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# Pancreatic-Duct Reflux and Acute Gallstone Pancreatitis

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A consecutive series of 614 operative cholangiograms was studied prospectively to determine the relationship of pancreatic-duct reflux to a previous history of acute gallstone pancreatitis. Of 53 patients who had previously had pancreatitis, 33 had pancreatic-duct reflux on their cholangiogram (62.3%), whereas, of 561 patients with no history of pancreatic disease, pancreatic-duct reflux was seen in only 82 (14.6%). In patients with a history of pancreatitis, reflux occurred into a wider pancreatic duct, at a greater angle between the bile and pancreatic ducts, and was associated with a longer functioning common channel. The wider cystic duct, wider common bile duct, and multiple small stones seen in patients with previous pancreatitis and pancreatic-duct reflux were suggestive of gallstone migration being associated with reflux. There was no correlation between pancreatic-duct reflux and the presence of choledochal calculi. Two patients developed recurrent severe pancreatitis after pancreatic-duct reflux of infected bile. Patients with gallstone pancreatitis appear to have an increased tendency for pancreatic-duct reflux that is mechanically facilitated by differences in the choledocho-pancreatic duct anatomy.

**A**CUTE GALLSTONE PANCREATITIS (AGP) is a common disease with a mortality rate of 10–15%.<sup>1–4</sup> Although the pathogenesis of AGP remains contentious, there is considerable evidence that bile or duodenal reflux is responsible. Such reflux may be resultant on a gallstone migrating through the ampulla of Vater into the intestine.<sup>5,6</sup> Recent reports<sup>7–11</sup> have found a high incidence of pancreatic-duct reflux on the operative cholangiograms of patients undergoing biliary surgery for AGP and have suggested that this might well point to an important mechanical initiator of pancreatitis. There has, however, been little evaluation of the reflux itself. This study was designed to investigate prospectively the association between AGP and pancreatic-duct reflux and to identify factors that might predispose to reflux in such patients.

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## Patients and Methods

The series consists of a prospective study of 614 consecutive patients who underwent cholecystectomy and operative cholangiography for biliary lithiasis in two surgical units, the Department of Surgical Gastroenterology, Manchester Royal Infirmary, and the Department of Clinical Surgery, Edinburgh Royal Infirmary. These operations were carried out by the same surgical team, and similar cholangiographic techniques were used in each case. There were 177 males and 437 females, with a median age of 52 years (range: 15–84). All patients had technically satisfactory operative cholangiograms, which were performed prior to opening the common bile duct by cystic duct cannulation (482) or by needle puncture of the common bile duct (132). The technique of cholangiography depended on the surgeon's preference; in a few cases, however, where difficulties were encountered in cannulating the cystic duct, needle puncture was carried out. Three films were obtained after the injection of 3, 8, and 16 ml of 25% "hypaque"; the dye was injected slowly to avoid a sudden increase in pressure. Every patient who underwent exploration of the common bile duct after the initial cholangiogram had a completion cholangiogram before the abdomen was closed and a T-tube cholangiogram was performed at 8 days. Cholangiograms were made with the patient lying supine on the operating table without tilting or the use of pillows. All cholangiograms were assessed by a single observer who was unaware of the final diagnosis. Muscular relaxants were used during the operation, drugs likely to cause sphincter spasm were avoided, and amyl nitrate was never used when drainage into the duodenum did not occur.

Acute gallstone pancreatitis was defined as a definite attack of clinical acute pancreatitis, biochemically proven



