

## Detection of gall stones after acute pancreatitis

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**SUMMARY** Four methods of gall stone diagnosis after an attack of acute pancreatitis are analysed. Of 128 consecutive patients with acute pancreatitis, 99 patients were discharged from hospital without a definite aetiology. These patients had biochemical tests performed on admission and ultrasonography and oral cholecystography performed six weeks later. The sensitivity for ultrasonography was 87% and the specificity was 93%; the respective figures for oral cholecystography were 83% and 90%. The predictive value of positive ultrasonography was 100% and of negative ultrasonography 75%; the respective values for oral cholecystography were 95% and 68%. A combination of ultrasonography and oral cholecystography failed to detect nine of 70 patients with gall stones (13%). Of 35 patients with normal ultrasonography and oral cholecystography, 33 patients had an endoscopic retrograde cholangiogram (ERCP) which showed gall stones in a further seven patients. All three methods failed to reveal gall stones in two patients, confirmed by laparotomy. The sensitivity of admission biochemical analysis was 73% and the specificity was 94%; the predictive value of a positive result was 97% and of a negative result was 57%. Biochemical analysis predicted gall stones in six of the seven patients shown by ERCP. Only 9% of patients were finally considered to be idiopathic. In conclusion ultrasonography is the investigation of choice and ERCP should be undertaken in all patients who have normal ultrasonography and/or oral cholecystography but have biochemical criteria indicative of gall stones.

After an attack of acute pancreatitis gall stone detection is important as surgical intervention will prevent recurrent attacks in 96-98% of patients.<sup>1-3</sup> The increasing tendency to perform cholecystectomy within the same admission has resulted in a need for accurate methods of gall stone detection during or soon after the acute attack. Ultrasonography,<sup>4</sup> biochemical analysis<sup>5</sup> and radio-nuclide biliary scanning<sup>6</sup> have all been proposed as reliable diagnostic methods during the acute phase of pancreatitis.

After recovery from the acute attack the combination of ultrasonography and oral cholecystography is widely accepted as adequate in the detection of gall stones. There are, however, no large series which have fully assessed the accuracy of these techniques in patients with gall stones associated with acute pancreatitis. These gall stones are often small and may evade detection by these techniques.<sup>7,8</sup>

Endoscopic retrograde cholangiopancreatography is one of the clearest methods of showing the biliary tree. The use of ERCP in the investigation of recurrent acute and chronic pancreatitis is well established,<sup>9-12</sup> but its exact role in the management of acute pancreatitis is yet to be defined.

The aim of this study was to assess the accuracy of ultrasonography and oral cholecystography performed six weeks after the acute attack in detecting gall stones and the value of ERCP and biochemical analysis when these investigations were normal. In addition the therapeutic management of biliary pancreatitis by endoscopic sphincterotomy with stone extraction was studied in a limited number of patients.

### Methods

#### PATIENTS

The study group consisted of 128 consecutive patients with acute pancreatitis admitted during the 36 months up to December 31st 1982. The diagnosis of acute pancreatitis was made if the serum amylase

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was greater than 1000 IU/l in the presence of a consistent clinical picture. There were 71 women and 57 men with a mean age of 58 years (range 19–97 years).

On admission a full alcohol and drug history was taken and blood obtained for biochemical analysis. During the first admission patients who had laparotomy, endoscopic sphincterotomy or who died were studied to ascertain the aetiology. After hospital discharge patients in whom the presence of gall stones had not been firmly established underwent ultrasonography and oral cholecystography at about six weeks after recovery. All patients with normal ultrasonography and oral cholecystography were requested to undergo ERCP irrespective of their alcohol consumption. The findings at laparotomy or necropsy during subsequent admissions were also taken into account in determining the final aetiology (if any) of the original attack of acute pancreatitis.

