Biochemical Identification of Patients with Gallstones Associated with Acute Pancreatitis on the Day of Admission to Hospital

death (N = 24), because of the development of a pancreatic collection (N = 32), or because of a persistent acute illness lasting more than 2 weeks (N = 22).[28] The present study was based upon data from 215 attacks that fulfilled two criteria. These were: 1) liver function tests (AST, alkaline phosphatase and bilirubin) were performed on the day of admission to hospital; and 2) subsequent investigations were considered adequate to confirm or refute the presence of gallstones.

An attack was classified as associated with gallstones if they were identified positively on radiologic or ultrasound examination or were found at laparotomy or autopsy. Conversely, an attack was classified as unassociated with gallstones if they were absent on at least one good quality contrast radiologic study, or if they could not be found on examination of the biliary tract at laparotomy or autopsy. A negative finding on ultrasonic scanning of the biliary tract was not considered sufficient evidence to classify an attack, neither was nonfilling of the gallbladder during a cholecystogram or cholangiogram.

Using these criteria, 132 attacks were associated with gallstones, and 83 attacks were unassociated with them (Table 1). An alternative etiologic factor to account for the pancreatitis was found in 41 of the attacks in the latter group, but in 42 attacks the etiology remains obscure (Table 2).

Plasma samples taken on the day of admission to hospital were sent to the routine clinical laboratory for measurement of AST (AST_0), alkaline phosphatase (AP_0), bilirubin (BR_0), and amylase (AM_0). A further plasma sample was taken for estimation of AST 48 hours after admission in 189 of the attacks (AST_{48}). Aspartate aminotransferase, alkaline phosphatase, and bilirubin were all measured using an automated analyser system (Vickers Instruments Ltd, York, UK). Aspartate aminotransferase activity was determined spectrophotometrically in a coupled reaction with malic dehydrogenase as detailed by Henry et al.[29] Alkaline phosphatase activity was determined by following the breakdown of phenyl phosphate using the method of King and Armstrong[30] as modified by Kind and King.[31] Total bilirubin was determined by the method of Jendrassik and Grof.[32] Amylase activity was measured chromogenically using a commercial reagent kit (Phadebas Amylase Test, Pharmacia Diagnostics, Uppsala, Sweden).[33]

In order to select a cut-off level of AST_0 that produced an optimal combination of sensitivity (proportion of test positives that were true-positives) and specificity (proportion of test negatives that were true-negatives) and was independent of the prevalence of gallstones in the population participating in the study, the predictive index (sensitivity multiplied by specificity) was calculated for a range of values of AST_0. The level of AST_0

TABLE 1. *Biliary Tract Investigations Accepted as Evidence of the Presence or Absence of Gallstones in 215 Attacks of Acute Pancreatitis*

Investigation	Associated with Gallstones (N = 132)	Unassociated with Gallstones (N = 83)
Laparotomy	76	8
Autopsy	8	1
Cholecystography and cholangiography*	30	74
Ultrasound alone	18	0

* ERCP was performed in six attacks associated with gallstones and 13 attacks not associated with gallstones.

that corresponded to the maximal calculated predictive index was then selected. Similarly, optimal cut-off levels of AP_0 and BR_0 were determined and the sensitivity, specificity, predictive value (proportion of attacks with gallstones that were test-positive) and diagnostic accuracy (proportion of attacks that were correctly diagnosed) of each of these three investigations were compared. The change in AST over the first 48 hours of admission was calculated, and its relationship to the presence of gallstones was assessed. The relationships between AST_0 and length of history, severity, age, and sex also were analyzed.

Statistical Analysis

Because the distribution of AST_0 was skewed heavily (skewness = 2.940, kurtosis = 12.906), it was plotted on a log_{10} scale, and statistical analysis, using Student's t-test, was performed on the log_{10} values that approximated to a normal distribution (skewness = 0.105, kurtosis = 0.776). Similar logarithmic transformations were applied to AP_0, BR_0, AM_0, and AST_{48} in order to obviate skewness. The normal approximation of Wilcoxon's two-sample rank-sum test (Z), corrected for continuity, and the chi square test incorporating Yate's correction for continuity, were used to test statistical significance for nonparametric data.

