

Progress report

Cystic fibrosis – a gastroenterological cornucopia

Cystic fibrosis, once the province of the paediatrician, has now entered the realm of the adult physician. The most common lethal Mendelian disease of Caucasians, it affects about 1 in 2000 births in Europe and North America. With recent advances in treatment about 60% of affected children can now expect to survive into adulthood, and many at least into their 30s. At least 1000 new patients are now expected to enter adulthood over the next five years. Adults usually come under the care of a chest physician, as the pulmonary manifestations of the disease usually determine survival. Until recently, therefore, both clinical research and management have tended to concentrate on the lungs. Gastrointestinal manifestations, however, occur in most adults and are increasingly recognised to impair the quality of life and to contribute to mortality. Furthermore, the disease may not be manifest until adulthood when it may present in a variety of guises to the gastroenterologist or even to the general surgeon. Cystic fibrosis (CF) therefore now concerns the gastroenterologist dealing with adults.

There have been three recent reviews of the gastrointestinal manifestations of CF,¹⁻³ of which the first is the most comprehensive. I have therefore selected for discussion those aspects where recent research in CF or in other fields of gastroenterology has improved treatment, or where advances in CF illuminate gastrointestinal physiology in general.

Pancreas

Pancreatic exocrine insufficiency is the cardinal gastrointestinal manifestation of CF, and I shall argue that it is also the central manifestation to which others are, at least in part, attributable. Quantitative histological abnormalities have been identified in premature neonates with CF⁴: the decrease in acinar volume and increase in luminal volume may account for the 'obstructive' rise of plasma immunoreactive trypsinogen concentration in neonates with CF now available for postnatal screening. By childhood about 85% of patients have frank steatorrhoea, and almost all have abnormal pancreatic function by the secretin-pancreozymin test⁵ and an abnormal pancreatic ultrasonograph.⁶

Pancreatic research originally concentrated on the value of pancreatic function testing in diagnosis and in the search for the 'basic defect'. Anderson's group, in an early study using hormonal stimulation,⁷ suggested that the secretion of bicarbonate into the duodenum was reduced more profoundly and more consistently than that of pancreatic enzymes, in contrast with other causes of pancreatic exocrine insufficiency in childhood. They argued that the primary abnormality was in ductular secretion of bicarbonate and water, and that this led to obstructive acinar damage and enzyme deficiency. This view of the pancreas was in keeping with con-

temporary models of CF as a disorder of electrolyte rather than macromolecular secretion.

More recent publications from Toronto⁸ and Vancouver⁹ have confirmed this important observation on a sounder statistical basis. The Toronto group went on to show¹⁰ that stimulated duodenal protein concentration was considerably higher in CF than in other pancreatic exocrine disorders at all levels of acinar function; water secretion was correspondingly lower so that protein output was normal. They suggested that the primary pancreatic abnormality might be a reduction in bicarbonate dependent ductular secretion of water. This can be considered analagous with the failure of chloride reabsorption in the sweat ductule and consistent with a single 'basis defect'.¹¹ In an elegant review¹² Anderson has speculated that this defect in electrolyte secretion may be linked with the seemingly distinct but characteristic abnormality in macromolecular secretion (hyperglycosylated mucin), through an abnormality in prostaglandin metabolism itself attributable to essential fatty acid deficiency.

The sweat test has now replaced the secretin-pancreozymin test in routine diagnosis, although the gastroenterologist should remember that sweat sodium may be raised in other conditions including chronic alcoholic pancreatitis.¹³ Unfortunately, none of the indirect pancreatic function tests explored in CF can detect the subtle changes diagnostic in patients without steatorrhoea, although the bentiromide test can be used to detect the development of steatorrhoea,^{14,15} as can the plasma immunoreactive trypsinogen concentration in older children.¹⁶

For the clinician, the main problem posed by pancreatic insufficiency is not how to diagnose it but how to treat it. Steatorrhoea seems particularly severe in CF, and particularly resistant to treatment with pancreatin. Many patients suffer severe steatorrhoea despite taking 30 or more pancreatin tablets daily. Such steatorrhoea is not only unpleasant and embarrassing, but also contributes to the severe growth failure and malnutrition so often seen in the disease. The purine content of large doses of pancreatin can cause hyperuricaemia,¹⁷ hyperuricosuria and occasionally renal damage in a dose predictable manner.¹⁸

