

Effect of intrajejunal acidity on aqueous phase bile acid and lipid concentrations in pancreatic steatorrhoea due to cystic fibrosis

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SUMMARY We have investigated whether jejunal hyperacidity leads to bile acid precipitation and thus limits lipid solubilisation in patients with pancreatic steatorrhoea. Jejunal contents from 12 adults with steatorrhoea due to cystic fibrosis were aspirated for three hours after a liquid test meal, and pooled according to their pH. Thirty eight per cent of the total aspirate was collected at $\text{pH} < 5$ in cystic fibrosis, compared with 18% in healthy controls ($p < 0.05$). Forty six per cent of the bile acids were precipitated at $\text{pH} < 5$, compared with 15% at $\text{pH} > 6$ ($p < 0.01$), leading to reduced aqueous phase bile acid concentration at low pH (4.7 mmol/l at $\text{pH} < 5$ vs 12.5 mmol/l at $\text{pH} > 6$, $p < 0.01$). Aqueous phase lipid concentrations were reduced at low pH (5.6 mmol/l at $\text{pH} < 5$ vs 10.2 mmol/l at $\text{pH} > 6$, $p < 0.01$). Lipolysis and total fatty acid concentrations were greatly reduced and did not vary with pH. We therefore conclude that jejunal hyperacidity leads to bile acid precipitation in pancreatic steatorrhoea due to cystic fibrosis, and imposes a further limitation on lipid solubilisation over that of lipase deficiency.

In patients with pancreatic exocrine insufficiency, steatorrhoea is usually attributed entirely to the reduction in pancreatic secretion of lipase. Pancreatic bicarbonate secretion is also reduced, and this might lead to a failure to neutralise the acid contents of the stomach on arrival in the duodenum,^{1,2} and thus to a reduction in the pH of postprandial jejunal contents. *In vitro* observations suggest that jejunal hyperacidity is likely to contribute to the pathogenesis of pancreatic steatorrhoea for three reasons; (i) glycine conjugated bile acids precipitate out of aqueous solution when the pH is reduced to below about 5,³ and hence may be unable to form micelles; (ii) fatty acids are protonated below pH 6 and partition out of micellar solution⁴; (iii) the three major pancreatic enzymes – lipase, trypsin and amylase – are progressively inactivated below pH 5⁵ and this is likely to affect any residual enzyme secretion in patients with pancreatic insufficiency. We have shown *in vivo* that all three of these phenomena occur even in health,

where only 17% of a meal was aspirated from the jejunum at pH below 5, and led to reduced lipid solubilisation at this pH.⁶

A much larger portion of the meal is likely to be affected in patients with pancreatic insufficiency, as bicarbonate secretion is also reduced. The importance of jejunal hyperacidity in limiting lipid solubilisation has been shown in a patient with Zollinger-Ellison syndrome.⁷ This problem has important therapeutic implications: pancreatin supplements protected from gastric inactivation by enteric coating fail to abolish steatorrhoea, but addition of cimetidine achieves almost complete abolition of steatorrhoea.⁸ It is not known whether this is achieved by prevention of enzyme inactivation, bile acid precipitation or fatty acid partitioning.

We chose to study a group of adult patients with pancreatic exocrine insufficiency due to cystic fibrosis, rather than alcoholic pancreatitis in which steatorrhoea is usually less severe. Pancreatic exocrine function is deficient in 95% of adult patients with cystic fibrosis⁹ and the resultant severe steatorrhoea often causes a therapeutic problem

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because it is so resistant to pancreatin therapy.¹⁰ In cystic fibrosis, gastric acid secretion may be increased,¹¹ while in chronic alcoholic pancreatitis it is often reduced.¹² Pancreatic bicarbonate secretion is usually even lower in cystic fibrosis than in other forms of chronic pancreatitis,¹³ so that a much larger proportion of a meal may enter the jejunum at pH<5 in cystic fibrosis than in alcoholic pancreatitis. A reduction in bile acid pool size has been reported in cystic fibrosis¹⁴ because of an increase in faecal bile acid loss^{15 16} equivalent to that reported in patients with ileal resection.¹⁷ It may lead to a further reduction in postprandial intraluminal bile acid concentration, as has been well documented in ileal resection.¹⁸