TABLE 2. *Etiologic Factors Identified in 173 Attacks of Acute Pancreatitis*

Etiologic Factors	N
Gallstones	132
Alcohol abuse	26
Post-ERCP	5
Hyperparathyroidism	3
Blind duodenal loop	2
Carcinoma of pancreas	1
Carcinoma of ampulla	1
Postoperative colectomy	1
Hypothermia	1
Drug-induced azothiaprine	1

FIG. 1. Plasma aspartate aminotransferase (AST) on the day of admission in 132 attacks of acute pancreatitis associated with gallstones and 83 attacks unassociated with gallstones.

Results

Figure 1 shows the distribution of AST_0 in the 215 attacks included in the study plotted on a logarithmic scale. The distributions of AP_0, BR_0, and AM_0, also plotted on logarithmic scales, are shown in Figures 2–4.

Levels of AST, bilirubin and alkaline phoshatase on the day of admission to hospital were significantly higher in attacks associated with gallstones than in those unassociated with them ($p < 0.01$ for AST_0, $p < 0.05$ for AP_0, and BR_0 using Student's t-test on the $\log_{10}$ values). Amylase levels were also higher in the gallstone-associated attacks, although the difference was not statisti-

cally significant ($0.05 < p < 0.1$ using Student's t-test on the $\log_{10}$ values). The optimal predictive index for the diagnosis of gallstones was obtained at a value of $AST_0 > 60$ IU/l (Fig. 5). Similarly, the predictive index was optimal for $AP_0 > 12$ K.A. units and for $BR_0 > 23$ μmol/l.

One hundred twenty-three attacks had an $AST_0 > 60$ IU/l, of which 111 (90.2%) were associated with gallstones. One hundred sixteen attacks had an $AP_0 > 12$ K.A. units/l of which 95 (81.9%) were associated with gallstones, and 94 attacks had a $BR_0 > 23$ μmol/l of which 76 (80.9%) were associated with gallstones. AST_0 was significantly more sensitive than either AP_0 ($X^2 = 4.97$, $p < 0.05$) or BR_0 ($X^2 = 21.19$, $p < 0.001$) for the prediction of gallstones (Table 3). It was also more

FIG. 2. Plasma alkaline phosphatase on the day of admission in 132 attacks of acute pancreatitis associated with gallstones and 83 attacks unassociated with gallstones.

Bilirubin (µmol/l)

FIG. 3. Plasma bilirubin on the day of admission in 132 attacks of acute pancreatitis associated with gallstones and 83 attacks unassociated with gallstones.

specific, but the differences were not statistically significant ($X^2 = 2.42$ and 1.02, respectively).

The effect of combining the individual liver function tests is shown in Table 4. Increasing the specificity by combination of AP_0 and BR_0 with AST_0 made little difference to the predictive value of a positive AST_0 test alone and did not improve the overall diagnostic accuracy for the patients in the study.