The poor efficacy of pancreatin is in part attributable to intragastric inactivation of its enzyme content by gastric acid, as in other forms of pancreatic steatorrhoea. Enteric coating of the pancreatin is, however, often ineffective in improving steatorrhoea. More recent work both in chronic pancreatitis¹⁹ and in CF²⁰ suggests that the failure of the pancreas to secrete bicarbonate leads to the acidification of postprandial jejunal contents often to a pH well below 5. Gastric acid hypersecretion – mediated not by gastrin, but perhaps by neurotensin hypersecretion in response to malabsorption – may also contribute.²¹ Below pH 5, protonated bile acids precipitate out of solution and protonated fatty acids partition into the oil phase, so that the whole process of micellar solubilisation of dietary fat is upset. This adds to the limitation of fat solubilisation caused by enzyme deficiency and impaired lipolysis.^{20,22} Hydrolysis of dietary and biliary lecithin by pancreatic phospholipase – an essential step in initiating lipolysis and adjusting micellar structure – is also pH-dependent and is now being investigated in CF.

Intraluminal hyperacidity explains why enteric coating often fails: the tablets remain intact in the stomach and are retained by the pylorus after the

meal has emptied. When the tablet eventually enters the duodenum, dissolution of the coating (designed to occur only above pH 6) is further delayed in the hyperacidic duodenum; intact tablets are sometimes seen in the stool. Enteric-coated tablets are, however, successful in some patients¹⁹ – perhaps those in whom the duodenum is not hyperacidic.

The recently introduced enteric-coated microspherule formulations (Pancrease and Creon) avoid the former problem but not the latter;²³ no formulation can circumvent intraluminal bile acid precipitation and fatty acid partitioning. These formulations seem to allow a reduction in the total dosage of pancreatin with equal^{23,24} or greater^{25–27} efficacy than with uncoated preparations as usually used in North America. Two recent studies^{28,29} have shown that these expensive new preparations are also more effective than the enteric-coated tablets usually used in the United Kingdom. Even if the improvement in fat absorption is small, the reduction in dosage which their use allows is appreciated by patients and should avoid hyperuricosuria.

The use of an histamine H₂-receptor antagonist to reduce gastric acid secretion provides a more radical solution to the problem. It restores intraluminal neutrality, prevents enzyme inactivation, bile acid precipitation and fatty acid partitioning, and restores fat solubilisation to normal both in CF³⁰ and in chronic pancreatitis.^{19,22} Well conducted studies have shown that adjunctive treatment with cimetidine can improve fat absorption in some patients almost to normal.^{19,31–36} In other studies it has performed poorly^{37–39} – probably because of the inclusion of patients with mild steatorrhoea unlikely to improve further (or to need such treatment), or because of technical inadequacies. Antacids can be used to the same end^{26,32,35} but the very high doses required are inconvenient and potentially hazardous.

In practice, patients should be started on enteric-coated tablets, taking up to 10 tablets at intervals throughout the meal. Higher doses seldom improve control and risk hyperuricosuria. If this fails, an enteric-coated microspherule formulation should be tried. If significant steatorrhoea still persists, adjunctive treatment with cimetidine should be considered. In adults, the dose of 400 mg must be given at least 30 minutes before each meal in order to act before eating: it is known to be ineffective if taken with the meal. A nocturnal dose is unnecessary, and its absence will relieve proponents of the nitrosamine hypothesis. When cimetidine is used, enteric coating is often redundant and a non-enteric-coated preparation in equal dose should be tried as it disperses more rapidly.

Unfortunately, there is no easy way of quantifying an individual's response to different therapeutic regimens. Repeated fat balances are impracticable; the bentiromide test can detect the effect of increasing doses of pancreatin and of adjunctive cimetidine on proteolysis,¹⁴ but neither this test nor the Pancreolauryl test will detect the more clinically beneficial changes in lipolysis and micellar solubilisation of fat. Treatment should be continued only if it improves stool quality convincingly, as it will need to be taken indefinitely.

A few patients continue to suffer severe steatorrhoea despite such optimal treatment. Hypolactasia and gluten sensitive enteropathy should then be excluded as they are at least as frequent as in the general population.^{1,40} The possibility that steatorrhoea in CF involves mucosal malabsorption as well as maldigestion and malsolubilisation has not been explored. Mucosal

malfunction in CF has been shown only in terms of reduced absorption of aminoacids^{41,42} and taurocholate,⁴³ but enhanced absorption of glucose⁴⁴ and EDTA.⁴⁵ The small intestinal villous-crypt ratio can be abnormal in severely affected patients,⁴⁶ whilst the mucosa is covered by a thick layer of adherent mucus which plugs the mucosal crypts and goblet cells.