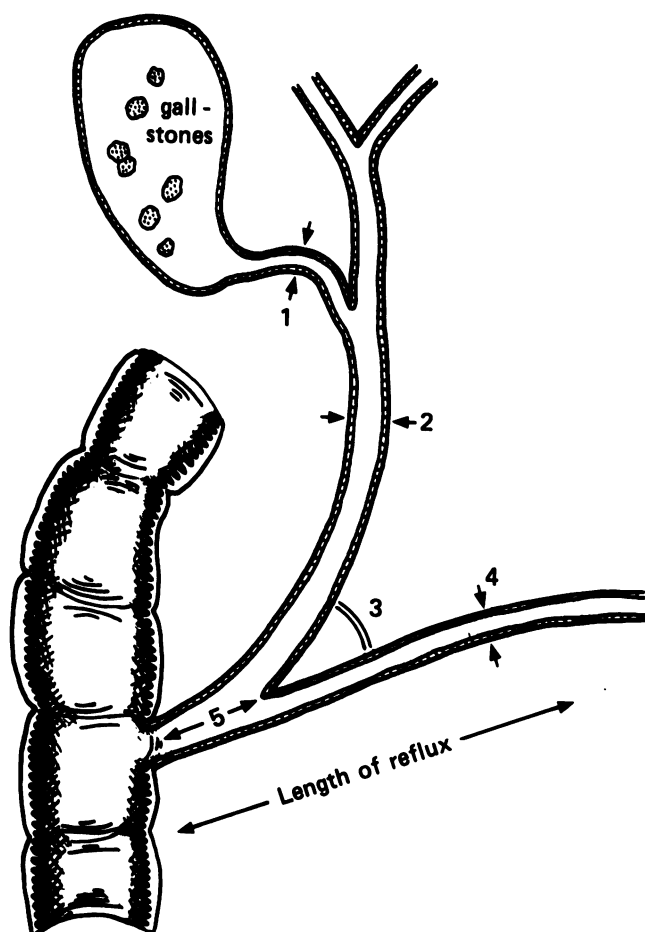


FIG. 1. Measurements of biliary tract taken from the operative cholangiogram. 1 = Diameter cystic duct. 2 = Diameter common bile duct. 3 = Angle of reflux. 4 = Diameter of pancreatic duct. 5 = Length of common channel.

by a serum amylase concentration of over 1000 IU/L, with gallstones found at operation in the absence of other etiological factors such as alcohol. No operations were performed within 1 week of the onset of an attack of gallstone pancreatitis; our initial policy had been to operate 6 weeks after resolution of pancreatitis, later this changed

TABLE 1. Clinical Features of Patients with and without Acute Gallstone Pancreatitis

	Pancreatitis		No Pancreatitis (controls)
Number	53		561
Age (median)	54		52
Male	25 (47%)	*	152 (27%)
Female	28 (53%)		409 (73%)
Jaundice	11 (21%)		131 (23%)
Common bile duct stones	16 (30.2%)	†	92 (16.4%)
Exploration of the common bile duct	26	*	115

\*  $p < 0.001$ . †  $p < 0.02$ .

to earlier surgery but the attack of pancreatitis had always resolved clinically prior to surgery. The presence of pancreatic-duct reflux was determined from the operative cholangiogram. When reflux occurred, a record was made of the greatest extent of reflux, the diameter of the pancreatic duct, the angle between the pancreatic and common bile ducts, and the length of the common channel (Fig. 1). Measurements were performed to the nearest millimeter using a caliper and the angle of reflux measured with a protractor to the nearest degree. Careful note was also made of the diameters of the cystic and common bile ducts, duodenal filling, and the presence of common bile duct calculi. At the end of the operation, the gallbladder was opened and the number of calculi coded as greater or less than 10. The size of the smallest gallstone was measured by caliper to the nearest millimeter.

Bile cultures were only routinely performed in those undergoing duct exploration; all of these patients and any other jaundiced patients received parenteral antibiotics, most commonly a cephalosporin.

Pancreatic-duct reflux was further assessed on completion and T-tube cholangiographic films to determine the consistency of reflux and its relationship to choledochal and ampullary pathology. All results were entered into a computer and statistical analysis was performed by the Department of Computation, University of Manchester. The analytical tests used were chi square, Fisher's exact test, and the Mann-Whitney U test.

## Results

Fifty-three of the patients (8.6%) had a previous attack of acute gallstone pancreatitis; 561 patients had no history of pancreatic disease and were termed controls. The clinical features of the patients with and without AGP are shown in Table 1. It should be noted that a previous attack of pancreatitis was significantly more common in males ( $p < 0.001$ ), and a greater proportion of patients with pancreatitis had common bile duct stones ( $p < 0.02$ ) and underwent exploration of the duct ( $p < 0.001$ ). No difference in the results existed between the two techniques employed at operative cholangiography, and diameter of the common bile duct was not significantly different between the first and the third film taken.