AST was re-estimated 48 hours after admission (AST_{48}) in 117 of the attacks associated with gallstones and in 72 attacks unassociated with stones. AST had fallen from its admission level in 106 (90.6%) of the attacks with stones, and in only 43 (36.8%) was it still greater than 60 IU/l. However, 32 of the 72 attacks unassociated with gallstones also showed a fall in AST over the first 48 hours of admission, including all those with $AST_0 > 60$ IU/l. Thus consideration of the decline in AST did not help in the diagnosis of gallstones.
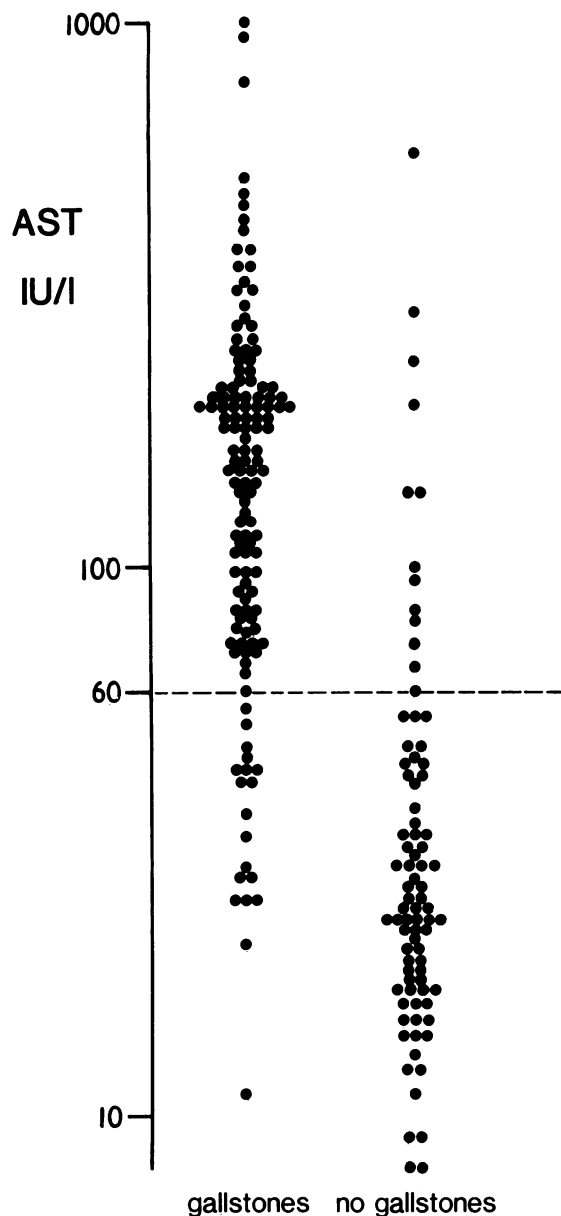
Amylase (IU/l)

FIG. 4. Plasma amylase on the day of admission in 132 attacks of acute pancreatitis associated with gallstones and 83 attacks unassociated with gallstones.

The delay between onset of symptoms and the time of admission to hospital was similar for attacks associated with gallstones (median 20 hours, range 2–144 hours)

FIG. 5. The relationship between cut-off level of aspartate aminotransferase (AST) on the day of admission to hospital and predictive index for the diagnosis of gallstones.

TABLE 3. *Sensitivity, Specificity, Predictive Value, and Diagnostic Accuracy of Aspartate Aminotransferase, Alkaline Phosphatase, and Bilirubin on Day of Admission to Hospital for Identification of Gallstones in 215 Attacks of Acute Pancreatitis*

Test	SS (%)*	SP (%)†	PV+ (%)‡	DA (%)§
$AST_0 > 60$ IU/l	84.1	85.5	90.2	84.7
$AP_0 > 12$ KA units/l	72.0	74.7	81.9	73.0
$BR_0 > 23$ umol/l	57.6	78.3	80.9	65.6
$AST_0 - AST_{48} > 0$ IU/l	83.8	56.9	76.0	73.5

* SS: sensitivity, † SP: specificity, ‡ PV+: predictive value of a positive result, and § DA: diagnostic accuracy.

Admission levels of aspartate aminotransferase (AST_0), alkaline phosphatase (AP_0), and bilirubin (BR_0). Level of aspartate aminotransferase at 48 hours (AST_{48}).

and attacks unassociated with gallstones (median 20, range 4–120 hours) ($Z = 0.187$, $p = 0.851$), and, despite the early fall in AST in the majority of the attacks, there was no significant correlation between the duration of symptoms and the level of AST_0 either for patients with gallstones ($r = 0.084$), for patients with another etiologic factor to account for their pancreatitis ($r = 0.197$) or for patients without identifiable etiologic factors ($r = 0.010$).

Forty-six (21.4%) of the 215 attacks were classified as severe. Fourteen died, 21 developed a pancreatic collection, and 11 had a prolonged acute illness. Twenty-nine (63%) were associated with gallstones. Twenty-three (50%) of the severe attacks had an $AST_0 > 60$ IU/l. Only one of the 17 severe attacks which were not associated with gallstones had an $AST_0 > 60$ IU/l, and none had an $AST_0 > 200$ IU/l. There was no evidence that a very high admission level of AST indicated a severe attack since only two (4.3%) of the severe attacks had an $AST_0 > 400$ IU/l compared with six (3.6%) of the 169 mild attacks.