The investigation of malabsorption in CF has also focused interest on alternative mechanisms of fat digestion. In most adults with CF, pancreatic enzyme secretion is virtually absent and yet fat malabsorption is seldom 100%; it varies in severity from person to person, and sometimes improves as patients get older so that a few are able to abandon pancreatin altogether. This suggests the existence of a compensatory mechanism. The tongue secretes an acid-resistant lingual lipase active down to pH 3.0 which is thought to be important in initiating fat digestion in the stomach, especially in neonates. In rats diversion of lingual lipase through an oesophageal fistula impairs fat absorption.⁴⁷ In patients with CF, the enzyme is active in the stomach and accounts for 90% of the lipase activity in the duodenum;⁴⁸ proof of a 'compensatory' role awaits direct comparison of its concentrations in CF with those of pancreatic lipase in health. No compensatory increase in lingual (or gastric) lipase has been found in alcoholic pancreatic insufficiency,⁴⁹ but this may reflect simply mucosal damage by alcohol. Its acid resistance should allow it to act in the duodenum, and its recent biosynthesis awaits therapeutic exploitation.

Lingual lipase probably explains why, despite the absence of pancreatic lipase, lipolysis still occurs, albeit reduced, in untreated CF patients.²⁰ This in turn probably explains the surprising finding that aqueous lipid solubilisation is only slightly reduced in CF²⁰ and in alcoholic pancreatic insufficiency.²² It seems that it may be the quality rather than the quantity of lipid in the aqueous phase that is disturbed. Lingual lipase generates predominantly diglyceride rather than monoglyceride, and such non-polar lipid may be solubilisable in aqueous nonmicellar forms.⁵⁰⁻⁵² Indeed, Borgström has recently suggested⁵³ that the micellar theory is an oversimplification even when applied to health.

Cystic fibrosis has also served to illuminate the importance of colipase in fat maldigestion. Pancreatic colipase binds to lipase and prevents amphipathic molecules, such as bile acid and phospholipid, from inhibiting the binding of lipase to the triglyceride-water interface. The Toronto group have shown that its presence is essential to the accurate measurement of lipase in duodenal aspirate, as even in health lipase is incompletely saturated with colipase. They went on to show⁵³ that in CF the secretion of colipase determines the presence or absence of steatorrhoea in patients with borderline lipase secretion, while in those with severe steatorrhoea fat malabsorption is determined not by the residual lipase and colipase secretion but by nonpancreatic factors – perhaps bile acid precipitation or a mucosal disorder as postulated above. It is clearly relevant to treatment to determine now whether sufficient colipase is present in hog pancreatin.

Meconium Ileus Equivalent

This term (MIE) is used to describe a form of distal small-intestinal obstruction unique to CF. It has not been described in other forms of pancreatic insufficiency, or in CF patients documented to have normal fat

absorption. The syndrome is a common cause of morbidity in older children and adults with CF, and can prove fatal particularly when diagnosis is delayed or management inappropriate. Despite the many published case reports and series,^{1,3,54,55} MIE is not mentioned in most general surgical or gastroenterological textbooks. This causes a particular problem when patients with established CF present to a general surgeon with acute intestinal obstruction which is considered unrelated to their disease,⁵⁶ or when the syndrome is the presenting manifestation of CF.¹ Meconium ileus equivalent is not related to the meconium ileus of infancy; it does not involve meconium and is not an ileus, and so the term 'distal intestinal obstruction syndrome' (DIOS) has recently been introduced.¹ The syndrome must be distinguished from simple constipation and from intussusception, both of which occur in CF;¹ it may also be confused with appendix abscess.⁵⁷

The syndrome occurs in two forms: acute and chronic.² Acute MIE presents like any other form of acute distal small intestinal obstruction. The chronic form presents with symptoms of recurrent partial obstruction: bouts of colicky abdominal pain, distension, anorexia and relative constipation lasting for a few days and occurring at irregular intervals over several years. Attacks may be precipitated by accidental omission of pancreatin, or by dehydration during a respiratory exacerbation. The clue to the diagnosis may come from a history of diarrhoea shortly before the attack, and from the finding of a mobile smooth indentable mass in the right iliac fossa; the usual signs of obstruction are present in the acute form. In the chronic form the mass may come and go with each attack. A plain supine abdominal radiograph typically shows a mass of stippled material in the right iliac fossa with dilatation of the ileum and an empty distal colon; fluid levels are seen on the erect film in the acute form.