Pancreatic-duct reflux was noted on the cholangiograms of 115 patients (18.7% of total) and was equally common in males (21.5%) and females (17.6%). Of the 53 patients with a previous history of AGP, 33 (62.3%) had pancreatic-duct reflux on their operative cholangiograms in contrast to only 82 of 561 control patients (14.6%). This difference was highly significant;  $\chi^2 = 72.22$ ,  $p < 0.0001$ . Sixteen of 38 male patients with pancreatic-duct reflux had previously had AGP, compared with 17 of 77 females ( $\chi^2 = 4.99$ ,  $p < 0.05$ ). The features of the 115 patients with pancreatic-duct reflux are illustrated in Table 2. Pan-



TABLE 2. Features of Patients with Pancreatic-Duct Reflux (N = 115)

	Pancreatitis		No Pancreatitis (controls)
Number	33		82
Age (median)	54	*	46
Male	16 (48.5%)	†	22 (26.8%)
Female	17 (51.5%)		60 (73.2%)
Jaundice	6	N.S.	20
Common bile duct stones	15	‡	9

\*  $p < 0.02$ . †  $p < 0.01$ . ‡  $p < 0.001$ . N.S. = not significant.

creatic-duct reflux occurred in patients with previous AGP in an older age group, more commonly in males and more often in association with common bile duct stones than in controls.

Pancreatic-duct reflux in patients with previous AGP was associated with a wider common bile duct than in controls (Table 3). Twenty-two of 33 patients with AGP had a common bile duct wider than 10 mm in contrast to 14 of 82 control patients ( $\chi^2 = 26.9$ ,  $p < 0.001$ ). The cystic duct was also markedly wider in patients with previous AGP. There was no difference in the numbers of gallbladder stones and the mean size of the smallest stone was similar in the two groups of patients. However, 28 of 33 patients with previous AGP had stones of less than 3 mm compared to 54 of 82 controls ( $\chi^2 = 4.15$ ,  $p < 0.05$ ). Fourteen patients with pancreatic-duct reflux had no duodenal filling on any of the cholangiographic films, seven with previous AGP and seven controls.

The features of pancreatic-duct reflux itself are shown in Table 4. The mean extent of pancreatic-duct reflux was similar in the two groups of patients. There was, however, a wide variation of measurements, which ranged from 5 to 140 mm in both groups. The pancreatic-duct was markedly ( $p < 0.001$ ) wider and the angle of reflux greater ( $p < 0.02$ ) in patients with previous AGP. Pancreatic-duct reflux occurred in patients with previous AGP in association with a longer common channel than in controls. Twenty-four of 33 patients with AGP had a common channel of greater than 5 mm compared to 16 of 82 of the control patients ( $\chi^2 = 29.4$ ,  $p < 0.001$ ). Examples of pancreatic-duct reflux are shown in Figures 2–4.

Correlation of pancreatic-duct reflux on completion and T-tube cholangiography is shown in Table 5. Three patients with previous AGP, who had pancreatic-duct reflux on their original cholangiograms, demonstrated no evidence of reflux on completion cholangiography after removal of choledochal stones. The same finding was noted in three patients without pancreatitis. Seven patients with previous AGP and six controls, who had pancreatic-duct reflux on their original cholangiograms, showed no evidence of reflux on T-tube cholangiography. It is noteworthy that two patients, with previous AGP, demonstrated pancreatic-duct reflux on their T-tube cholangio-

TABLE 3. Features of Biliary Tract in Patients with Pancreatic-Duct Reflux (N = 115)

	Pancreatitis		No Pancreatitis (controls)
Number	33		82
Diameter of common bile duct (mm)	11.4 ± 3.66*	†	8.5 ± 2.81
Diameter of cystic duct (mm)	5.14 ± 1.65	†	3.4 ± 1.47
Size of smallest gallbladder stones (mm)	3.0 ± 3.85	N.S.	3.84 ± 3.48
Number of >10 gallbladder stones	23	N.S.	45
No duodenal filling	7	N.S.	7

\* Mean ± S.D. †  $p < 0.001$ . N.S. = not significant.

grams, although there was no evidence of reflux on the original operative films. Where reflux occurred on the T-tube cholangiograms, measurement of the various parameters gave similar results to those obtained from the initial films.