There was a significant correlation between admission AST and the age of the patient ($r = 0.1505$, $p < 0.05$)

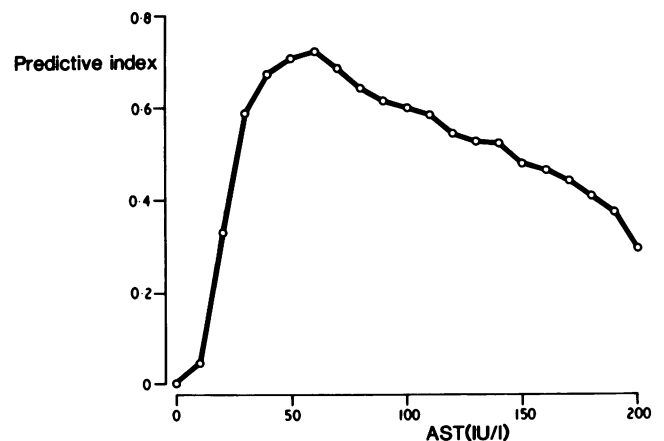TABLE 4. *Sensitivity, specificity, predictive value, and diagnostic accuracy of aspartate aminotransferase on day of admission to hospital, in combination with alkaline phosphatase and bilirubin on the day of admission, and with aspartate aminotransferase 48 hours after admission for the diagnosis of gallstones in 215 attacks of acute pancreatitis**

Test combination	SS (%)†	SP (%)‡	PV+ (%)§	DA (%)‖
$AST_0 > 60$ IU/l and $AP_0 > 12$ KA units/l	66.7	90.4	91.7	75.8
$AST_0 > 60$ IU/l and $BR_0 > 23$ umol/l	53.0	91.6	90.9	67.9
$AST_0 > 60$ IU/l and $AST_0 - AST_{48} > 0$ IU/l	78.6	88.9	92.0	82.5

* A test combination is considered positive only when both individual tests are positive.

† SS: sensitivity, ‡ SP: specificity, § PV+: predictive value of a positive result, and ‖ DA: diagnostic accuracy.

Admission levels of aspartate aminotransferase (AST_0), alkaline phosphatase (AP_0), and bilirubin (BR_0). Level of aspartate aminotransferase at 48 hours (AST_{48}).

FIG. 6. Scattergram of aspartate aminotransferase (AST) on the day of admission to hospital and age for patients with gallstones (circles), patients with other etiological factors (squares) and patients without identifiable etiological factors (triangles).

(Fig. 6). The mean age of the patients in the 132 attacks associated with gallstones (mean = 61.0, SD = 14.7 years) was similar to that of the 42 patients of unknown etiology (mean = 62.1, SD = 17.0 years, t = 0.369). However, the 41 patients who had another etiologic factor to account for their pancreatitis were significantly younger than those with gallstones (mean = 48.8, SD = 17.4 years, t = 4.43, p < 0.001). When etiology was taken into account, there was no significant correlation between age and AST_0 (r = 0.0614 for patients with gallstones; r = 0.0689 for patients with other known etiologic associations; r = 0.1937 for patients with unknown etiology).

AST_0 was significantly higher in women than in men (t = 3.299 after $\log_{10}$ transformation, p < 0.01). The sex ratio for attacks associated with gallstones (45 men: 87 women) was similar to that for attacks of unknown etiology (19 men: 23 women, $X^2 = 1.26$) but was significantly different for attacks associated with another known etiologic association (30 men: 11 women, $X^2 = 17.90$, p < 0.001). When etiology was taken into account, there was no significant difference in AST_0 between women and men (t = 0.605 for patients with gallstones; t = 0.542 for patients with other known etiology; t = 1.225 for patients with unknown etiology).

Discussion

Several hypotheses have been advanced to explain the association between acute pancreatitis and gallstones,[34] but there is accumulating evidence that the majority of attacks are precipitated by transient obstruction of the ampulla of Vater by a migrating gallstone.[35,36] Acosta found gallstones impacted at the ampulla in 75% of patients who underwent surgical exploration within 48 hours of the onset of symptoms, but in only 25% of patients who underwent operation 4 to 13 days after

onset.[37] Stone[12] reported common bile duct stones in 75% of patients subjected to operation within 72 hours of admission, which contrasts with the 15–30% incidence in patients operated on at a later stage during the acute admission[2,7,8] and the 10–28% incidence in those undergoing elective cholecystectomy during a subsequent hospital admission.[8,12,34]

