Effect of cimetidine on enzyme inactivation, bile acid precipitation, and lipid solubilisation in pancreatic steatorrhoea due to cystic fibrosis

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SUMMARY In pancreatic steatorrhoea, both pH-dependent bile acid precipitation and enzyme inactivation may limit the efficacy of pancreatic enzyme supplements and both may be preventable by addition of cimetidine. To separate these effects we compared postprandial jejunal aspirate from eight adults with steatorrhoea due to cystic fibrosis on three randomised treatment regimens (pancreatin, cimetidine, and both together). We also compared the results with those of previous studies of patients on no treatment, and of healthy subjects. On pancreatin 60% of the test meal entered the jejunum at pH<5 compared with 17% in health. Lipase concentration and lipolysis increased over the values on no treatment (14.2 vs 4.4 U/l, p<0.01; 16% vs 11%, p<0.02) but bile acid precipitation was not reduced (38% vs 27%, NS), and aqueous-phase lipid concentration decreased (6.7 vs 8.6 mM/l, p<0.05). On cimetidine, bile acid precipitation fell (19% vs 38%, p<0.05); although lipase concentration and lipolysis were lower than on pancreatin (4.8 U/l vs 14.2 U/l, p<0.01; 9% vs 16%, p<0.01) lipid solubilisation increased (8.8 vs 6.7 mM/l, p<0.05). On the combination, there was a marked improvement (p<0.02) in lipid solubilisation (18.3 mM/l), reflecting the improvement both in lipase (38.4 U/l) and lipolysis (24%), and in bile acid precipitation (5.6%). We conclude that the efficacy of pancreatin is limited by pH-dependent bile acid precipitation in addition to enzyme inactivation. The action of cimetidine in improving the efficacy of pancreatin depends on prevention of both these effects.

Steatorrhoea caused by pancreatic exocrine insufficiency is an unpleasant symptom, and often also leads to severe malnutrition and malabsorption of fat-soluble vitamins,1 essential fatty acids2 and bile acids.3 4 Pancreatic steatorrhoea can pose a difficult therapeutic problem because treatment with pancreatic enzyme supplements (pancreatin) often fails to restore fat absorption to normal.5 It is a particular problem in patients with pancreatic insufficiency due to cystic fibrosis6 who may take 10 or more tablets per meal without relief of their steatorrhoea. Such high doses can lead to hyperuricaemia7 and renal damage8 attributable to the high purine content of pancreatin.

The failure of pancreatin to correct fat malabsorption is usually attributed to inactivation of its enzyme content in the stomach, as the three major pancreatic enzymes – lipase, trypsin and amylase – are irreversibly inactivated by acid.9 In patients with pancreatic steatorrhoea about 90% of the enzyme content of pancreatin is inactivated in the stomach, so that even with a large dose duodenal enzyme activities do not achieve 10% of the normal concentrations10 the minimum required for normal digestion.11 Enteric coated tablets12 and microspheres,13 designed to protect the enzymes during their passage through the stomach, do not abolish steatorrhoea, although they reduce it in some patients. This suggests that mechanisms other than gastric inactivation must contribute to the failure of pancreatin therapy.

In pancreatic insufficiency, bicarbonate as well as enzyme secretion is reduced.14 We have recently shown, in a study of 12 untreated adults with steatorrhoea due to cystic fibrosis,15 that this leads to postprandial jejunal hyperacidity: 40% of a test meal entered the jejunum at a pH below 5, at which pH bile acids precipitated out of aqueous
solution leading to a reduction in aqueous phase bile acid concentration. Lipid solubilisation, already reduced because of lipase deficiency, was further reduced in samples of pH<5 because of this reduction in aqueous phase bile acid concentration. Treatment with pancreatin might be expected to improve lipolysis but not jejunal hyperacidity;10 pH-dependent bile acid precipitation might therefore continue to limit lipid solubilisation. Protonation of fatty acids at pH<6 increases their partitioning into the oil phase16 and might also limit lipid solubilisation during treatment.