The aim of this study was to investigate whether a reduction in postprandial jejunal pH contributed a further limitation to lipid solubilisation over that imposed by lipase deficiency. We have therefore measured the proportion of a meal entering the jejunum below the critical pH of 5 in untreated adult patients with steatorrhoea caused by cystic fibrosis, and investigated whether bile acid precipitation and bile acid deficiency occur and limit lipid solubilisation below pH 5. To facilitate this, aspirates were pooled according to their pH in three pH pools; pH<5, pH 5-6 and pH>6. We used a technique of acid inactivation to arrest lipolysis in jejunal aspirate, which we have shown to be less cumbersome and more accurate⁶ than the conventional method of heat inactivation.

Methods

PATIENTS

Twelve adults (seven men and five women) with cystic fibrosis were studied, average age 23 years, average weight 52 kg. They all had documented

steatorrhoea, but were not selected for the severity of their malabsorption. Patients with severe chest disease or abnormal liver function were excluded. All patients were taking pancreatic enzyme supplements (pancreatin 5-25 tablets/meal) until the night before the study. Women with regular periods were studied within 10 days of the onset of menstruation. All patients gave informed consent according to the declaration of Helsinki. The protocol was approved by the local hospital ethical committee on 4 May 1977. The experiment involved a radiation exposure of 100 mrad to the whole body and 30 mrad to the bone marrow. Results were compared with those of a simultaneous study of 14 healthy subjects already described.⁶

The methods used were exactly as described and referenced previously,⁶ and are given here in abbreviated form.

CLINICAL PROCEDURES

A weighted double lumen nasojejunal tube was passed under fluoroscopic control after an overnight fast so that its tip lay approximately 6 inches beyond the duodeno-jejunal flexure. A Lundh test meal (dextrose 40 g, skimmed milk powder 15 g, corn oil 18 g and polyethylene glycol 4000 (PEG), 2.5 g thoroughly mixed with water 230 ml) was drunk without pancreatin supplements. Frequent small samples of jejunal aspirate were collected over three hours and their pH measured immediately with a glass electrode. Half of each sample was treated immediately with acid to inactivate lipase⁶ and the treated and untreated samples pooled separately according to pH and hour as described previously (Fig. 1).

LABORATORY PROCEDURES (Fig. 1)

Each pool was analysed for total saponifiable lipid

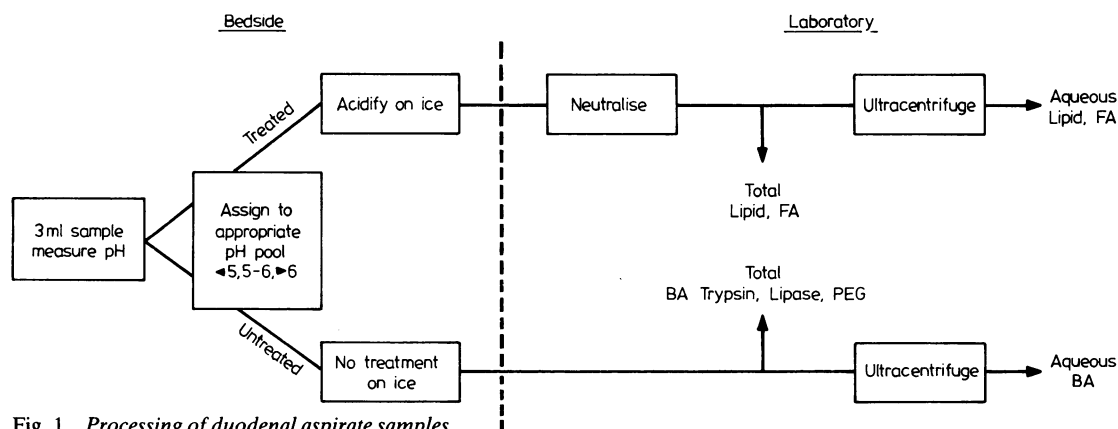


Fig. 1 Processing of duodenal aspirate samples.

