatography (ERCP), percutaneous or intravenous cholangiography in 38 patients with non-gallstone chronic pancreatitis. Stenosis of the intrapancreatic portion of the distal common bile duct was demonstrated in 11 patients. Ten of the 11 developed transient cholestasis during exacerbations of their chronic pancreatitis. In six cholestasis eventually persisted requiring surgical relief. Secondary biliary cirrhosis was present in one patient. No evidence of pancreatic carcinoma was found in the patients explored surgically. Ten of the patients are alive more than one year after diagnosis. Chronic pancreatitis was of alcoholic aetiology in 10 of the patients with biliary stenosis. Cholestasis and biliary stricture are common but poorly recognised complications of non-gallstone chronic pancreatitis, especially when pancreatitis is severe and due to alcohol.

Although extrahepatic biliary obstruction is a well known presenting feature of pancreatic carcinoma (Sherlock, 1975), it is not recognised as a common complication of chronic pancreatitis in the absence of gallstones. Hitherto it has not been possible, without surgery or necropsy, to delineate the anatomy of the distal common bile duct and pancreatic duct in patients with non-gallstone pancreatitis, who are jaundiced (DuVal, 1957; Weinstein *et al.*, 1963; Marks *et al.*, 1968; Owor, 1972; McCollum and Jordan, 1975; Snape *et al.*, 1976). The advent of endoscopic retrograde cholangiopancreatography (ERCP) (Kasugai *et al.*, 1972a, b) and Chiba needle percutaneous cholangiography (Okuda *et al.*, 1974) have allowed this to be done.

The morphology of the bile ducts was assessed in 38 patients with non-gallstone chronic pancreatitis. In 11 of them stenosis of the intrapancreatic portion of the distal common bile duct was demonstrated.

Methods

Thirty-eight patients with non-gallstone chronic pancreatitis were studied by means of ERCP (30 patients), Chiba needle percutaneous cholangiography (two patients), and infusion cholangiography (six patients).

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In conformity with the Marseilles symposium on pancreatitis (Perrier, 1964) chronic relapsing pancreatitis was defined as an exacerbation of abdominal symptoms in a patient known to have pancreatic insufficiency; and chronic pancreatitis as pancreatic insufficiency without acute exacerbations.

Cholestasis was defined by a serum bilirubin level greater than 50 μ mol l^{-1} (normal range 5-17) with serum alkaline phosphate greater than 30 KA units dl^{-1} (normal range 3-13) (Sherlock, 1975) and liver histology consistent with obstruction of the large bile duct (Scheuer, 1973). Persistent cholestasis was defined as cholestasis lasting more than four weeks.

The diagnosis of chronic pancreatitis was established by pancreatic histology from surgical biopsy or necropsy (Nakamura *et al.*, 1972; Baggenstoss 1973), or by the presence of two or more of the following abnormalities: (1) pancreatic calcification (Sarles, 1974) shown on anteroposterior and lateral plain radiographs of the abdomen; (2) abnormalities of the pancreatic ducts characteristic of chronic pancreatitis (Kasugai *et al.*, 1972b; 1973; Rohrmann *et al.*, 1974); (3) abnormal ^{75}Se-selenomethionine pancreatic scanning (Bouchier *et al.*, 1972) and diminished duodenal tryptic activity after a standard Lundh test meal (James, 1973) assessed by measurement of radioselenium in duodenal aspirate (Youngs *et al.*, 1971).

The radiology of the pancreas and of the biliary tract was assessed blind by three experienced

observers. Chronic pancreatitis was classified by the criteria of Kasugai (Kasugai *et al.*, 1973) as minimal, moderate, and advanced, and defined as dilatation and irregularity of the main pancreatic duct and branch ducts.

Results

PATIENTS WITH BILIARY STENOSIS

Eleven patients with chronic pancreatitis were found to have distal common bile duct stenosis with or without cholestasis. The aetiology of chronic pancreatitis was alcoholic in 10 of these patients.