#### BIOCHEMICAL ANALYSIS

The serum amylase was performed immediately on admission. The serum alkaline phosphatase, alanine transaminase and bilirubin were measured using a Technicon Smac-1 analyser, which was operated between 9 am and 5 30 pm on weekdays and 9 am and 1 pm on Saturdays. These tests were thus performed within 24 hours in the vast majority and within 48 hours in the few patients admitted between Saturday afternoon and Sunday morning.

#### ULTRASONOGRAPHY

Ultrasonography was carried out by one consultant (DF) using a Philips Sonodiagnost B and Diagnostic sonar real time. Scans were performed in the longitudinal and transverse planes, in the supine and right anterior oblique positions. A diagnosis of gall stones was only made if an echogenic area was seen within a clearly defined gall bladder.

#### ORAL CHOLECYSTOGRAPHY

This was performed using a double dose of Solubiloptin, after taking control radiographs. Patients were only allowed clear fluids after the evening meal and at 10.45 pm took a single dose of Solubiloptin. At 7 am the following morning a second dose of Solubiloptin was taken and further radiographs were taken two hours later. Erect, supine, and prone oblique views were taken before and after a standard fatty meal. All radiographs were subsequently reviewed by a single consultant radiologist (DF).

#### ENDOSCOPIC RETROGRADE CHOLANGIO-PANCREATOGRAPHY

Endoscopic retrograde cholangiopancreatography

was performed by one endoscopist (DCL) using a Fujinon DUO-X duodenoscope under intravenous diazepam sedation by a standard technique.<sup>9</sup> Endoscopic sphincterotomy was performed as previously described<sup>13 14</sup> using a Classen-Demling sphincterotome and Erbotom T175D diathermy unit. After endoscopic sphincterotomy complete clearance of common bile duct calculi was attempted by basket or balloon extraction.

The results of the above diagnostic methods were compared with each other and with the findings at laparotomy or necropsy. Analysis of the biochemical results was made by the Mann-Whitney ranking test using the Minitab computing system.

#### Results

##### TREATMENT AND OUTCOME

Thirteen patients who were clinically jaundiced and had gall stones shown by ultrasonography underwent endoscopic sphincterotomy during their first admission. In 12 of these patients endoscopic stone extraction was performed successfully and without complication. In three of these patients endoscopic stone extraction was carried out for stones in the common bile duct at one, 10, and 15 years postcholecystectomy. In five high operative risk patients endoscopic stone extraction was performed without subsequent cholecystectomy. A further four patients had endoscopic stone extraction followed by cholecystectomy alone. None of these patients have suffered further gall bladder symptoms or recurrent acute pancreatitis in a follow up period of 8–30 months (mean 21 months). The remaining patient, an 84 year old woman who had five poor prognostic signs on admission<sup>15 16</sup> died. She was initially treated by supportive therapy but deteriorated. Nine days after admission ERCP revealed a large common bile duct stone, endoscopic sphincterotomy was performed but stone extraction failed. Surgery was not undertaken and she died six days later. At necropsy haemorrhagic pancreatitis and bronchopneumonia were found.

Three patients who were shown to have gall stones by ultrasonography had a cholecystectomy after clinical improvement during the same admission. Six elderly patients (mean age 85 years, range 74–96 years) died within 48 hours and necropsy was not performed. A further three patients died from severe pancreatitis after surgery at one to four weeks (all underwent necropsy) and two of these had gall stones. Two other patients survived laparotomy but preoperative radiological examination was considered satisfactory in only one of these (no gall stones). Three patients with acute

pancreatitis had malignancy: one had started chemotherapy for lymphoma, and two had secondary deposits in the pancreas, one each from bronchial and gastric carcinomas; these patients, who died two to eight weeks later, did not have gall stones at necropsy.