Enteric coating of pancreatin probably fails because it delays dissolution of the tablet in the hyperacidic jejunum17 and because it cannot prevent bile acid precipitation and fatty acid partitioning. Raising the postprandial pH of the gastric and duodenal contents, on the other hand, might improve the efficacy of pancreatin by preventing both intragastric enzyme inactivation, and intrajejunal bile acid precipitation and fatty acid partitioning.

The aim of our study was therefore to determine whether gastroduodenal neutralisation would prevent these three pH-dependent effects, and which would contribute most to any improvement in lipid solubilisation. We studied adult cystic fibrosis patients, who tend to have particularly resistant steatorrhoea,9 perhaps because pancreatic bicarbonate secretion is even lower18 and gastric acid secretion often higher19 than in other forms of chronic pancreatitis. We again used the technique of acid inactivation to arrest lipolysis in jejunal aspirate which we have shown to be simpler and more accurate than the conventional heat inactivation technique.20

Methods

Subjects

Eight adult patients with steatorrhoea due to cystic fibrosis were studied, four male and four female, average age 21 years (range 13–29 years), average weight 51 kg (range 45–61 kg). These subjects were selected from the 12 already studied on no treatment,15 on the basis that they were fit and willing to undergo further intubation. They were not selected for the severity of their steatorrhoea. None had clinical evidence of liver disease. All subjects gave informed consent according to the declaration of Helsinki. Women with regular periods were studied within 10 days of menstruation.

Design of Experiment

Postprandial jejunal aspiration was carried out on three different treatment regimens: (i) pancreatin alone (P); (ii) cimetidine alone (C); (iii) pancreatin + cimetidine (P+C). Each regimen was given on a separate occasion separated by at least two weeks, in random order according to a Latin square design. In three subjects, who lived far from the hospital, the studies had to be done on three successive days; in order to avoid depleting their bile acid pool, all aspirate not required for analysis was returned to the patient at the end of the study, so that after the second study a maximum of only 180 ml of aspirate (1.8 mM of bile acid) had been removed for analysis. This represents less than 10% of the bile acid pool size measured in a group of untreated children with cystic fibrosis in whom bile acid pool size was known to be markedly reduced.21 A constant diversion of at least 20% of the enterohepatic recirculation of the bile acid pool is required to reduce bile acid secretion.22

Medication and Meal

Pancreatin was given with the test meal as seven Pancrex V capsules (specially formulated to be equipotent to Pancrex V Forte tablets – Paines and Byrne Ltd) containing 39 000 BP units of lipase in total. Cimetidine was given in a total dose of 400 mg in aqueous solution; in four patients it was administered as an intravenous injection of 100 mg immediately before the test meal followed by an intravenous infusion of 100 mg/h for the three hours of the test. In the other four patients poor veins prevented venepuncture and the entire dose was instilled via the aspiration tube into the jejunum 40 minutes before the test meal. There was no difference in gastric or duodenal pH between these two groups. The Lundh-type test meal (40 g dextrose, 15 g skimmed milk powder, 2.5 g polyethylene glycol 4000 (PEG) dissolved in 230 ml water and thoroughly mixed with 18 g corn oil) was drunk recumbent within four minutes. On the cimetidine regimens, 2 g sodium bicarbonate was added to the test meal (pH 7.6) so as to be certain of maintaining duodenal pH above 6, because in an early study of two patients with alcoholic pancreatitis only the addition of alkali to metiamide achieved duodenal neutralisation.23 On the pancreatin alone regimen, no alkali was added to the meal (pH 6.6) and cimetidine placebo solution was infused or instilled as appropriate.

Intubation and Aspiration Procedures

These have been described and referenced previously20 and are given here in abbreviated form. After an overnight fast a double lumen tube was passed to the duodenojejunal flexure under fluoroscopic control, and the patient drank the test meal after appropriate medication. As much jejunal content as
possible was collected continuously by syphoning and syringe aspiration into ice cooled 10 ml measuring cylinders. The pH of each 3 ml sample was measured immediately with a glass electrode. Half of each sample was adjusted to pH 3 immediately with acid to inactivate lipase, and the treated and untreated samples pooled separately according to their measured pH (<5, 5–6, >6) and time (1st, 2nd, 3rd hour) as described previously (Fig. 1).