Clinical course (Table 1)

Repeated attacks of cholestasis occurred in nine patients in association with painful relapses of their pancreatitis. Cholestatic jaundice persisting for more than four weeks developed in five of these patients and was the presenting feature in a sixth. The eleventh patient had distal common bile duct stenosis but had never had cholestatic jaundice.

Five of the six patients who came to surgery are well more than one year afterwards. One patient died three weeks after surgery from a pancreatic abscess. Choledochojejunostomy was the surgical procedure of choice. The remaining five patients, who had presented with transient cholestasis during the relapses of chronic pancreatitis, have remained well for more than one year. Four of these patients were alcoholic and have now stopped drinking.

Evidence of chronic pancreatitis

The data on which the diagnosis of chronic pancreatitis was established are presented in Tables 2 and 3. Attacks of upper abdominal pain occurred in 10 patients and were associated with a raised serum amylase in five of them. Oral glucose tolerance was impaired in seven patients and faecal fat excretion exceeded 6 g/24 h in eight patients. Pancreatic scanning was abnormal in all patients. Tryptic activity was reduced in the four patients in whom it was measured. Three patients had pancreatic calcification on plain radiographs of the abdomen. In nine patients endoscopic retrograde pancreatography showed irregularity and tortuosity of the main pancreatic duct and its secondary radicles consistent with the presence of moderate to advanced chronic pancreatitis (Figs. 1 and 2b). Two patients had pancreatic cysts (Fig. 3) in addition to the duct changes of chronic pancreatitis. Another patient had a pseudocyst communicating with the main pancreatic duct. The pancreatic duct was normal in one patient. The diagnosis of chronic pancreatitis was confirmed histologically in four patients, in whom there was no evidence of pancreatic carcinoma.

Evidence for extrahepatic biliary obstruction (Tables 2 and 3)

Ten patients had extrahepatic cholestasis. Nine of them had had one or more episodes of transient cholestasis. Liver biopsy showed histological features consistent with large duct obstruction in six patients. Secondary biliary cirrhosis was present in one patient and alcoholic cirrhosis in another. Liver biopsy was not performed in three patients. Stenosis of the intrapancreatic portion of the distal common bile duct (Figs. 1, 2a, and 3) was demonstrated by endoscopic retrograde cholangiography (seven patients), Chiba needle percutaneous cholangiography (two patients), and infusion cholangiography (two patients).

PATIENTS WITHOUT BILIARY STENOSIS

Twenty-seven patients had non-gallstone chronic pancreatitis without cholestasis. The aetiology was alcoholic (13 patients), cystic fibrosis (one patient), type IV hyperlipoproteinaemia (one patient), and nutritional (one patient of East African origin). No

Table 1 *Clinical data: 11 patients*

Patient	*Age (yr)*	*Abdominal pain*	*Pruritis*	*Cholestasis*	
				Transient attacks	*Persistent*
1	38	+	++	5	+
2	62	+	++	2	+
3	55	+	++	0	+
4	62	+++	O	0	O
5	29	++	++	2	+
6*	53	+	O	2	+
7	43	++	++	3	+
8	45	+	O	2	O
9	47	+	O	3	O
10	51	O	+	4	O
11	52	+	O	1	O

*Non-alcholic chronic pancreatitis.

Table 2 *Biochemical data: 11 patients*

Patient	*Serum*				*Oral glucose intolerance*	*Faecal fat excretion (g/24 h)*	*Tryptic† activity*
	*Bilirubin μmol l⁻¹ *(n.r. 5-17)*	*Alkaline phosphatase KAU dl⁻¹ (n.r. 3-13)*	*Aspartate transaminase IU l⁻¹ (n.r. 4-15)*	*Amylase IU l⁻¹(n.r. 150-350)*			
1	310	37	49	273	+	18	
2	155	30	27	160	+	15	↓
3	10	34	18	270	+	40	
4	10	11	15	600	+	8	
5	95	32	23	340	○	8	↓↓
6	85	28	31	350	○	—	
7	100	31	110	555	○	6	
8	30	27	50	220	+	7	↓↓
9	60	36	33	400	+	10	
10	52	35	23	750	+	—	
11	60	32	20	390	○	7	↓

*n.r.: normal range values.
†Assessed in patients indicated.