Two patients with previous AGP developed postoperative recurrence of their pancreatitis, one after simple cholecystectomy, and one died following transduodenal sphincterotomy. Both patients showed marked pancreatic-duct reflux and their bile cultures demonstrated a heavy growth of coliform organisms. One control patient, who did not have pancreatic-duct reflux, developed postoperative pancreatitis following a transduodenal sphincterotomy.

## Discussion

Although gallstones are responsible for over half the cases of acute pancreatitis seen in the United Kingdom, only a small number of those with gallstones will develop pancreatitis.<sup>1,3,4</sup> In this study, 8.6% of an unselected group of patients with gallstones developed pancreatitis, a slightly higher incidence than has been reported.<sup>12</sup> Migration of small calculi from the gallbladder down the common bile duct and through the ampulla into the duodenum is an

TABLE 4. Pancreatic-Duct Reflux in the Two Groups of Patients

	Pancreatitis (N = 53)		No Pancreatitis (controls) (N = 561)
Pancreatic duct reflux	33 (62.3%)	*	82 (14.6%)
Extent of reflux (mm)	33.5 ± 19 <sup>  </sup>	N.S.	35.7 ± 29
Diameter of pancreatic duct (mm)	4.9 ± 1.0	†	2.6 ± 1.3
Angle of reflux (°)	40 ± 12	‡	21 ± 15
Length of common channel (mm)	8 (4–16)	§	4 (2–44)

\*  $p < 0.0001$ . †  $p < 0.001$ . ‡  $p < 0.02$ . §  $p < 0.01$ . <sup>||</sup> Mean ± S.D., median with range. N.S. = not significant.



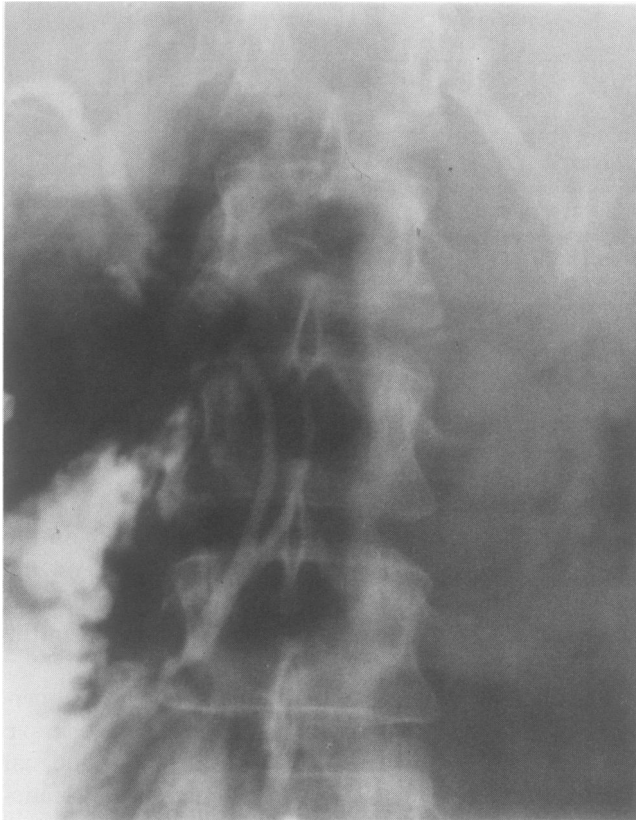


FIG. 2. Operative cholangiogram. Pancreatic-duct reflux down whole length of duct. Common channel = 36 mm, angle of reflux =  $28^{\circ}$ .