Ninety nine patients were discharged from hospital and were further investigated for gall stones. Fifty nine of these patients who underwent cholecystectomy on the basis of these investigations had gall stones. Two other symptomatic patients had cholecystectomy but no gall stones were found: one patient was found to have gross features of chronic pancreatitis but in the other patient the laparotomy findings were normal. Both these patients had a 'non-useful' ultrasonography and one had a non-functioning gall bladder whereas the other had a poorly functioning gall bladder on oral cholecystography. A third patient who had a poorly functioning gall bladder on oral cholecystography and a normal gall bladder on ultrasonography, was also shown to have pseudocyst by ultrasonography. No gall stones were found on subsequent laparotomy.

Nine patients were found to have gall stones by radiological examination but three refused surgery (gall stones were confirmed in one patient at surgery for an aortic aneurysm) and three were considered unfit for surgery. The remaining three patients died while on the waiting list, two from unrelated causes (cerebrovascular accident and myocardial infarction) and one from a recurrent attack of acute pancreatitis.

Two further patients underwent laparotomy for symptoms despite normal ultrasonography, oral cholecystography and endoscopic retrograde cholangiography and both were found to have several small gall stones in the gall bladder: one patient had had persisting right hypochondrial pain and the other had had a small pseudocyst (shown by ultrasonography and ERCP) which had failed to resolve.

Of the 99 patients investigated as outpatients the presence of gall stones was established in 70 patients. Overall 122 of the total of 128 were considered to have been fully evaluated and a causative factor was established in 111 patients (Table 1).

#### ULTRASONOGRAPHY

In the biliary group gall stones were detected in 61 patients, and there were nine false negative scans. In the non-biliary group no gall stones were detected in 27 patients and the gall bladder could not be located in two others. There were no false positive scans. The sensitivity was 87% and the specificity was 93%

Table 1 *Aetiology in patients with acute pancreatitis*

<i>Aetiology</i>	<i>Patients (no)</i>
Biliary*	86
Biliary + alcoholic	2
Alcoholic†	18
Trauma	1
Steroids	1
Cytotoxics	1
Metastases in pancreas	2
Idiopathic	11
Total‡	122

\* Three postcholecystectomy calculi included.

† One patient shown to have carcinoma of body of pancreas.

‡ Does not include six patients who died within 24 hours of admission.

(owing to the two non-useful scans). The predictive value of a positive scan was 100% and the predictive value of a negative scan was 75%.

#### ORAL CHOLECYSTOGRAPHY

Thirty four patients were found to have a functioning gall bladder with stones. Nineteen had a non-functioning gall bladder and of these one was found to have a normal biliary tree at laparotomy and gall stones were confirmed in the other 18 patients at operation. Thirty eight patients had a normal oral cholecystography of which 12 were found to have gall stones at operation. In eight patients a poorly functioning gall bladder was shown, six of which were subsequently shown to have gall stones. The sensitivity was 83% and the specificity 90%. The predictive value of an abnormal oral cholecystography was 95% and the predictive value of a normal oral cholecystography was 68%.

Ultrasonography detected gall stones in all the patients with an abnormal oral cholecystography who were subsequently shown to have stones and in a further three patients who had a normal oral cholecystography.

#### ENDOSCOPIC RETROGRADE CHOLANGIO-PANCREATOGRAPHY

Thirty three of the 35 patients with both normal ultrasonography and oral cholecystography agreed to undergo ERCP. Eighteen had no known aetiology at the time of ERCP and 15 were alcoholic (a daily intake of 100 g of alcohol or more). Endoscopic retrograde cholangiopancreatography revealed a further seven patients with gall stones, including two previously thought to be purely alcoholic in aetiology (Table 2). Endoscopic retrograde cholangiopancreatography showed the gall stones to be in the gall bladder with a clear common bile duct in all seven patients. In each case

Table 2 Results of ERCP in 33 patients

ERCP	Patients (no)
'Unknown aetiology'	
Normal ERCP	10 (1*)
Normal ERC and pseudocyst	1 (1*)
Gall stones	5
Pancreas divisum	2
'Alcoholic patients'	
Normal ERCP	6
Chronic pancreatitis	4
Gall stones	2
Pancreatic carcinoma	1
Pancreas divisum	1
Failed ERC and normal ERP	1