Table 3 *Scanning, radiology, histology: 11 patients*

Patient	*Abnormal pancreatic scan*	*Radiology*		*Histology*	
		Common bile duct	*Pancreas*	*Liver*	*Pancreas*
1*	+++	DS	CP	EHBO*	CP
2*	+++	DS	Calcification CP	EHBO	Calcific pancreatitis
3*	+++	DS	Calcification CP cyst	Secondary biliary cirrhosis	Calcific pancreatitis
4	++	DS	CP	Cirrhosis	—
5*	+	Stenosis cyst lower common duct	Calcification CP	—	—
6*	+	DS	Psuedocyst	EHBO	CP
7	+	DS	CP	—	—
8*	+	DS	CP	EHBO	—
9	++	DS	CP cyst	EHBO	—
10	+	DS	CP	EHBO	—
11	+	DS	Normal duct	—	—

*Laporotomy performed.
EHBO: histology associated with extrahepatic biliary obstruction. DS: distal stenosis. CP: chronic pancreatitis.

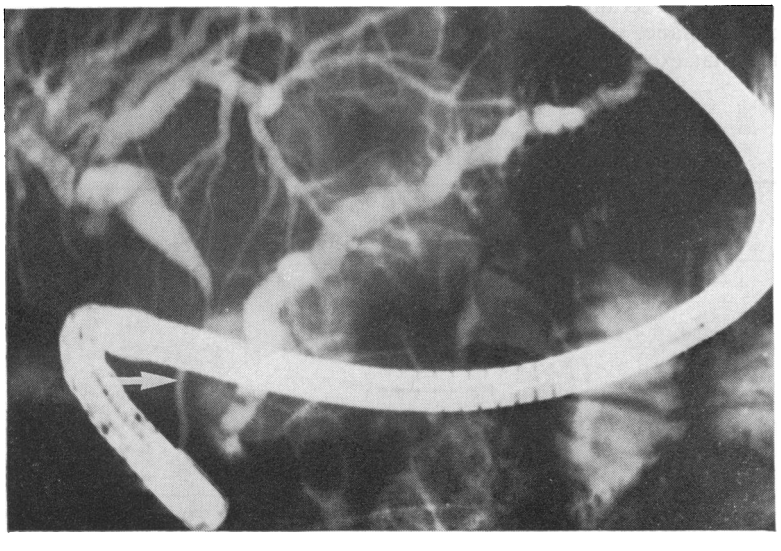
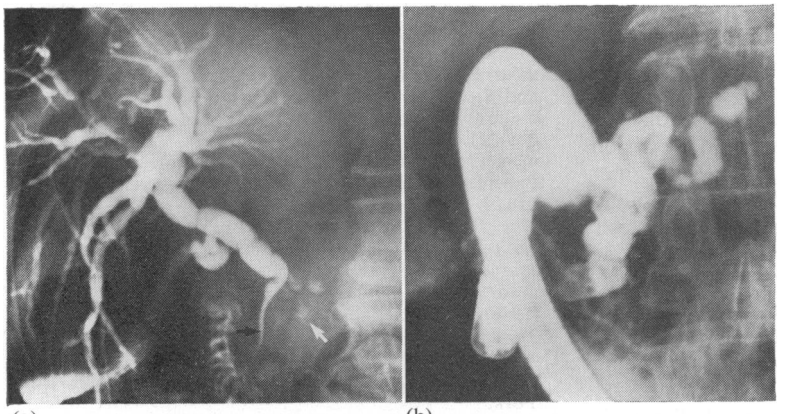