attractive explanation for the mechanical induction of acute gallstone pancreatitis.<sup>5,6</sup> Such migration may be associated with biliary or duodenal reflux into the pancreatic duct and thus initiate pancreatic inflammation. Although pancreatic-duct reflux is observed on 15 to 35% of operative cholangiograms, its importance has, until recently, remained debatable.<sup>7,13-15</sup> Pancreatic-duct reflux is more commonly observed on the operative cholangiograms of patients undergoing surgery for AGP, as is shown in a summary of reported figures in Table 6.<sup>7-11,16-18</sup> The findings in this study are in close agreement, as 62.3% of patients with previous pancreatitis showed pancreatic-duct reflux in contrast to only 14.6% of controls. Operations performed in the acute phase of pancreatic inflammation are accompanied by a much lower incidence of pancreatic-duct reflux, which may be resultant on ampullary and pancreatic duct edema.<sup>19-21</sup>

It is of interest that more patients with previous pancreatitis were male than in the control group. Although the reason for this observation is unclear, it has been previously reported<sup>7</sup> and may relate to a different anatomical disposition of the sphincteric muscle. The cystic and common bile ducts were wider in those patients who demonstrated pancreatic-duct reflux when there was a history of acute pancreatitis. These features confirm earlier reports<sup>11,22</sup> and may predispose such patients to gallstone migration. While it may be tempting to assume that the wider common bile duct is casually associated with in-

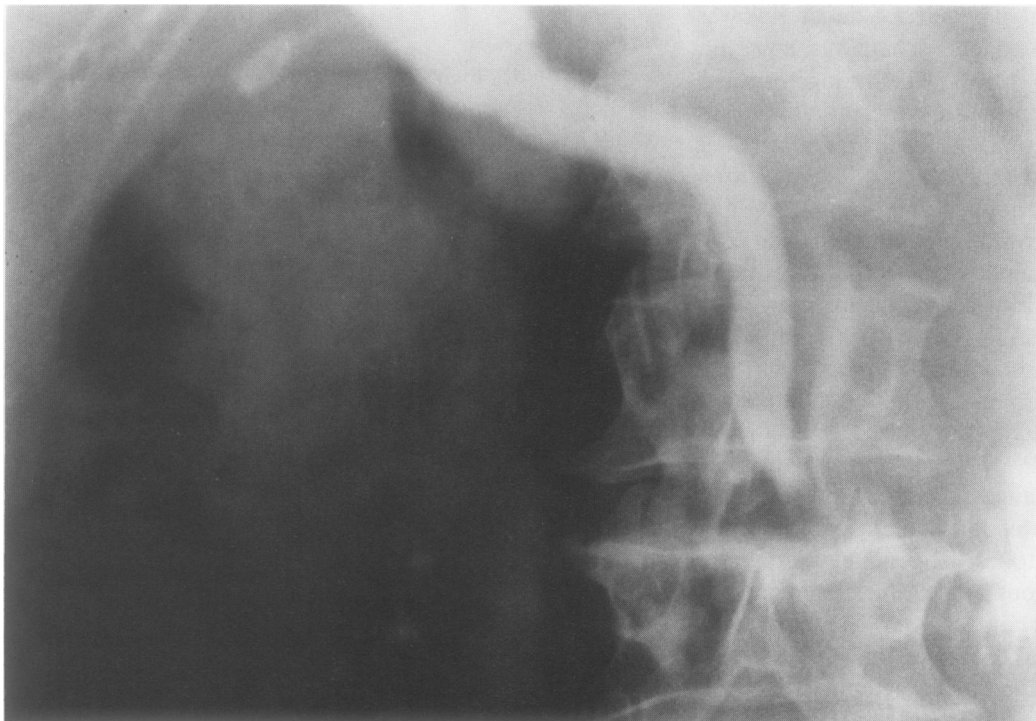


FIG. 3. Operative cholangiogram. Pancreatic-duct reflux in association with stones in the common bile duct.