and fatty acid concentration (treated pools), and bile acid, trypsin, lipase and PEG concentrations (untreated pools). The aqueous phase was separated by ultracentrifugation overnight at 100 000 g 37°C, and analysed for bile acid, saponifiable lipid and fatty acid. In addition, the glycine: taurine ratio was measured. The precipitate obtained by ultracentrifugation of each untreated pool was resuspended in 2N-NaOH to redissolve precipitated bile acid. The bile acid from this suspension and from the corresponding whole sample was extracted using XAD2 resin (Amberlite),¹⁹ redissolved in methanol, concentrated in a rotary evaporator and the conjugates separated by thin layer chromatography in ethanol-chloroform-acetic acid water (12:8:4:1). The spots corresponding to each conjugate were scraped and assayed using 3 α hydroxysteroid dehydrogenase.

Mathematical analysis and statistical comparison of the pH and hourly pools was performed as described before.⁶ The cystic fibrosis and healthy subject results were compared using the Wilcoxon rank sum test for unpaired samples. Data are given as mean \pm SEM.

Results

COMPARISON BETWEEN pH POOLS IN CYSTIC FIBROSIS (Table 1) AND OF CYSTIC FIBROSIS WITH HEALTHY SUBJECTS (Table 2)
pH

Of the total PEG aspirated 38.2% was recovered at the critical pH<5, twice as much as in healthy subjects (17.7%; $p<0.05$). This suggests that all the effects of jejunal hyperacidity described below are quantitatively more important in cystic fibrosis than in healthy subjects. In several patients the pH fell

below four for much of the test period, and in one patient remained below three for the entire test.

The proportions of lipid aspirated at each pH paralleled those of PEG, indicating as in healthy subjects that these pH effects apply equally to the aqueous and lipid portions of the meal. PEG concentrations were similar at each pH, suggesting as in healthy subjects that gastric contents and pancreato-biliary fluid had mixed completely before sampling and that differences in concentrations of other substances at each pH were not because of differences in meal dilution. Overall mean concentrations of PEG tended to be only slightly higher in cystic fibrosis than in healthy subjects.

Pancreatic enzymes (not shown)

Trypsin activity was not detected in any cystic fibrosis sample. Lipase activity did not in any cystic fibrosis sample exceed 5% of the healthy subjects overall mean, and in the cystic fibrosis group overall did not differ significantly from zero.

Lipid digestion

Total lipid concentration did not vary significantly with pH, again suggesting complete mixing of gastric contents and pancreatobiliary fluid. Fatty acid concentration and lipolysis were both much lower in cystic fibrosis than in healthy subjects and did not vary with pH. Nevertheless, significant amounts were detected in cystic fibrosis despite the almost complete absence of lipase.

Bile acids

There was a marked, significant reduction in aqueous phase bile acid concentration at pH<5, the pH 5-6 result being intermediate, but only a small pH gradient in total bile acid concentrations