In the first four subjects a triple lumen tube was used; the third lumen ended in the gastric antrum and allowed postprandial gastric samples to be aspirated, their pH measured, and returned to the stomach every 15 minutes. Gastric pH remained above 7 throughout the test in four patients on each cimetidine regimen, compared with below 2 on pancreatin alone. Checking gastric pH therefore appeared to be unnecessary; as it added to discomfort the third lumen was not used in the last four patients.

**Laboratory procedures** (as described and referenced previously)

Each treated pool was analysed for total saponifiable lipid and fatty acid concentration after restoration to its original pH, and each untreated pool for bile acid, trypsin, lipase and PEG concentrations. All pools were ultracentrifuged overnight at 100 000 g, and each aqueous phase removed in its entirety, mixed and analysed for lipid and fatty acid (treated pools) and bile acid (untreated pools).

**Mathematical analysis** (as described previously)

In each subject the pH pools were compared after mathematically pooling the separate hourly pools for each pH, taking account of the volume of each pool and converting pH values to hydrogen-ion concentrations before pooling. The three hourly pools were compared after similarly pooling the separate pH pools for each hour. The overall mean was calculated by pooling all the separate pools. Statistical comparison of the pools within treatments and of the overall means between treatments was performed by the Wilcoxon's signed rank test for paired samples. Differences significant only at 10% (0.05<p<0.10, two-tailed test) have been indicated in the results in order to avoid the possibility of a type II error (n=8) where differences were large. Data are expressed as mean±SEM.

**Results**

The results on pancreatin alone were compared with those of the same eight patients on no treatment, taken from our previous study of 12 cystic fibrosis patients on no treatment; although the studies on no treatment were undertaken up to two years earlier, and are therefore not randomised in order, the comparison is still of interest. Because the untreated results quoted here are the means of eight rather than 12 subjects, they are similar but not identical to those already reported. The results on cimetidine alone and pancreatin plus cimetidine were compared with those on pancreatin alone as these three regimens were randomised in order. Results from our study of 14 healthy subjects have also been included where relevant.

**Comparison of pH pools on pancreatin alone** (Table 1)

**pH**

A mean of 49% of the PEG added to the meal was aspirated in total over the three hour test period on pancreatin. Of this, 60% was aspirated at pH<5, significantly more than at pH>6, and considerably
more than on no treatment (45% NS); a similar increase was observed for the proportion of lipid aspirated at pH<5 (Table 2). The proportions of lipid aspirated at each pH paralleled those of PEG, suggesting that the pH-effects described below applied equally to the aqueous and lipid portions of the meal. Polyethylene glycol concentrations did not vary significantly with pH, although the trend to increased values at low pH would suggest that significant reductions in concentrations of other substances at pH<5 were not because of differences in meal dilution.

Pancreatic enzymes

Activities of both trypsin and lipase increased with pH, showing the effect of enzyme inactivation at pH<5. For trypsin, the pH<5 value (2.9 IU/ml) exceeded 10% of the overall mean (18 IU/ml) in our healthy subjects20 and the pH>6 value (14.4 IU/ml) fell within our normal range (12–23 IU/ml). For lipase the pH<5 value (8.6 U/l) failed to achieve 10% of our normal mean (170 U/l) and the pH>6 value (44.9 U/l) was well below our normal range (100–240 U/l).

Lipid digestion

Total lipid concentrations did not vary significantly with pH. Total fatty acid concentrations and lipolysis increased with pH; the pH<5 values were similar to the overall means on no treatment (Table 2), but the pH>6 values were similar to the overall means in our healthy subjects (total fatty acid 8.2 mM/l and lipolysis 26% in health).

Bile acids

Total bile acid concentrations were similar to those on no treatment; similarly, half of the available bile acid was precipitated at pH<5 while the value for bile acid precipitation at pH>6 was not significantly different from zero. This resulted in a marked pH-gradient for aqueous phase bile acid concentration similar to that observed on no treatment.

Lipid solubilisation

Both aqueous phase lipid and fatty acid concentrations showed a marked increase with pH. The pH<5 value for fatty acid was similar to that on no treatment (1.1 vs 0.8 mM/l, NS), whereas the pH>6 value was considerably higher (8.1 vs 3.0 mM/l, p<0.05). The proportion of fatty acid in the aqueous phase also showed a marked pH-gradient similar to that on no treatment.