At laparotomy or autopsy the obstruction is usually in the terminal ileum, caecum or ascending colon which are filled with a tenacious putty like material resembling inspissated chyme. The adjacent mucosa, gut wall and mesentery are often inflamed and friable. No anatomical cause for the obstruction is apparent and no primary mucosal abnormality has ever been described. The histopathology and histochemistry have recently been described in detail.⁵⁸

Despite the many published case reports the cause of MIE is unknown and uninvestigated. Nevertheless, observations drawn from several fields of gastroenterology are now beginning to fit together to suggest several possible mechanisms:² (i) The restriction of MIE to CF patients with steatorrhoea, particularly those with poorly controlled steatorrhoea, suggests that the thickening of chyme with undigested protein and fat may contribute. (ii) The restriction of MIE to CF as a cause of steatorrhoea suggests that the particular reduction in pancreatic bicarbonate secretion in CF may contribute.^{8,9} Anion secretion is disturbed in many other organs, so that bicarbonate secretion may be reduced throughout the small intestine,¹² leading to ileal hyperacidity and precipitation of undigested dietary protein. (iii) The volume of pancreatic secretion is also greatly reduced in CF, which may lead to a failure of dilution of chyme in the duodenum. The viscosity of fasting duodenal aspirate is, conversely, increased because of the higher protein concentration of pancreatic fluid¹⁰ and the abnormal structure of intestinal mucoprotein (see below). More recent evidence relates the hyperviscosity of CF mucus glycoprotein to an excess of covalently

bound lipids and fatty acids, which is in turn attributable to increased acyltransferase activity in gastric and rectal mucosa.⁵⁹ (iv) The small intestinal mucosa in CF is covered with a thick layer of mucus which occludes the crypt orifices,^{46 58} and may impede the secretion of water and retard the passage of the already thickened chyme. The Toronto group have shown that CF intestinal mucin is abnormally dense and branched as a result of hyperglycosylation. This renders it resistant to tryptic digestion, and more likely to gel particularly in a hyperacidic milieu rich in albumin and calcium as occurs in CF duodenal fluid.⁶⁰ They suggested that such coagulation might denude the intestinal mucosa allowing excessive water absorption in the distal ileum. Increased jejunal water absorption⁴⁴ and intestinal permeability to EDTA⁴⁵ have recently been shown in CF, and attributed to a decrease in the thickness of the unstirred water layer⁴⁴ because of abnormal surface mucus. (v) In health, perfusion of the ileum with various fats impairs jejunal motility⁶¹ and prolongs small intestinal transit,⁶² probably by stimulating release of enteroglucagon and neurotensin. Postprandial plasma enteroglucagon and neurotensin concentrations are increased in CF,^{63 64} and small intestinal transit as measured by the lactulose hydrogen breath test is prolonged.⁶⁵ Meconium ileus equivalent may be the first described pathological consequence of this adaptive mechanism.

TREATMENT

The treatment of MIE has been described in detail elsewhere.^{6 54 55}

Acute MIE

Successful treatment depends on recognising the condition and avoiding the temptation of laparotomy, which may result in the death of the patient from respiratory or surgical complications. Intravenous rehydration and nasogastric drainage should be started. The mainstay of treatment is 20% N-acetyl cysteine (Airbron); 30 ml diluted with 120 ml water is given by mouth or tube twice daily and a similar dilution as a retention enema.⁵⁴ This mucolytic agent is thought to cleave the protein matrix of the inspissate, and usually disperses it within a few days. Diatrizoate (Gastrografin) given by mouth may be used to delineate the site of the obstruction radiologically, and its hypertonicity gives it a therapeutic effect by stimulating fluid secretion.⁶⁶ Given as an enema it also helps by excluding intussusception. When the attack has subsided, attention must be paid to optimising the treatment of the patient's steatorrhoea; a policy of reducing pancreatin dosage to induce diarrhoea has been advocated but is irrational and possibly hazardous.

Chronic MIE

The part played by malabsorption and intestinal hyperacidity postulated above suggests that controlling the former properly using high doses of pancreatin, and controlling the latter with cimetidine should prevent recurrent acute MIE and relieve chronic MIE. Since pursuing such a policy at the Brompton Hospital, the prevalence of these disorders has fallen dramatically. No controlled trial has been reported, but in some patients the symptoms and right iliac fossa mass return promptly on stopping cimetidine and disappear on restarting it. A few patients require prolonged 'maintenance' treatment with N-acetyl cysteine. A recent small open study⁶⁷

has suggested that intestinal lavage with a non-absorbable solution improves symptoms and radiological appearances, but follow up was limited to a few weeks.