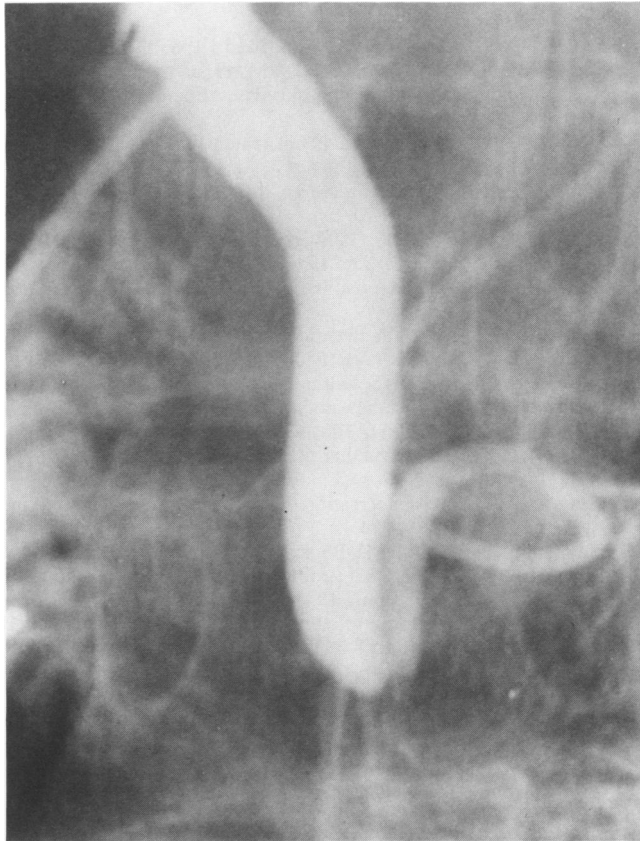


FIG. 4. T-tube cholangiogram. Pancreatic-duct reflux. Note loop in pancreatic duct.

creased frequency of pancreatitis, it is possible that the wider common bile and pancreatic ducts were secondary to pancreatitis rather than the cause thereof.

The importance of pancreatic-duct reflux during cholangiography remains controversial. Schulenberg<sup>14</sup> suggested that it was of little import, whereas Cuschieri<sup>15</sup> found that 27% of pancreatic ducts into which reflux occurred were abnormal. Howell and Bergh<sup>17</sup> found a positive correlation between biliary-pancreatic reflux of contrast material and the subsequent elevation of serum amylase following cholecystectomy and operative cholangiography and further showed that injection of bile produced marked hyperamylasemia. Conversely, Thomas and associates<sup>23</sup> could find no relationship between pancreatic-duct reflux and hyperamylasemia but rather implicated surgical trauma to the sphincter of Oddi. Cuschieri and coworkers<sup>15,24</sup> found pancreatic-duct reflux to occur regardless of the pressure of contrast injection and could find no relationship between reflux and obstructive pathology of the lower choledochus or biliary hypertension. Schein and Beneventano<sup>25</sup> reported that pancreatic-duct reflux was painless and that it occurred before the common bile duct was maximally dilated. They further suggested that, in the absence of biliary-pancreatic ob-

TABLE 5. *Pancreatic-Duct Reflux and Cholangiography\**

Cholangiogram	Pancreatitis	No Pancreatitis (controls)
Initial, operative	33/53	82/561
Completion, after removal of choledochal stones†	12/15	6/9
T-tube, after choledochotomy†	15/20‡	8/14

\* Figures are number showing reflux/number having investigation.

† Cholangiograms performed on 115 patients with pancreatic-duct reflux.

‡ Includes two patients with no reflux on initial films.

struction, pancreatic-duct reflux was harmless. Taylor and Rimmer<sup>7</sup> have described a possible role for reflux of infected bile, as it is well known that gallstones are associated with a high incidence of infected bile.<sup>26</sup> It is noteworthy therefore that two patients in this study developed recurrent severe pancreatitis following surgery, and both demonstrated marked pancreatic-duct reflux with heavily infected bile.