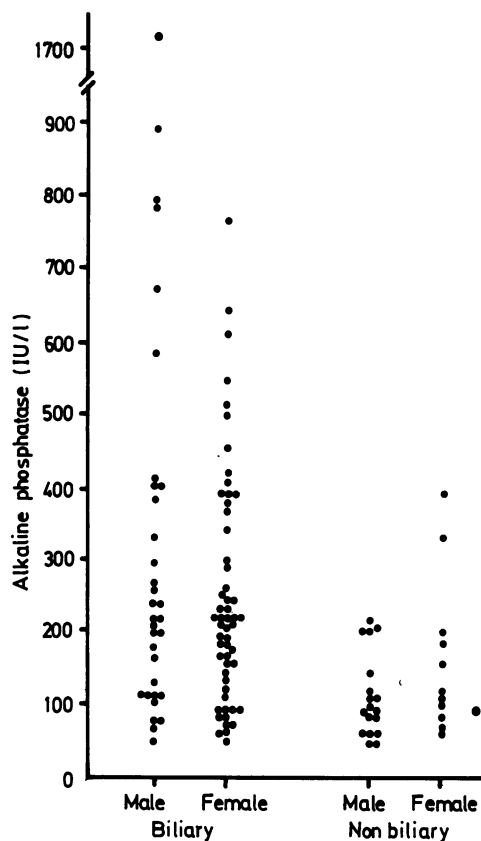
\* Patients with gall bladder stones at laparotomy.

multiple small gall stones were found at laparotomy. As detailed above, ERCP failed to detect gall stones in two other patients shown to have gall stones at surgery. Also shown by ERCP were four patients with chronic pancreatitis and one patient with pancreatic carcinoma. In addition three patients were shown to have pancreas divisum. A review of 1092 ERCPs performed during the study period on patients with symptoms suggestive of pancreatic or biliary disease, revealed 31 cases of pancreas divisum, and incidence of 2.8%.

#### BIOCHEMICAL ANALYSIS AND CLINICAL CRITERIA (FIGS 1-5)

The median values (range) for the biliary group were alkaline phosphatase 215 (48-1715) IU/l, alanine transaminase 137 (5-789) IU/l and bilirubin 27 (6-184)  $\mu\text{mol/l}$ . These values were all significantly different from the non-biliary group ( $p < 0.0005$ ) namely, alkaline phosphatase 110 (47-394) IU/l, alanine transaminase 30 (6-163) IU/l, and bilirubin 12 (5-39)  $\mu\text{mol/l}$ . There was no significant difference between the amylase values of the biliary group 3174 (1104-17160) IU/l and the non-biliary group 3200 (1100-8010) IU/l ( $p > 0.5$ ).

Cut off values which provided a good separation between the biliary and non-biliary groups were alkaline phosphatase 225 IU/l, alanine transaminase 75 IU/l and bilirubin 40  $\mu\text{mol/l}$ . A positive result was taken when one or more of these biochemical results were equal to or greater than the cut off values (indicating gall stones) and a negative result was taken when all three of the biochemical results were less than the cut off values. The sensitivity of biochemical analysis was then 73% and the specificity 94%. The predictive value of a positive result was 97% and the predictive value of a negative result was 57%. The amylase results provided no useful additional diagnostic information.



Figs. 1-5 These show the relationships between alkaline phosphatase, alanine transaminase, bilirubin, amylase and age, with respect to sex and to the two main aetiological groups.

When these results were applied to the nine patients who had a normal ultrasonography and oral cholecystography, a positive biochemical test predicted six of these patients including five of the seven revealed by ERCP.