Gallstones

Cholesterol gall stones – often within a shrunken (micro) gall bladder – occur in up to 12% of young people with CF,⁶⁸ but far fewer suffer truly related symptoms. The hazards of cholecystectomy in patients with chronic pulmonary disease are claimed to be less than anticipated.⁶⁹ Although, therefore, not a serious clinical problem cholelithiasis does raise interesting pathophysiological questions.

Faecal bile acid excretion is markedly increased in children with CF and steatorrhoea, to an extent correlated with faecal fat excretion and comparable with that in patients with ileectomy steatorrhoea. This leads to a reduction in bile acid pool size⁷⁰ and rise in the proportion of glycine conjugates^{71,72} as in other diseases where bile acid loss exceeds the liver's ability to compensate. The end result is a rise in cholesterol saturation of gall bladder bile in CF patients with steatorrhoea (but without gall stones)⁷¹ comparable with that in other gall stone patients. Treatment with pancreatin reduces faecal bile acid loss, in parallel with faecal fat excretion, and increases bile acid pool size markedly because of a reduction in fractional turnover rate rather than an increase in synthesis.⁷⁰ This reversibility by pancreatic replacement suggests that the interruption of enterohepatic recirculation is the result of an intraluminal rather than a mucosal disorder, but its cause remains controversial.⁶⁸

Most investigators have argued that the decrease in faecal bile acid excretion with pancreatin, or with substitution of dietary fat by medium chain triglyceride,⁷³ suggests that active transport of bile acid in the terminal ileum is intact but inhibited by the presence of unabsorbed fat in the ileum. This argument is based on an analogy with the well established finding that lecithin inhibits mucosal uptake of bile acid *in vitro* by expanding the micelle. It is supported by the finding in rats that the diversion of lingual lipase by oesophagostomy increased both faecal fat and bile acid excretion, but not faecal nitrogen.⁴⁷ The hypothesis is challenged, however, by two rat experiments^{72,74} in which perfusion of the duodenum or ileum with triglyceride or its lipolytic products at physiological concentration did not inhibit bile acid absorption.

An alternative argument is that the correlation between faecal bile acid and faecal fat excretion may, in fact, be a cocorrelation of the true causal relationship with faecal nitrogen excretion. Many food proteins bind bile acid; this binding increases as pH falls, whilst precipitation of bile acids is added below their pKa. The presence of undigested protein in the ileum and the reduction in intraluminal pH would promote both phenomena, whilst the preponderance of glycine conjugates (which have a high pKa) would promote precipitation. Treatment with pancreatin reduced faecal nitrogen as well as fat excretion,³² whilst addition of cimetidine had an additional effect in reducing bile acid precipitation.³⁰ Substitution of dietary protein with a fat free aminoacid feed greatly reduced faecal bile acid excretion without reducing faecal nitrogen;⁷⁵ the decrease could be attributed far more to a reduction in degradation of primary bile acids and binding to undigested

protein than to the reduction in fat excretion. The hypothesis is further supported by a careful study⁷⁶ in which faecal bile acid excretion was more strongly correlated with nitrogen than with fat excretion, and showed a dose related reduction with cimetidine treatment.

A mucosal contribution to bile acid malabsorption in CF cannot, however, be dismissed. In the study cited above,⁷⁶ statistical analysis showed that bile acid excretion could not be accounted for entirely by nitrogen and fat excretion: another factor was suggested. Reduced biliary bile acid secretion rates⁷⁷ and postprandial plasma cholic acid concentrations⁷⁸ have been reported even in patients without steatorrhoea or liver disease. *In vitro* uptake of taurine conjugates by ileal biopsies from CF patients is reduced,⁴³ perhaps because the mucosa is covered by a thick layer of mucus whose viscosity may determine the rate of bile acid absorption.