Table 1 Cystic fibrosis - comparison of pH pools

| | <i>pH</i> <5 | <i>pH</i> 5-6 | <i>pH</i> >6 | Significance* <i>pH</i> <5 vs <i>pH</i> >6 |
|--|----------------|-----------------|------------------|---|
| PEG recovery (%) | 38.2 \pm 9.5 | 20.4 \pm 5.9 | 41.4 \pm 10.8 | NS† |
| Lipid recovery (%) | 36.6 \pm 8.5 | 25.2 \pm 4.6 | 38.2 \pm 9.0 | NS† |
| PEG concentration (g/l) | 2.9 \pm 0.4 | 2.8 \pm 0.2 | 3.0 \pm 0.3 | NS† |
| Total lipid (mmol/l) | 31.5 \pm 4.9 | 43.5 \pm 8.7 | 41.4 \pm 12.8 | NS† |
| Total fatty acid (mmol/l) | 2.5 \pm 0.5 | 3.6 \pm 0.8 | 2.9 \pm 0.4 | NS† |
| Lipolysis (%) | 8.6 \pm 1.4 | 9.1 \pm 1.6 | 10.4 \pm 2.5 | NS† |
| Total bile acid (mmol/l) | 8.3 \pm 1.2 | 10.6 \pm 1.6 | 13.4 \pm 2.0 | $p<0.05$ |
| Aqueous phase bile acid (mmol/l) | 4.7 \pm 0.9 | 9.0 \pm 1.5 | 12.5 \pm 2.0 | $p<0.01$ |
| Bile acid precipitation (%) | 45.7 \pm 5.0 | 18.2 \pm 4.0 | 14.5 \pm 8.0 | $p<0.01$ |
| Aqueous phase lipid (mmol/l) | 5.6 \pm 1.0 | 9.0 \pm 1.4 | 10.2 \pm 1.2 | $p<0.01$ |
| Aqueous phase fatty acid (mmol/l) | 0.9 \pm 0.3 | 1.4 \pm 0.3 | 2.6 \pm 0.3 | $p<0.01$ |
| Aqueous phase glycerides (mmol/l) | 5.2 \pm 0.8 | 8.4 \pm 1.1 | 8.2 \pm 1.0 | $p<0.01$ |
| Proportion fatty acid in aqueous phase (%) | 41.3 \pm 8.7 | 53.0 \pm 10.4 | 103.2 \pm 10.4 | $p<0.01$ |

* Wilcoxon signed ranks test. NS = Not significant. † No difference between any pools (Friedmann test).

Table 2 Comparison cystic fibrosis and healthy subjects

| | Proportion PEG at pH<5 (%) | Proportion lipid at pH<5 (%) | Overall mean PEG (g/l) | Overall mean total bile acid (mmol/l) | Corrected total bile acid mass (mmol) |
|------------------|----------------------------|------------------------------|------------------------|---------------------------------------|---------------------------------------|
| Cystic fibrosis | 38.2±9.5 | 36.6±8.5 | 3.1±0.1 | 10.2±1.1 | 8.4±1.0 |
| Healthy subjects | 17.7±4.8 | 18.6±5.3 | 2.7±0.2 | 5.7±0.5 | 5.7±0.8 |
| Significance* | p<0.05 | p<0.05 | NS | p<0.01 | p<0.05 |

| | Overall mean aqueous phase lipid (mmol/l) | Overall mean total fatty acid (mmol/l) | Lipolysis (%) | Overall mean aqueous phase fatty acid (mmol/l) | Overall mean proportion of fatty acid in aqueous phase (%) |
|------------------|---|--|---------------|--|--|
| Cystic fibrosis | 7.9±0.9 | 2.7±0.4 | 8.8±1.1 | 1.6±0.4 | 65.7±7.1 |
| Healthy subjects | 9.6±2.3 | 8.2±2.0 | 26.3±3.0 | 4.8±1.6 | 54.7±7.3 |
| Significance* | NS | p<0.01 | p<0.01 | p<0.01 | NS |

* Wilcoxon rank sum test.

attributable to precipitation onto unrecovered debris at pH<5. Thus, nearly half of the available bile acid was precipitated at pH<5, three times that at pH>6.

Overall mean total bile acid concentration was significantly higher in cystic fibrosis than in healthy subjects. The 'corrected mass of bile acid' (Table 2) associated with the meal was calculated as the total mass of bile acid aspirated multiplied by the ratio of PEG administered to total PEG aspirated. This was also significantly higher in cystic fibrosis than in healthy subjects suggesting that the increased bile acid concentration in cystic fibrosis was not solely attributable to decreased meal dilution by endogenous secretions. The glycine:taurine ratio in the whole samples was much higher in cystic fibrosis (mean 9.6±1.7:1) than those reported in health (3:1),²⁰ and negligible taurine conjugates could be demonstrated in the precipitates.

Lipid solubilisation

Both aqueous phase lipid and fatty acid concentrations were significantly lower at pH<5 than at pH>6, the pH 5-6 results again being intermediate. As lipolysis and total fatty acid concentrations did not vary with pH, this suggests that either bile acid precipitation or the partitioning of fatty acid into the oil phase, or both, might exert a limiting effect on lipid solubilisation at low pH. The distinction between these two pH-dependent effects will be analysed in the discussion. Overall mean aqueous phase fatty acid concentration was significantly lower in cystic fibrosis than in healthy subjects, reflecting the greatly reduced lipolysis. Overall mean aqueous phase lipid concentration was only slightly lower in cystic fibrosis than in healthy subjects. Absence of a significant difference was not due to differences in meal nutrition.