Transient ampullary obstruction causing a rapid rise in bile duct pressure and consequent liver cell damage is the most probable explanation for the early and short-lived elevation of AST, which we observed in the majority of the patients with gallstone pancreatitis. Obstructive jaundice usually is characterized by a modest rise in AST compared with the elevation in alkaline phosphatase.[38,39] However, high values have been observed in very early obstruction of the biliary tract,[40] and marked rises in patients with acute cholecystitis also have been reported.[41] Increased plasma transaminase activity is a sensitive indicator of liver cell damage, and early elevation is usual in diseases that produce hepatocellular injury.[42] In contrast, liver cell necrosis does not release large amounts of alkaline phosphatase into the circulation, and the high levels associated with cholestasis are probably due to a combination of regurgitation via the sinusoids and increased synthesis in the bile canaliculi.[43] Thus alkaline phosphatase rises in parallel with bilirubin, and a significant elevation may not occur if the bile duct is obstructed only transiently. A marked elevation of alkaline phosphatase and bilirubin in patients with acute gallstones pancreatitis may be a sign of prolonged ampullary obstruction. The rapidity of the changes in AST levels may explain the failure to detect markedly raised levels of transaminase in the majority of patients with obstructive jaundice. The speed with which changes in AST can occur was demonstrated in a 63-year-old women with gallstones who developed acute pancreatitis in hospital while undergoing treatment for a chest infection (Fig. 7). Aspartate aminotransferase, which was within the normal range 12 hours previously, had risen to 210 IU/l two hours after the onset of abdominal pain and hyperamylasaemia but fell to 56 IU/l during the next 12 hours. The rapidity with which transaminase can change may be the explanation for some of the false-negative results. Although no correlation could be found between the duration of symptoms and the level of AST_0, it is possible that in patients with gallstones, but an $AST_0 < 60$ IU/l, the stone already has migrated into the duodenum with relief of choledochal hypertension. If this hypothesis is correct, determination of AST may be particularly useful for the identification of patients who might benefit from surgical or endoscopic disimpaction.

Of greater concern, however, were the 12 attacks in which AST_0 was elevated markedly but which were
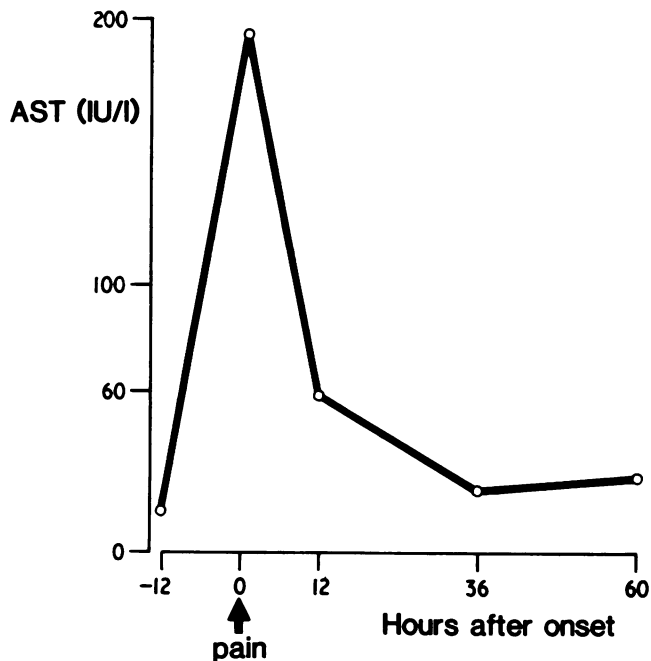

FIG. 7. Changes in plasma aspartate aminotransferase (AST) over a 3-day period in a patient who developed gallstone pancreatitis while in the hospital.