The association between common bile duct stones and pancreatic-duct reflux was assessed by comparing reflux on the initial and completion cholangiograms. There appeared to be little correlation between the presence of choledochal calculi and pancreatic-duct reflux, as only six patients showed loss of reflux following removal of stones. The constancy of pancreatic-duct reflux was evaluated by comparing reflux on the initial and T-tube cholangiograms. Seven patients with previous pancreatitis and six controls demonstrated loss of reflux, implying a degree of variability in any one patient. Of interest are the two patients with previous AGP who showed pancreatic-duct reflux on their T-tube cholangiograms but not on the initial films. This observation emphasizes that measurement of pancreatic-duct reflux during operative cholangiography may well be an underestimate of the frequency of actual reflux, as suggested by Thomas and colleagues.<sup>23</sup>

Noting the presence of pancreatic-duct reflux alone on

TABLE 6. *Pancreatic-Duct Reflux and Acute Gallstone Pancreatitis in Reported Series\**

Author	Pancreatitis	No Pancreatitis
Taylor & Rimmer <sup>7</sup>	11/21	45/271
Kelly <sup>6</sup>	30/45	8/45
Kelly <sup>9</sup>	30/35	
Osborne et al. <sup>8</sup>	21/49	11/50
Thurston <sup>14</sup>	4/6	24/84
Howell & Bergh <sup>15</sup>	14/18	13/47
Carey <sup>16</sup>	7/9	4/11
McMahon <sup>11</sup>	21/42	17/69
Kelly <sup>10</sup>	50/75	14/75
Present study	33/53	82/561
Totals	221/535 (62.6%)	218/1213 (18.0%)

\* Figures are number showing reflux/total number of patients.

$\chi^2 = 270.0$ ;  $p < 0.00001$ .



cholangiography is a relatively crude assessment of its importance, as reflux may occur to a small degree or down the entire duct. It has been reported that patients who develop AGP have a high incidence of anatomic factors that predispose them to pancreatic-duct reflux.<sup>10,16</sup> This study measured several parameters of reflux in an attempt to determine differences in pancreatic-duct reflux between patients with and without previous pancreatitis. The mean length of reflux down the pancreatic duct was similar in the two groups of patients and was comparable to reported figures,<sup>7</sup> although there was considerable individual variation. In the present study, patients with previous pancreatitis had much wider pancreatic ducts than did controls, and, while it is debatable whether this dilation was primary or secondary to previous pancreatic inflammation, there is no doubt that a dilated pancreatic duct will mechanically facilitate reflux. This finding has not been reported previously, and it is of interest that Csendes and colleagues<sup>27</sup> have noted the pancreatic duct of patients with gallstones to be twice as wide as that of normal control patients. A note of caution must be sounded, however, as the pancreatic duct dilates with age,<sup>28</sup> and in this study patients with pancreatitis were older than controls. Measuring the angle of reflux on cholangiograms is an original idea, and it is interesting to hypothesize that our finding of an increased angle in patients with previous AGP may be an additional anatomical feature that mechanically facilitates reflux.

A functioning common channel at the junction of pancreatic and bile ducts is found in approximately 80% of normal subjects,<sup>13,29</sup> and Kelly<sup>6,9,10,30</sup> found this feature to be present in 87% of patients who had stones recovered from the feces after an attack of pancreatitis. In this study, patients with previous pancreatitis and pancreatic-duct reflux demonstrated a significantly longer functioning common channel than did controls. It is of interest that 72% of such patients had a common channel 5 mm or longer in contrast to only 20% of controls. As the mean size of the smallest gallstones in patients with pancreatitis was 3 mm, these results imply that passage of small calculi, or microlithiasis,<sup>31</sup> through the ampulla may be associated with pancreatic-duct reflux.

This report has clearly shown that pancreatic-duct reflux is more commonly observed on the cholangiograms of patients with previous acute gallstone pancreatitis. Moreover, reflux in these patients occurred into a wider pancreatic duct, at a greater angle, and was associated with a longer functioning common channel than in controls. As pancreatic-duct reflux can occur without untoward effects in many patients, it may well be that the bile refluxed in patients with pancreatitis contains noxious agents and infective organisms. Migration of calculi in patients with gallstone pancreatitis appears to be associated with pancreatic-duct reflux, which is mechanically facilitated by anatomical differences in the choledochopancreatic duct anatomy.

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