COMPARISON OF HOURLY POOLS (Table 3)

Meal recovery

An average of 18±2% of the PEG administered was recovered during the three hour study, somewhat less than in healthy subjects (30±3%). This may be because of the more viscous samples obtained in all cystic fibrosis patients. The concentration of PEG fell significantly from the first hour to the third hour, while that for total lipid increased significantly. These findings suggest that emptying particularly of the lipid phase of the meal from the stomach was delayed in cystic fibrosis.

pH and bile acids

pH decreased slightly but not significantly from first to third hour. This small change was accompanied by a significant increase in bile acid precipitation and decrease in fatty acid solubilisation. Total bile acid concentration remained unchanged throughout the test.

Discussion

We have shown that in pancreatic steatorrhoea due to cystic fibrosis, a large proportion of a meal enters the jejunum at pH<5, significantly more than in health (38.2% vs 17.7%, p<0.05). Postprandial intrajejunal pH has not been investigated in detail before in cystic fibrosis. Our findings are consistent with reports of low resting intrajejunal pH in cystic fibrosis.^{21 22} Postprandial pH has been variously reported as low^{1 23 24} or normal²⁵ in other forms of pancreatic steatorrhoea. In health, pH rises further down the intestine.²⁶ Ileal pH has not been investigated in cystic fibrosis, but is thought unlikely to rise²⁷ as the abnormality in electrolyte secretion in the pancreas may well affect the small intestine.²⁸ Our finding of PEG concentrations only slightly higher in cystic fibrosis than in healthy subjects

Table 3 Cystic fibrosis – comparison of hourly pools

| | 1st hour | 2nd hour | 3rd hour | Significance* 1st hour vs 3rd hour |
|--|----------|-----------|----------|---------------------------------------|
| PEG recovery (%) | 38.7±6.4 | 36.5±5.7 | 24.7±4.2 | NS† |
| Lipid recovery (%) | 25.2±3.3 | 35.6±4.5 | 39.3±3.9 | NS† |
| PEG concentration (g/l) | 3.4±0.2 | 3.2±0.3 | 2.3±0.3 | p<0.02 |
| pH | 5.6±0.3 | 5.2±0.3 | 5.0±0.3 | NS† |
| Total bile acid (mmol/l) | 12.5±2.1 | 9.2±1.1 | 10.8±1.8 | NS† |
| Aqueous phase bile acid (mmol/l) | 11.3±2.3 | 7.0±1.1 | 8.3±1.9 | NS† |
| Bile acid precipitation (%) | 16.2±5.7 | 30.4±6.9 | 30.7±6.4 | p<0.05 |
| Total lipid (mmol/l) | 26.4±6.0 | 38.3±6.8 | 40.9±6.1 | p<0.05 |
| Total fatty acid (mmol/l) | 3.4±0.9 | 2.5±0.5 | 2.9±0.4 | NS† |
| Lipolysis (%) | 12.8±1.6 | 8.0±1.6 | 8.2±1.4 | NS† |
| Aqueous phase lipid (mmol/l) | 9.2±1.3 | 7.4±0.9 | 7.8±1.3 | NS† |
| Aqueous phase fatty acid (%) | 2.1±0.5 | 1.4±0.2 | 1.8±0.5 | NS† |
| Proportion fatty acid in aqueous phase (%) | 77.8±9.9 | 63.3±13.1 | 57.4±9.3 | p<0.05 |

* Friedman + Wilcoxon's critical range test. † No difference between any hours (Friedmann test).

suggests that decreased pancreatobiliary secretion is not the only explanation for the thicker, more viscous intestinal contents frequently reported in cystic fibrosis.^{28, 29}

Bile acid precipitation was three times greater at pH<5 than at pH>6, and this was associated with a significant reduction in lipid solubilisation. Similar acid-mediated bile acid precipitation has been observed in health⁶ but is likely to be more important in cystic fibrosis because of the increased proportion of meal entering the jejunum at pH<5. These findings are consistent with a recent study of chronic alcoholic pancreatitis²⁷ published since we completed our study. This study showed a decrease in pH in the third hour of the test, leading to an increase in bile acid precipitation and a small reduction in peak micellar bile acid concentrations in comparison with controls. The unconventional use of peak rather than mean concentrations is not explained and make these data difficult to evaluate.