Blamey *et al*<sup>17</sup> have more recently shown that an age of greater than 50 years and a female sex may be combined with biochemical analysis to improve the prediction of gall stones. By using all five factors, a positive result was taken if two or more factors were present and a negative result if none or one factor were present. The sensitivity of this method was 84% and the specificity 74%. The predictive value of a positive result was 89% and of a negative result 64%. Using this method eight of the nine patients with a normal ultrasonography and oral cholecystography would have been detected including all seven patients revealed by ERCP.

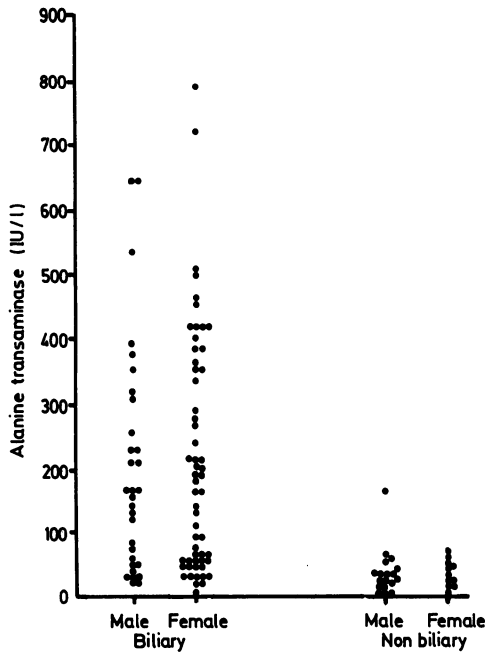


Fig. 2 See legend for Fig. 1

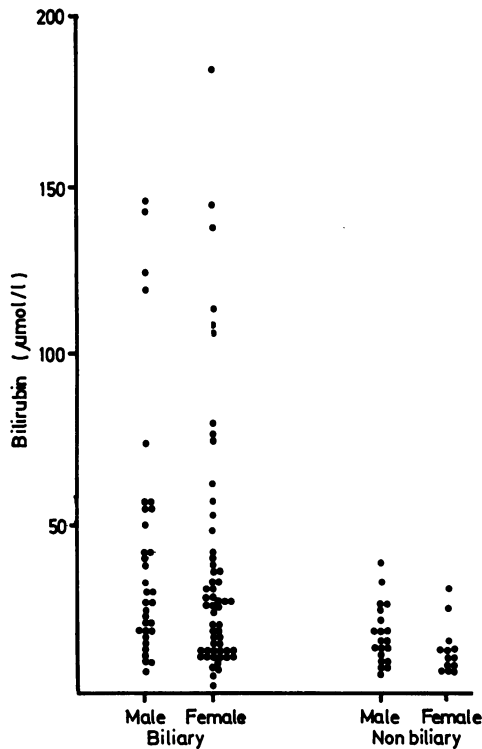


Fig. 3 See legend for Fig. 1

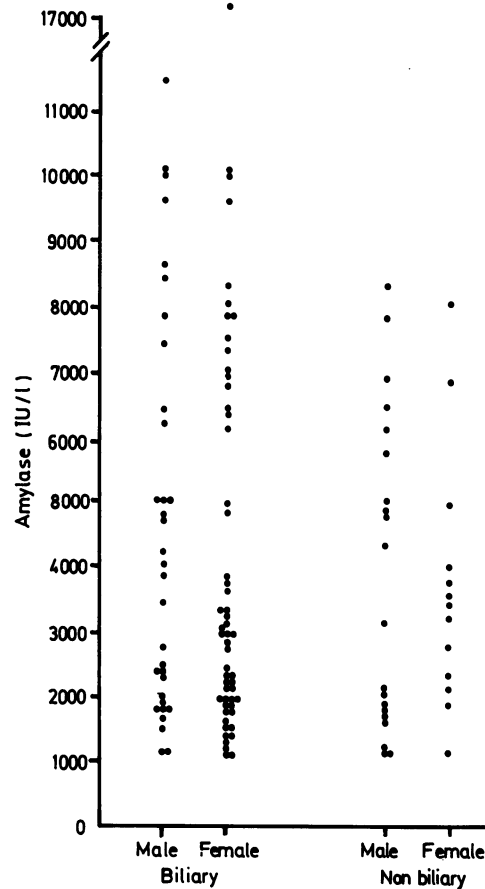


Fig. 4 See legend for Fig. 1

**Discussion**

After an attack of acute biliary pancreatitis, cholecystectomy is traditionally carried out during a subsequent admission. This allows time for gall stone detection by routine radiology. Unfortunately this delay leads to recurrent pancreatitis before the second admission in 33–48% of patients.<sup>1 3 18 19</sup> Although the severity of subsequent attacks tends to be less than that of the original,<sup>20</sup> some patients will suffer severe symptoms, and may even die, as happened to one patient in this study.<sup>18 21</sup>