COMPARISON OF OVERALL MEANS ON EACH REGIMEN (Table 2)

Pancreatin alone

Significant concentrations of trypsin and lipase were detected on pancreatin, but only trypsin achieved 10% of the mean value in health. Nevertheless there was a small but significant increase in both lipolysis and total fatty acid concentration in comparison with no treatment. Pancreatin did not reduce bile acid precipitation or increase aqueous phase bile acid concentration. As a result, although aqueous phase fatty acid concentration rose significantly, aqueous phase lipid concentration did not; it was significantly lower on pancreatin than on no treatment.

Cimetidine alone

All the aspirate was at pH>6 on treatment with cimetidine. Trypsin was undetectable, as on no treatment, and lipase activities remained minimal. Lipolysis and total fatty acid concentrations were significantly lower than on pancreatin alone. Total bile acid concentration was similar to that on
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<th>Pancreatin</th>
<th>Sig P:C</th>
<th>Cimetidine</th>
<th>Sig C:P+C</th>
<th>Pancreatin + cimetidine</th>
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<td>Bile acid precipitation (%)</td>
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<td>Proportion fatty acid in aqueous phase (%)</td>
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* Results of the eight patients in the current study extracted from those of 12 patients previously described.15
Effect of cimetidine on enzyme inactivation, bile acid precipitation and lipid solubilisation

pancreatin alone, but bile acid precipitation was greatly reduced, resulting in an increase in aqueous phase bile acid concentration. Despite the reduced lipolysis, this improvement was associated with a small but significant increase in aqueous phase lipid concentration and in the proportion of fatty acid in the aqueous phase.

Cimetidine plus pancreatin
All aspirate was at pH>6. Trypsin and lipase were markedly higher than on pancreatin alone, the trypsin concentration being almost 50%, and lipase 25%, of the normal mean. Lipolysis increased markedly compared with pancreatin alone, achieving a concentration similar to that observed in our healthy subjects (26%). Total fatty acid concentration increased even further (14-8 vs 8-2 mM/l in health) attributable to higher total lipid concentration (67-1 vs 36-9 mM/l in health). There was a further, but not significant, reduction in bile acid precipitation almost to zero, but no associated increase in aqueous phase bile acid concentration. Aqueous phase lipid and fatty acid concentrations increased markedly to values more than twice those on pancreatin alone, and above those achieved in health (lipid 18-3 vs 9-6 mM/l in health, fatty acid 12-2 vs 4-8 mM/l), again attributable to supranormal total lipid and fatty acid concentrations.

Comparison of hourly pools (Tables 3 and 4)
On both cimetidine regimens the proportion of lipid aspirated in the third hour was significantly less than that aspirated in the first hour (Table 3) or than in the third hour on pancreatin or no treatment (Table 4). No such differences were observed for the aqueous portion of the meal. Although the study was not designed to measure the rate of gastric emptying, these findings suggest that treatment with cimetidine, with or without pancreatin, corrects the delay in gastric emptying of lipid suggested by our study of untreated cystic fibrosis subjects.15 This may explain the higher total lipid concentrations on both cimetidine regimens, particularly in the first hour (not shown).

Discussion

This study has shown the effects of gastroduodenal neutralisation on each of the three pH-dependent processes we suggested might limit the therapeutic response to pancreatin in cystic fibrosis: intragastric enzyme inactivation, and intraduodenal bile acid precipitation and fatty acid protonation. Duodenal neutralisation was achieved by the use of cimetidine 400 mg and sodium bicarbonate 2 g. The bicarbonate was probably superfluous, as on both cimetidine regimens jejunal pH remained above 7-0 and gastric pH above 6-0. In patients with chronic alcoholic pancreatitis, sodium bicarbonate 2-5 g alone did not control gastroduodenal pH, but cimetidine 300 mg did.24 From now on, therefore, we will refer to the effect of cimetidine rather than that of cimetidine plus bicarbonate. The results of our study can be analysed to show the contribution of each pH-dependent process separately.