One important study stands alone in challenging this interesting example of interruption of the enterohepatic circulation. In a study of older children with CF,⁷⁹ faecal bile acid excretion was similar to that in adults with acquired pancreatic insufficiency, and only slightly higher than in cited 'normal values' (there were no concurrent controls). The glycocholate breath test gave, surprisingly, subnormal results. Clearly, the latter finding may be attributable to an abnormality in colonic flora⁸⁰ perhaps caused by longterm antibiotic usage.⁸¹ The former finding (if valid) may be explained by the decrease in bile acid excretion in older patients⁸² in whom liver disease is more prevalent. Liver disease in CF decreases biliary bile acid secretion⁸³ and hence delivery to the ileum, but this seems unlikely to reduce the putatively obligatory interruption of the enterohepatic circulation. It seems more likely that, with increasing age, the compensatory mechanisms which decrease protein and fat malabsorption also decrease bile acid malabsorption.

The increasing use of antibiotics may also contribute. In patients taking multiple antibiotics a reduction in the proportion of anaerobic faecal flora was associated with a decrease in the proportion of secondary and free bile acids in the faeces and in duodenal fluid⁸³ – those most susceptible to precipitation – and with a reduction in faecal excretion of bile acids but not of fat.⁸¹

It has long been suggested that the interruption in enterohepatic circulation of bile acids in CF might lead to a reduction in biliary secretion, and hence inadequate postprandial intraluminal bile acid concentration and impaired lipid solubilisation. Biliary bile acid secretion rates, in two recent studies using similar stimulation and marker perfusion techniques in patients without liver disease, were normal in children⁸³ but reduced in adults.⁷⁷ Postprandial bile acid concentrations seem to be low⁷² or normal⁸² in children, but normal in adults.²⁰ The proportion of glycine conjugates^{20 71 72} and primary bile acids⁸³ is, however, consistently increased thus promoting intraluminal bile acid precipitation and impairing lipid solubilisation. The longterm administration of taurine can reverse this imbalance, and in one study reduced steatorrhoea by about 20%.⁸⁴ The inclusion of free bile acids in some commercial pancreatin preparations is pointless because of their high pKa, whilst their use for gall stone dissolution seems unlikely to succeed. Clinical experience has not been reported, but the absorption of ursodeoxycholic acid is reduced in CF.⁸⁵

Optimal treatment of steatorrhoea should help in several ways: by reducing faecal bile acid loss, increasing pool size,⁷⁰ and decreasing cholesterol saturation index⁷¹ it should help prevent gall stones and improve

bile acid composition. Addition of cimetidine, by reducing precipitation and binding of bile acids³⁰ had an additional effect demonstrated in one study⁷⁶ but not in another.³³ Whether improved recirculation of bile acid might prevent the hepatic complications of CF⁶⁸ remains a challenging postulate.^{71 83 86}

Malnutrition

Malnutrition is perhaps the most pressing problem now to be tackled in the management of CF. In adults it is most clearly manifest by delayed puberty and by relative underweight for height.⁸⁷ The degree of underweight is a strong determinant of survival, but the argument that it is dependant on the severity more of pulmonary than of gastrointestinal disease⁸⁸ is not entirely convincing. Malnutrition comprises not only overt protein-calorie deficiency,⁸⁹ but also widely documented deficiencies,^{90 91} of the fat soluble vitamins A, D, E⁹² and occasionally K and, less consistently,⁹³ essential elements including zinc⁹⁰ and selenium.⁹⁴ Vitamin B₁₂ malabsorption is common, but usually corrected by pancreatin therapy; other water soluble vitamins appear to be absorbed normally.⁹² Overt deficiency syndromes are rare^{90 91} but those recently reported include osteomalacia,⁹⁵ and a spinocerebellar syndrome and sensory abnormalities from vitamin E deficiency.^{96 97}

Of greatest interest is the extensively documented deficiency of essential fatty acid⁹⁰ which is now considered to be a consequence of reduced intake⁹⁸ and malabsorption^{99 100} – compounded by inadequate energy intake – rather than of any primary defect in metabolism.¹⁰¹ Overt manifestations of essential fatty acid deficiency are rare, but there is evidence that deficit of the degree found in CF may contribute to the pulmonary manifestations of the disease by impairing prostaglandin metabolism¹⁰² and erythrocyte membrane function,¹⁰³ whilst many other membrane disorders have been described in animal models. Indeed, essential fatty acid deficiency has been involved in an hypothesis for the ‘basic defect’ in CF.¹² This central role may explain why the few patients with normal absorption have milder respiratory disease, lower sweat sodium and live longer.¹⁰⁴ Oral or intravenous supplementation with essential fatty acid alone can restore linoleate concentrations and reverse prostaglandin disturbances.^{102 105} Early claims of a reduction in sweat sodium concentration and more general clinical improvements have not, however, been confirmed¹⁰⁵ and a recent controlled trial of regular intravenous supplementation failed to demonstrate any convincing benefit.¹⁰⁶ Total energy deficiency aggravates essential fatty acid deficiency and both must be restored together.¹⁰⁷ This makes it difficult to interpret the specific effects of essential fatty acid supplementation in other studies.