In an attempt to avoid the complications of delayed surgery, there has been a move towards earlier definitive treatment of gall stone pancreatitis. Two alternative treatment regimes have been proposed, immediate surgery<sup>22</sup> performed within 48 hours of admission or early surgery<sup>19 23</sup> carried out after resolution of the acute attack, but during the

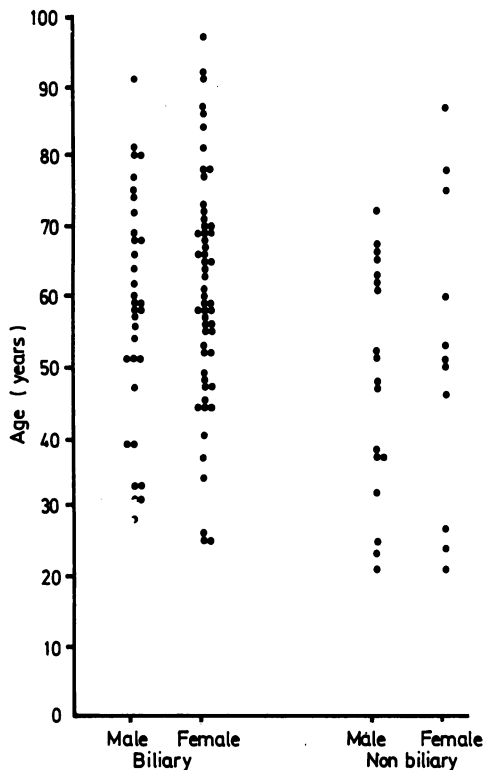


Fig. 5 See legend for Fig. 1

same admission, usually at five to 10 days.

The tendency to perform earlier surgery has exposed the problem of gall stone diagnosis during the original admission. Oral cholecystography and intravenous cholangiography have been shown to be unreliable during an attack of acute pancreatitis because of transient non-opacification of the gall bladder.<sup>24-26</sup> The use of radionuclide biliary scanning during the acute phase of pancreatitis is controversial, some studies have shown it to be accurate<sup>6 27</sup> but others have doubted its reliability to differentiate biliary from non-biliary pancreatitis.<sup>17 28 29</sup> Early ultrasonography has been shown to be accurate in detecting the presence or absence of gall stones, but suffers from frequent failure to identify the gall bladder.<sup>4 30</sup>

McMahon and Pickford have proposed biochemical analysis as a method of predicting gall stones performed within 48 hours of admission in patients with acute pancreatitis.<sup>5</sup> The results of a West German study, however, showed a very poor relationship between biochemical analysis and the biliary status of the patient.<sup>29</sup> McKay and colleagues have gone as far as stating with regard to

biochemical analysis 'that any practical value of differentiation is doubtful'.<sup>4</sup>