Our observation of a reduction in aqueous phase bile acid concentration at pH>6 suggests binding of bile acids, because pH-dependent precipitation cannot occur at this pH. We have performed *in vitro* experiments which show bile acid binding to the undigested protein component of the Lundh meal.³⁰ This binding is unlikely to be reversed further down the small intestine when proteolysis is impaired by pancreatic insufficiency. The combination of bile acid precipitation and binding may explain the increase in faecal bile acid loss well demonstrated in cystic fibrosis.^{15, 16}

As we discussed in our study of healthy subjects,⁶ three factors may in theory reduce the digestion and solubilisation of dietary lipid at low intraluminal pH: lipase inactivation, bile acid precipitation, and fatty acid protonation and consequent partitioning out of the micellar phase.⁴ The first of these is not relevant

to cystic fibrosis as lipase was absent and we found no pH-gradient for lipolysis or total fatty acid concentration. The effect of bile acid precipitation and fatty acid partitioning can be separated only mathematically⁶ as both are necessarily linked *in vivo*. Analysis of covariance reveals a significant linear relationship between the proportion of fatty acid in the aqueous phase and bile acid precipitation (Fig. 2; $F=34.2$, $p<0.01$). The intercept of the regression line indicates, however, that in the absence of bile acid precipitation 105% of the fatty acid is in the aqueous phase. In the presence of bile acid precipitation, 65.7% of the fatty acid was actually in the aqueous phase. Bile acid precipitation was therefore entirely responsible for the

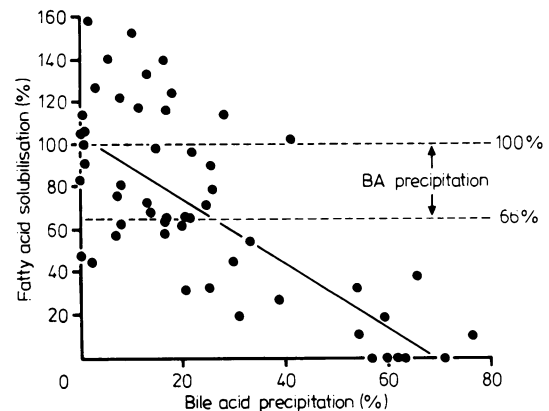


Fig. 2 Relationship between fatty acid solubilisation (adjusted for variation between individuals) and bile acid precipitation ($F = 34.2$, $p < 0.01$). This shows absence of fatty acid partitioning since fatty acid solubilisation at zero bile acid precipitation = $105 \pm 15\%$. (Overall mean fatty acid solubilisation observed = $66 \pm 7\%$).

deficient solubilisation of fatty acid in cystic fibrosis, whereas in our healthy subjects⁶ it accounted for only 36% of the deficit, the rest being attributable to fatty acid partitioning. The failure to detect any fatty acid partitioning in cystic fibrosis may be because of the very small concentrations of fatty acid present.

The pH gradient for aqueous phase glyceride concentrations (Table 1) can be attributed only to bile acid precipitation, as glycerides are not susceptible to pH-dependent partitioning.^{4, 31} This analysis suggests that in pancreatic steatorrhoea, bile acid precipitation, but not fatty acid partitioning, is responsible for an extra limitation of lipid solubilisation at low intraluminal pH beyond that provided at all pHs by deficient lipolysis.

Our finding of an increased total bile acid concentration in cystic fibrosis is unexpected in view of the well-documented reduction in bile acid pool size in cystic fibrosis children,¹⁴ variously accompanied by reduced³² normal¹⁴ or increased³³ total bile acid concentrations depending on experimental method and on the age of the patients.³⁴ As argued in the results, the increased total bile acid concentration cannot be attributed to decreased meal dilution, and we cannot explain it.