Fig. 1 *(Patient 1) There is stenosis of the distal third of the common bile duct (arrowed). The main pancreatic duct is dilated and irregular.*



(a) (b)

Fig. 2 *(Patient 2) (a) There is a smooth narrowing of the lower third of the common bile duct (black arrow). Calcification (white arrow) is present in the head of the pancreas. (b) The main pancreatic duct is tortuous, irregular and dilated.*

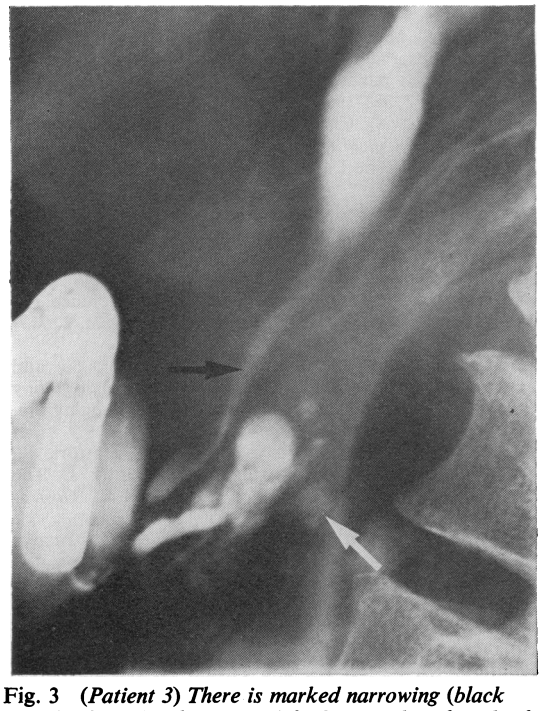


Fig. 3 *(Patient 3) There is marked narrowing (black arrow) of the distal common bile duct. A short length of irregular, main pancreatic duct ends in a small cyst. Calcification is present in the head of the pancreas (white arrow).*

cause was found in the other 11 patients. Twenty-five of the patients without cholestasis had minimal to moderate chronic pancreatitis. In only two patients were changes advanced.

None of these 27 patients had serum bilirubin levels greater than 25 μmol l^{-1}. Two of the patients had raised alkaline phosphatase levels of 18 and 21 KA units dl^{-1}. Cholangiography was normal in all 27 patients: and none of those in whom liver biopsy was performed had evidence of mechanical cholestasis.

Discussion

Cholestasis is said to complicate non-gallstone chronic pancreatitis in 3 to 25% of patients (Comfort *et al.*, 1946; Coffey, 1954; Bockus *et al.*, 1955; DuVal, 1957; Owor, 1972). In our series 11 of the 38 patients (27%) with non-gallstone chronic pancreatitis had evidence of extrahepatic biliary obstruction. All except one of our patients with cholestasis had alcoholic chronic pancreatitis. The high frequency of biliary complications in our series probably reflects the special role of the Royal Free Hospital as a referral centre for the assessment of hepatobiliary disease, but is also likely to result from an increased facility in demonstrating the pathological anatomy of this complication by use of ERCP and Chiba needle percutaneous cholangiography.

Distal common bile duct stenosis was shown by ERCP, Chiba needle percutaneous or infusion cholangiography to be the anatomical basis for both recurrent and persistent cholestasis. The anatomical basis for the transient jaundice occurring during exacerbations of non-gallstone chronic pancreatitis has not previously been adequately demonstrated (Weinstein *et al.*, 1963; Snape *et al.*, 1976; Warshaw *et al.*, 1976). It has been variously attributed to such causes as bile duct compression (Weinstein *et al.*, 1963; Snape *et al.*, 1976; Warshaw *et al.*, 1976), parenchymal liver disease (Beckett, *et al.*, 1961; Goldberg and Thompson, 1961), or gallstones which have been passed (Acosta and Ledesma, 1974).