The severe malabsorption so evident in CF clearly contributes greatly to malnutrition, but is not the sole cause as has so long been assumed. Dietary studies in North America¹⁰⁸ and Europe¹⁰⁹ concur that patients with CF often eat less than 80% of the recommended daily energy intake (based on their actual weight) in health unless they attend a centre practising ‘nutritional rehabilitation’.¹¹⁰ Contrary to the classical teaching in pancreatic insufficiency, appetite is poor outside infancy. It seems to be impaired by abdominal symptoms (colic, distension and foul stools) arising from

malabsorption itself, and from pulmonary symptoms (foul sputum, dyspnoea and coughing during meals). Anorexia often complicates any form of severe malnutrition, although in one study food intake in underweight patients with CF was no lower than in apparently well nourished patients with other gastrointestinal disorders.¹¹¹ Finally, to compound decreased intake and absorption, energy requirements are probably increased¹¹² because of the increased work of breathing, coughing, physiotherapy and the metabolic response to infection and fever.

Faced with the unpleasantly obvious loss of fat in the stools, physicians have traditionally advised a low fat diet. No doubt the dietary and social constraints imposed by fat restriction sufficient to avoid steatorrhoea also contribute to anorexia. Such a diet also deprives the patient of a rich source of energy and of essential fatty acids.⁸⁷ Replacement of dietary fat with medium chain triglyceride replaces energy but not essential fatty acids, and has never been shown to promote growth. Many patients find MCT distasteful and its use can lead to essential fatty acid deficiency. Most patients replace the fat they do not eat with protein, so that protein intake is often well above the recommended daily intake¹¹⁰ whilst azotorrhoea is less severe than steatorrhoea.³² Dietary protein supplementation is therefore superfluous: the muscle wasting so obvious in CF reflects energy deficiency and secondary protein catabolism rather than protein deficiency.^{87,89} Energy supplementation has been shown to improve nitrogen utilisation, muscle mass and growth by reducing protein catabolism rather than by increasing protein anabolism.^{112,113}

The nutritional management of the CF patient must therefore aim to increase energy intake; a level of at least 125% RDI based on ideal weight-for-height (rather than actual weight) has been recommended.¹¹⁰ This is done most efficiently (and acceptably) by allowing fat to provide between 30–40% of energy intake^{87,91} given mainly as vegetable fat to supply copious essential fatty acid. Fat soluble vitamin supplements (A, D, and E) should be given to supply a normal recommended intake;⁹² safflower oil and artificial sources of linoleate have also been used.⁹⁸

This advice runs contrary to the 'low-fat, high-protein' diet so long advocated in CF but reflecting therapeutic impotence rather than nutritional sense. It is, however, increasingly being accepted in CF centres.^{87,91} Most patients can tolerate a substantial fat intake³² if careful attention is paid by their physician to optimising pancreatic replacement therapy. The dose of pancreatin is increased (and different formulations tried) to control steatorrhoea, and to gain the patient's confidence after a life time of fat restriction. Fat intake is then increased until satisfactory weight gain is achieved; further pancreatin and adjunctive cimetidine may prove necessary. The effect of cimetidine on weight gain in controlled trials has, however, been disappointing^{34,35,114,116} – probably because recruitment was not restricted to patients likely to benefit, whilst the effect of cimetidine was not exploited by increasing food intake.¹¹⁷

Artificial feeding has, by contrast, achieved impressive benefits in a few controlled trials. In a sequentially controlled trial¹¹⁸ a three week period of peripheral parenteral hyperalimentation led to 'catch up' gains in weight and height, and impressive improvements in anthropometry, pulmonary function, infection rate and well being which were sustained over the following six months. In an uncontrolled study,¹¹⁹ however, three weeks

central venous nutrition improved anthropometry and respiratory muscle strength but not pulmonary function; these improvements were not sustained, perhaps because the patients were older and their disability longer established. In a recent similar study¹²⁰ peripheral hyperalimentation during admission for respiratory exacerbation produced sustained weight gain in some patients, but seemed to suppress appetite in others; local phlebitis was common. Although twice-yearly ‘top-up’ parenteral nutrition seems attractive (and without pulmonary hazard in the trials), it is unlikely to be welcomed by patients.