In the present study ultrasonography was found to be superior to oral cholecystography in detecting gall stones. As many series have used oral cholecystography as the main method of detecting gall stones after acute pancreatitis it is possible that a significant group of patients who might benefit from surgery may be incorrectly classified as idiopathic. Despite the use of both ultrasonography and oral cholecystography gall stones were not detected in nine out of 70 patients who had not already been treated in hospital. A greater accuracy for these investigations have been reported<sup>32-34</sup> but these studies were not carried out exclusively in patients with acute pancreatitis. It is probably the tendency for many patients with biliary pancreatitis to have small gall stones which explains the lower detection rate.<sup>7 8</sup>

Endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography provide the clearest view of the biliary tree but are impractical as routine diagnostic tests. For the purpose of this study, however, all patients with normal ultrasonography and oral cholecystography were requested to undergo ERCP. A further seven patients were thus shown to have gall stones, two of whom had a history of alcoholism. There were two false negative ERCP investigations, both patients having the presence of gall stones shown at laparotomy.

The use of biochemical tests in this study (alkaline phosphatase, alanine transaminase and bilirubin) correctly predicted 73% of the patients with gall stones with a specificity of 94%. Six of the seven patients with gall stones revealed by ERCP were predicted by biochemical analysis. Only three patients had a false prediction of gall stones on the basis of these three factors. The additional use of age and sex as diagnostic factors increased the sensitivity of predicting gall stones. Thus eight of the nine patients with gall stones who had a normal ultrasonography and oral cholecystography were predicted by these five factors. This was, however, at the expense of specificity and nine patients had a false prediction.

Unlike the recent reports by Blamey *et al*<sup>17 35</sup> we found no useful application for the serum amylase in predicting gall stones. Also, in the same studies these authors rejected the use of bilirubin. This may reflect differences in the patient population, but it is also possible that a more rigorous process of investigation may have revealed further patients with gall stones and altered the basis of their conclusions.

In this study the use of intensive diagnostic

methods resulted in an idiopathic group of 9% compared with other recent British series of approximately 30%.<sup>36-38</sup> The idiopathic rate reported from Glasgow is much lower (13%) but this figure may be influenced by the very high proportion of patients with alcohol induced pancreatitis.<sup>16 39</sup> Within our small idiopathic group, ERCP showed pancreas divisum in two patients, an incidence of 18.2%. Gregg has suggested this as a cause for recurrent pancreatitis in some patients.<sup>40</sup> The finding that pancreas divisum was present in only 2.8% of the 1092 who underwent ERCP during the study period gives some support to this theory. In all ERCP revealed pathological changes in 15 of the 33 patients endoscoped (45%).

Endoscopic stone extraction was performed in 13 patients. There were three distinct indications for endoscopic stone extraction within this group. Firstly the established role of endoscopic sphincterotomy in patients with retained or recurrent calculi after cholecystectomy<sup>41</sup> was performed in three patients. Secondly, endoscopic stone extraction was carried out in six patients with the gall bladder *in situ* who were at high operative risk. The low incidence of subsequent gall bladder symptoms following this treatment has now been established.<sup>42 43</sup> Finally, in four patients with a relatively high operative risk endoscopic stone extraction was performed as a preliminary to cholecystectomy, and this approach has also been shown to be successful in a larger series.<sup>43</sup> A further therapeutic potential for endoscopic stone is stone extraction during the acute phase of pancreatitis.<sup>44</sup>

In conclusion ultrasonography was found to be more effective than oral cholecystography in detecting gall stones after an attack of acute pancreatitis but there was still a failure rate of 13%. Biochemical criteria offered the best means of selecting those patients with normal ultrasonography and oral cholecystography who should have an ERCP. This approach may reduce the currently high incidence of patients with 'idiopathic' pancreatitis and allow these patients to be considered for surgery before sustaining subsequent attacks of acute pancreatitis.

We would like to extend our gratitude to all the surgeons and physicians at the Leicester Royal Infirmary for allowing us to include their patients in this study.

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