Transient jaundice is probably the result of oedema

and swelling of the pancreas with compression of the bile duct in its intrapancreatic course. Persistent cholestasis complicates severe destructive chronic pancreatitis and has been shown, by dissection of surgical and necropsy specimens, to be due to cicatrisation of the lower common bile duct within the head of the pancreas (DuVal, 1957; Weinstein *et al.*, 1963; Marks *et al.*, 1968; Owor, 1972; McCollum and Jordan, 1975). Prolonged persistent cholestasis was the cause of a secondary biliary cirrhosis in one of our patients.

The pronounced pancreatic duct changes which are demonstrated by ERCP have been shown to correlate most closely with severe deforming pancreatic pathology (Howard and Nedwich, 1971; Nakamura *et al.*, 1972). Such advanced disease is unusual in non-alcoholic chronic pancreatitis (James *et al.*, 1974; Sarles, 1974). In the western world, excessive consumption of alcohol is the most common cause of non-gallstone chronic pancreatitis (Dreiling *et al.*, 1964; Howat, 1968; James *et al.*, 1974). It is noteworthy that, of the 27 patients without cholestasis in our series, only two had advanced pancreatic duct abnormalities and only 13 admitted alcohol abuse.

In the management of the jaundiced alcoholic patient, needle liver biopsy in conjunction with ERCP or Chiba needle percutaneous cholangiography have proved useful in making the important distinction between alcoholic liver disease, benign biliary stricture, gallstones, and pancreatic carcinoma. Gradual tapering of the bile duct within its intrapancreatic course in association with the pancreatic duct changes of chronic pancreatitis is more characteristic of the benign stricture which may complicate chronic pancreatitis than of pancreatic carcinoma.

We conclude that cholestasis is a common but poorly recognised complication of severe alcoholic chronic pancreatitis and that ERCP and Chiba needle percutaneous cholangiography are useful techniques in demonstrating this association.

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Reference

Acosta, J. M., and Ledesma, C. L. (1974). Gallstone migration as a cause of acute pancreatitis. *New England Journal of Medicine*, **290**, 484-487.

Baggenstoss, A. H. (1973). *Pancreatitis*, pp. 195-200. Edited by E. E. Gambill. Mosby: St. Louis.

Beckett, A. G., Livingstone, A. V., and Hill, K. R. (1961). Acute alcoholic hepatitis. *British Medical Journal*, **2**, 1113-1119.

Bockus, H. L., Kalser, M. H., Roth, J. L. A., Bogoch, A. L., and Stein, G. (1955). Clinical features of acute inflammation of the pancreas. *Archives of Internal Medicine*, **96**, 308-321.

Bouchier, I. A. D., Youngs, G. R., and Agnew, J. E. (1972). Pancreatic scanning. *Clinics in Gastroenterology*, **1**, 105-118.

Coffey, R. J. (1954). The relationship of acute and chronic cholecystitis to acute pancreatitis. *Southern Medical Journal*, **47**, 448-451.

Comfort, M. W., Gambill, E. E., and Baggenstoss, A. H. (1946). Chronic relapsing pancreatitis. *Gastroenterology*, **6**, 376-408.

Dreiling, D. A., Janowitz, P. I. D., and Perrier, C. V. (1964). *Pancreatic Inflammatory Disease*, p. 49. Hoeber: New York.

DuVal, M. K., Jr. (1957). Pancreatico-jejunostomy for chronic pancreatitis. *Surgery*, **41**, 1019-1028.

Goldberg, M., and Thompson, C. M. (1961). Acute fatty metamorphosis of the liver. *Annals of Internal Medicine*, **55**, 416-432.

Howard, J. M., and Nedwich, A. (1971). Correlation of the histologic observations and operative findings in patients with chronic pancreatitis. *Surgery, Gynecology, and Obstetrics*, **132**, 387-395.

Howat, H. T. (1968). Chronic pancreatitis: medical aspects. *Postgraduate Medical Journal*, **44**, 733-736.