The contribution of enzyme inactivation and its prevention is shown by the pancreatin alone and pancreatin + cimetidine regimens. Treatment with pancreatin alone resulted in small but significant increases in overall mean trypsin, lipase, lipolysis and total fatty acid concentration over no treatment (Table 2). These changes occurred in the pH>6 pools (Table 1), where enzyme activities on pancreatin alone were well above the 10% of the mean values in health shown to be necessary for normal absorption,11 and achieved a total fatty acid concentration and lipolysis similar to those in our healthy subjects.20 This suggests that acid mediated inactiva-

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<th>Table 3</th>
<th>Hourly meal recovery on each regimen – lipid and aqueous portions</th>
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<tr>
<td>Lipid recovery (% of total aspirated)</td>
<td>1st hour</td>
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<tr>
<td>No treatment</td>
<td>27±4</td>
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<tr>
<td>Pancreatin</td>
<td>31±5</td>
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<tr>
<td>Cimetidine</td>
<td>52±10</td>
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<tr>
<td>Pancreatin + cimetidine</td>
<td>51±8</td>
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PEG recovery (% of total aspirated)

| No treatment | 46±9 | 43±7 | 20±6 | NS |
| Pancreatin | 40±9 | 38±8 | 22±5 | NS |
| Cimetidine | 40±8 | 42±6 | 18±6 | NS |
| Pancreatin + cimetidine | 33±8 | 38±5 | 28±7 | NS |

* By Friedmann analysis of variance by ranks and Wilcoxon's critical range test.

<table>
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<th>Table 4</th>
<th>Lipid recovery in each hour – regimens compared</th>
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<tr>
<td>3rd hour</td>
<td>Cimetidine (10%)</td>
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<td>No treatment (43%)</td>
<td>p&lt;0-01</td>
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<td>Pancreatine (29%)</td>
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<tr>
<td>1st hour</td>
<td>Cimetidine (52%)</td>
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<tr>
<td>No treatment (27%)</td>
<td>NS</td>
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<td>Pancreatin (31%)</td>
<td>p&lt;0-05</td>
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tion in the stomach, and in duodenal samples of pH<5 which constituted 60% of the meal, was responsible for the inadequate mean enzyme activities and lipolysis on pancreatin alone. It also indicates that seven PancreX V capsules (a modest dose in our patients) would be sufficient to restore normal digestion were it not for this inactivation. The addition of cimetidine, by abolishing the pH<5 and pH 5–6 samples, prevented this inactivation and led to a major improvement in enzyme activities to levels well above the minimum level required for normal fat absorption. It also achieved a level of lipolysis and total fatty acid concentration commensurate with our healthy subjects.

The Mayo Clinic study of patients with steatorrhea caused by chronic alcoholic pancreatitis (reported since we started this study) also showed an improvement in enzyme activities with addition of cimetidine to pancreatin. The authors attributed this improvement to prevention of intragastric inactivation, and also to inhibition of gastric secretion and thus reduced dilution of intestinal contents. In our study, the similarity in lipase and trypsin activities, and in PEG concentration, between the cimetidine + pancreatin regimen (Table 2) and the pH>6 pool on pancreatin alone (Table 1), suggests that it was only the prevention of inactivation that was responsible for this effect of cimetidine.

The effect of bile acid precipitation and its prevention is shown by the pancreatin alone and cimetidine alone regimens. On pancreatin alone overall bile acid precipitation and aqueous phase bile acid concentration were no better than on no treatment, as 60% of the meal was at pH<5 (Table 2). The pH-gradient for aqueous phase lipid and fatty acid concentration, and for the proportion of fatty acid in the aqueous phase, confirm that bile acid precipitation at pH<5 continues to limit lipid solubilisation at this pH (Table 1), just as it does in untreated patients. This explains the failure of pancreatin alone to improve lipid solubilisation despite its effect in increasing lipolysis. Cimetidine alone, on the other hand, halved bile acid precipitation and increased aqueous phase bile acid concentration. This led to a small but significant increase in aqueous phase lipid concentration, despite lipase activity and lipolysis significantly lower than on pancreatin alone (Table 2). Furthermore, at pH>6 on pancreatin alone, bile acid precipitation was minimal and, with the improved lipolysis, aqueous phase lipid and fatty acid concentrations approached those on the combined regimen.