Artificial oral feeds have long been used in CF, both as the sole source of nutrition and – more commonly – to supplement food intake. Many have been low fat, high protein formulations which are easy to absorb but supplement mainly what is not needed. Many patients dislike artificial feeds and longterm compliance is often poor. In a sequentially controlled study,¹²¹ a one year period of oral supplementation rich in essential fatty acid promoted growth only slightly, and mainly in younger and less severely affected patients. In a more recently sequentially controlled trial¹²² a one year period of increased energy intake, achieved partly by specific dietary advice as well as by artificial supplementation, normalised growth when energy intake exceeded 110% RDI.

Enteral infusion of the feed has been tried in an attempt to circumvent patients’ dislike of oral feeds. The authors of the most impressive trial of intravenous hyperalimentation¹¹⁸ have now reported a well controlled trial of mainly nasogastric supplemental feeding lasting one year,¹²³ and demonstrated improvements in growth, pulmonary function, and infection rate; body composition was unfortunately not studied. Longterm nocturnal nasogastric feeding, used to supplement oral intake which remained inadequate despite counselling, increased lean body mass slightly and decreased the frequency of pulmonary exacerbations but did not improve pulmonary function.¹²⁴ Nasogastric feeding is often poorly tolerated because of cough and nasal polyps. Stoma feeding has, however, been well tolerated in two longterm studies using endoscopically placed gastrostomy¹²⁵ or surgical jejunostomy.¹²⁶ Growth and muscle mass improved, but benefits in pulmonary function were unconvincing. Supplementary nocturnal enteral feeding may suppress daytime appetite so that total intake is little increased.

No adequately controlled trial has yet shown sustained improvements in appetite, anthropometry, or pulmonary function with invasive methods of feeding, and few have adequately distinguished muscle reconstitution from weight gain including water retention.⁸⁷ Many authorities doubt the real benefit of intensive and invasive feeding regimens. Some feel it may be a question of ‘too little too late’. Trials continue, but pending the confirmation of Shepherd’s finding¹¹⁸ – sustained improvement in appetite, growth and pulmonary function – it seems reasonable to concentrate on helping patients to eat more real and enjoyable (but appropriately chosen) foods, reserving artificial supplementation perhaps for patients during or recovering from severe respiratory exacerbations.

Liver

Hepatic abnormalities are common in CF, and range from hepatic steatosis to a characteristic focal biliary fibrosis and eventual multilobular cirrhosis

and portal hypertension.^{68,86} Many patients have abnormal liver function tests and hepatic ultrasonography⁶ but these do not predict the type or severity of abnormality present. Only a few patients suffer symptoms specifically attributable to liver disease – usually those of cirrhosis, oesophageal varices or massive splenomegaly.

I shall not discuss liver disease at length here because little is known of its pathogenesis, prevention or treatment. Theories have moved away from bile ductule obstruction,¹²⁷ analogous to the obstructive damage in the pancreas, to the possible roles of hepatotoxic bile acid metabolites^{83,86} and essential fatty acid deficiency, but facts are lacking. Of great interest is the finding of cellular immune responses to liver membrane antigens in CF patients with liver disease,¹²⁸ although this is not accompanied by a humoral response to liver-specific lipoprotein.¹²⁹ Treatment is confined to the conventional management of cirrhosis and variceal haemorrhage. Earlier optimism⁸⁶ about the place of splenorenal shunting for repeated bleeding has waned, but the role of endoscopic sclerotherapy in CF has not been formally assessed. No method of slowing the very variable progression of focal biliary fibrosis is known, and no benefit has been shown from screening – by liver biopsy or other means – for its development.

Other manifestations

Many other gut diseases have been described in adults with CF.^{1,3} These include recurrent acute pancreatitis, pancreatic cholestasis, coeliac disease, gastro-oesophageal reflux and intussusception; recent reports discuss duodenal ulcer and stricture,¹³⁰ Crohn's disease,¹³¹ pneumotosis coli,¹³² and pancreatic, biliary and ileal adenocarcinoma.^{69,94} As patients get older, they will presumably become liable to the same range of gastrointestinal disease as are healthy adults.

Conclusions

Cystic fibrosis has become a disease of adults. Its gastrointestinal manifestations are common and unpleasant, whilst malnutrition is probably the greatest therapeutic problem to be overcome. Gastroenterologists will meet the disease with increasing frequency and would do well to cultivate an interest in it; it is rewarding to treat and fascinating to study.

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