James, O. (1973). The Lundh test. Progress report. *Gut*, **14**, 582-591.

James, O., Agnew, J. E., and Bouchier, I. A. D. (1974). Chronic pancreatitis in England: a changing picture? *British Medical Journal*, **2**, 34-38.

Kasugai, T., Kuno, N., and Kizu, M. (1973). Endoscopic pancreatocholangiography with special reference to Manometric method. *Medical Journal of Australia*, **2**, 717-725.

Kasugai, T., Kuno, N., Kizu, M., Kobayashi, S., and Hattori, K. (1972b). Endoscopic pancreatocholangiography II. The pathological endoscopic pancreatocholangiogram. *Gastroenterology*, **63**, 227-234.

Kasugai, T., Kuno, N., Kobayashi, S., and Hattori, K. (1972a). Endoscopic pancreatocholangiography I. The normal endoscopic pancreatocholangiogram. *Gastroenterology*, **63**, 217-226.

McCollum, W. B., and Jordan, P. H. (1975). Obstructive jaundice in patients with pancreatitis without associated biliary tract disease. *Annals of Surgery*, **182**, 116-120.

Marks, I. N., Bank, S., and Louw, J. H. (1968). The diagnosis and management of pancreatitis. *Progress in Gastroenterology*, **1**, 412-472.

Nakamura, K., Sarles, H., and Payan, H. (1972). Three-dimensional reconstruction of the pancreatic ducts in chronic pancreatitis. *Gastroenterology*, **62**, 942-949.

Okuda, K., Tanikawa, K., Emura, T., Kuratomi, S., Jinnouchi, S., Urabe, K., Sumikoshi, T., Kanda, Y., Kukuyama, Y., Musha, H., Mori, H., Shimokawa, Y., Yakushiji, F., and Matsuura, Y. (1974). Nonsurgical percutaneous transhepatic cholangiography—Diagnostic significance in medical problems of the liver. *American Journal of Digestive Diseases*, **19**, 21-36.

Owor, R. (1972). Chronic pancreatic disease: a common cause of obstructive jaundice in Ugandan Africans? *East African Medical Journal*, **49**, 614-619.

Perrier, C. V. (1964). Symposium on the etiology and pathological anatomy of chronic pancreatitis. Marseilles, 1963. *American Journal of Digestive Diseases*, **9**, 371-376.

Rohrmann, C. A., Silvis, S. E., and Vennes, J. A. (1974).

Evaluation of the endoscopic pancreatogram. *Radiology*, **113**, 297-304.

Sarles, H. (1974). Chronic calcifying pancreatitis—chronic alcoholic pancreatitis. *Gastroenterology*, **66**, 604-616.

Scheuer, P. J. (1973). *Liver Biopsy Interpretation.* 2nd edn, p. 25. Baillière Tindall: London.

Sherlock, S. (1975). *Diseases of the Liver and Biliary System.* 5th edn. Blackwell: Oxford.

Snape, W. J., Jr, Long, W. B., Trotman, B. W., Marin, G. A., and Czaja, A., J. (1976). Marked alkaline phosphatase elevation with partial common bile duct obstruction due to calcific pancreatitis. *Gastroenterology*, **70**, 70-73.

Warshaw, A. L., Schapiro, R. H., Ferrucci, J. T., Jr, and Galdabini, J. J. (1976). Persistent obstructive jaundice, cholangitis and biliary cirrhosis due to common bile duct stenosis in chronic pancreatitis. *Gastroenterology*, **70**, 562-567.

Weinstein, B. R., Korn, R. J., and Zimmerman, H. J. (1963). Obstructive jaundice as a complication of pancreatitis. *Annals of Internal Medicine*, **58**, 245-258.

Youngs, G. R., Agnew, J. E., Levin, G. E., and Bouchier, I. A. D. (1971). Radioselenium in duodenal aspirate as an assessment of pancreatic exocrine function. *British Medical Journal*, **2**, 252-255.