The cimetidine alone results thus separate the effect of preventing bile acid precipitation from that of preventing enzyme inactivation; both prove to be important in improving lipid solubilisation. The Mayo Clinic studies also showed that cimetidine prevents both processes, but were unable to show the separate contributions of each to improved lipid solubilisation. This distinction is important: while appropriate formulation of pancreatin preparations might avoid inactivation of their enzyme content, only postprandial duodenal neutralisation can prevent bile acid precipitation and fatty acid partitioning. Furthermore, the use of heat to inactivate lipase in the Mayo Clinic studies increases lipolysis and might therefore have artefactually exaggerated the differences between treatments.

The effect of fatty acid partitioning is shown by the pancreatin alone regimen. To separate fatty acid partitioning from bile acid precipitation in vivo is problematic because a reduction in pH affects both simultaneously. We used the mathematical approach explained in our study of lipid solubilisation in health to reveal a significant linear relationship between the proportion of fatty acid in the aqueous phase and bile acid precipitation (Fig. 2). The intercept of the regression line indicates that in the absence of bile acid precipitation, 90% of the fatty acid would be in the aqueous phase – a figure not significantly different from 100%. In the presence of bile acid precipitation only 65% of the total fatty acid available was actually solubilised (Table 2). Most of this deficit in fatty acid solubilisation could therefore be attributed to bile acid precipitation and very little to fatty acid partitioning.

Treatment with pancreatin + cimetidine prevented both enzyme inactivation and bile acid precipitation, and greatly increased aqueous phase lipid and fatty acid concentrations to normal levels. The increase seems more than would be expected from the individual effects of enzyme inactivation and bile acid precipitation. Part of this ‘synergistic’ effect may be explained by the further fall in bile acid precipitation on addition of pancreatin to cimetidine (Table 2), to virtually zero. This may reflect reduced binding of bile acid to protein (appearing as ‘precipitation’ above pH 6) due to improved proteolysis.

Our results show events at the duodenojejunal flexure. In health, pH rises to neutrality further down the intestine. Bile acid precipitation (but not enzyme inactivation) is reversible in vitro by neutralisation of hyperacidic postprandial aspirate but it is not known if this would occur in vivo if hyperacidity were reversed. Postprandial ileal pH has not been investigated in cystic fibrosis, but is thought unlikely to rise as the abnormality in pancreatic bicarbonate secretion may well affect the small intestine. Patients with cystic fibrosis sometimes pass intact enteric coated pancreatin tablets in the
Effect of cimetidine on enzyme inactivation, bile acid precipitation and lipid solubilisation

stool, suggesting hyperacidity of the whole gut.

The results of our intraluminal study concur with those of several fat balance studies showing marked improvement in fat absorption with addition of cimetidine to pancreatin. Addition of an antacid does not achieve a comparable effect unless an unacceptably high dose is used. As cimetidine's effect depends in part on preventing bile acid precipitation, its use is likely to prove worthwhile only in patients with jejunal hyperacidity and severe steatorrhoea – the patients likely to respond least well to enteric coated pancreatin.

This study was presented at the British Society of Gastroenterology Spring Meeting 1981 (Abstract Gut 1981; 22: A431).

We would like to thank the Cystic Fibrosis Trust for generously financing this project, Paines and Byrne Ltd for additional financial assistance and for the supply of specially formulated Pancrex V capsules, and Smith Kline and French Ltd for the supply of cimetidine and placebo. We are most grateful to Sister M E Gannon for nursing assistance, to Mr N James for technical assistance, and to Dr M R

Fig. 2. Relationship between fatty acid solubilisation (adjusted for variation between individuals by analysis of covariance) and bile acid precipitation ($F = 23.7$, $p<0.01$; intercept $90.2 \pm 13.6\%$).
Boudry, PhD, for assistance in the computerised analysis of results.

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34. Boyle BJ, Long WB, Badolati WR, Widzer SJ, Huang N. Effect of cimetidine and pancreatic enzymes on serum and faecal bile acids and fat absorption in cystic
Effect of cimetidine on enzyme inactivation, bile acid precipitation and lipid solubilisation