without evidence of stones on subsequent investigation. Only three had a recognized alternative etiologic factor to account for their pancreatitis. One had a carcinoma at the ampulla; another developed pancreatitis following ERCP examination; and in the third, the only attack of alcoholic pancreatitis with $AST_0 > 60$ IU/l, pancreatitis was diagnosed only at laparotomy during which the common bile duct was palpated in order to exclude choledocholithiasis. The plasma sample for the present study was collected after surgery. Thus all three had factors that might have caused temporary bile duct obstruction. Of the remaining nine false-positives, two previously had undergone cholecystectomy for gallstones, and three others gave a history suggestive of biliary disease. The age and sex distributions for attacks without identifiable etiologic factors were similar to those for attacks associated with gallstones, and we are uncertain of the reliability of negative biliary tract radiology since it is well known that gallstones can be elusive in patients with acute pancreatitis.[44] We recently have seived the faeces of 81 patients with acute pancreatitis and have retrieved stones from 11 who had negative radiologic investigations. This suggests that the incidence of gallstones in our study may be higher than suspected.

The data suggest that early prediction of gallstones using AST_0 compares favorably with alternative investigations. McKay et al[19] evaluated early grey-scale ultrasound scanning in acute pancreatitis and found that, while the technique had a high specificity, the initial scan

failed to outline the gallbladder in over 30% of patients. The principal cause of failure was the presence of intestinal gas, but a contracted gallbladder containing stones may be difficult to demonstrate,[45] and common bile duct stones are missed frequently.[18] The role of radionuclide biliary imaging is more controversial. Glazer[20] reported 100% diagnostic accuracy for the recognition of stones in patients with acute pancreatitis when a $^{99}Tc^m$ HIDA scan was performed within 3 days of admission, but a more recent report has contradicted this finding, concluding that hepatobiliary isotope scanning was of no clinical value during the acute phase of pancreatitis.[21]

Other groups[46,47] have found that analysis of multiple clinical and laboratory criteria (including AST or ALT) on admission allows accurate diagnosis of gallstone pancreatitis. Thompson,[46] who included age as one of the predictive criteria, suggested that gallstones were more common in younger patients. This is at variance with our results, which suggest that AST_0 shows a positive correlation with age only because gallstones are found more frequently in older patients. Similarly the sex difference in AST_0, which we recorded, resulted from the increased incidence of gallstones in female patients. Blamey[47] measured AST during the first 48 hours of admission but found that, while it was a significant factor in separating gallstone and alcohol-associated acute pancreatitis, a multiple factor approach was necessary to predict cholelithiasis accurately. We have shown that AST is accurate provided that it is measured on the day of admission.

AST has been incorporated in systems of prognostic criteria used to predict the severity of an attack of acute pancreatitis.[48,49] Ranson[3] suggested that a higher cut-off level (500 Sigma-Frankel units/100 ml) was more appropriate as a prognostic criterion for attacks of acute pancreatitis, which are associated with gallstones than the 250 Sigma-Frankel units/100 ml level used in his original prognostic system, which had been based upon predominantly alcoholic patients. Imrie[7] also has modified his original prognostic criteria for use in patients with gallstones, increasing the cut-off level of AST from 200 to 400 IU/l. We were unable to demonstrate an association between AST_0 and severity. Only two of 29 attacks of severe pancreatitis associated with gallstones had an $AST_0 > 400$ IU/l while, for the 17 severe attacks without gallstones, none had an $AST_0 > 200$ IU/l. It is possible that the association between AST and severity observed by Ranson in his original study reflected the 8% mortality rate that he recorded in patients with gallstones compared with the 3% mortality rate in his alcoholic patients.

Wettendorff and his colleagues have confirmed the value of transaminase elevation as evidence of gallstones in patients with acute pancreatitis,[26,27] but others have found it to be of little predictive value.[24,25] While the timing of blood samples may explain this discrepancy in part, an account also must be taken of the change in predictive value with change in the prevalence of the common etiologic factors in different populations.[50] For example, if the proportion of attacks associated with gallstones in our study had been only 20% (c.f., 61%), then the predictive value of AST_0 would have been reduced from 90% to approximately 60%. Measurement of AST on admission may be less helpful in centers with predominantly alcoholic patients, but may be the most useful early investigation in regions where the majority of attacks are associated with gallstones.

In summary, elevation of AST above 60 IU/l on the day of admission to hospital provides a useful method for the identification of gallstones in patients with acute pancreatitis, enabling rapid selection of patients who might be considered for urgent approaches to the ampulla. The comparative value of AST and imaging techniques is unclear at present but is the subject of a prospective study.

Acknowledgments

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