Although a greater proportion of the meal was at $\text{pH} < 5$ in cystic fibrosis than in healthy subjects, and hence susceptible to bile acid precipitation, the higher total bile acid concentration in cystic fibrosis resulted in higher aqueous phase concentrations at each pH. Bile acids are, however, likely to be protonated below pH 5: *in vitro* studies have shown that protonated bile acid can be held in solution by ionised bile acid, rather than precipitating.³ This suggests that although aqueous phase concentration was higher in cystic fibrosis than in healthy subjects, a greater proportion of the bile acid mass in this phase may be concerned with solubilising protonated bile acid, leaving a smaller amount available to solubilise lipid.³⁵

The reduction in bile acid pool size in children with cystic fibrosis has been attributed to greatly increased faecal bile acid loss.^{15, 16} Our calculation of an increased total mass of bile acid associated with the meal in our cystic fibrosis adults suggests that bile acid pool size is not reduced, at least in the absence of liver disease. The high glycine:taurine ratio suggests that this is achieved by a greatly increased rate of synthesis of bile acid²⁰ to replace bile acid lost in the faeces.

Our finding of a gradient of lipid and fatty acid solubilisation with pH is consistent with the recent study in patients with chronic alcoholic pancreatitis²⁷ where a positive correlation between lipid solubilisation and pH was shown. In our study overall mean aqueous phase lipid concentration was

not significantly reduced by comparison with healthy subjects, despite the greatly reduced lipolysis in cystic fibrosis, whereas Regan *et al*²⁷ found a significant, albeit small, difference in peak micellar lipid concentrations between untreated patients and controls, although the mean values were not stated. In their study lipolysis and lipid solubilisation in controls may have been artefactually raised because of the inaccuracies inherent in the heat inactivation technique,^{6, 36} and because inactivation was not performed until the completion of a 30 minute pool, allowing ample time for artefactual lipolysis. Heat inactivation would not affect samples from patients with pancreatic disease as they have very little, if any, lipase. Thus, the smaller difference in lipid solubilisation between cystic fibrosis patients and healthy patients in our study may reflect the more successful arrest of lipolysis in healthy subjects using our technique of acid inactivation.⁶

Our results suggest that dietary lipid may be solubilised in the aqueous phase after only a small degree of lipolysis. This lipolysis, in the absence of pancreatic lipase, may be attributable to lingual lipase which is acid stable.³⁷ In health, aqueous phase lipids consist mainly of fatty acid and monoglyceride with only very small proportions of diglyceride and triglyceride.³⁸ *In vitro*, however, diglyceride and triglyceride can be solubilised by bile acid in the presence of only small concentrations of fatty acid and monoglyceride.³⁹ Thus, the presence of low levels of lipolysis in our patients may produce sufficient fatty acid and monoglyceride to allow the solubilisation of substantial quantities of diglyceride and triglyceride. Current knowledge suggests that these lipids would not be absorbed and thus steatorrhoea would still ensue. The glyceride composition of the aqueous phase of intestinal contents has not been investigated in pancreatic disease.

These findings may have therapeutic implications. Our finding of low jejunal pH suggests that enteric coated pancreatin supplements, either in tablet or microsphere form, are unlikely to disperse in the duodenum as the enteric coating is designed to dissolve only at $\text{pH} > 6$. If they do disperse, their contents may be inactivated as seen in patients with chronic pancreatitis.^{8, 23} Improvement in lipolysis with pancreatin supplements is unlikely to improve steatorrhoea if bile acid precipitation continues to limit lipid solubilisation and partitioning of the resulting fatty acid into the oil phase interferes further with lipid absorption. Total bile acid deficiency does not, however, contribute to the problem and treatment with bile acid supplements is unlikely to improve steatorrhoea.

Our study suggests that jejunal hyperacidity and

consequent bile acid precipitation impairs lipid solubilisation and may therefore contribute to the pathogenesis of pancreatic steatorrhoea. Prevention of these effects may account for the well documented action of cimetidine in enhancing the efficacy of pancreatin therapy.⁸

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