

Gastrointestinal and nutritional aspects

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Cystic fibrosis is the most frequent cause of pancreatic insufficiency and chronic lung disease with progressive pulmonary failure in childhood. Though most cases are diagnosed in childhood, because affected individuals now live beyond their 20th birthday¹ cystic fibrosis is encountered more often by physicians dealing with adults. It has become a major cause of refractory malnutrition and new management approaches to nutrition are important in the care of these patients. This article will review the pancreatic, intestinal, hepatobiliary, and nutritional disturbances characteristic of cystic fibrosis and some current developments in our understanding of their pathogenesis, and in our approaches to management.

Pathogenesis

The primary defect in cystic fibrosis is unknown. The gene locus has been identified on the long arm of chromosome 7, cloned, and sequenced, but the function of the protein product remains unknown at the time of writing. The gene is consistently expressed in epithelial cells and abnormal regulation of epithelial ion transport can account for the

experimental findings in several tissues classically affected in the disease (fig 1). Chloride impermeability in the sweat duct gives rise to the well known finding of a raised sweat chloride concentration in cystic fibrosis. Exocrine glands that depend on the epithelial transport of anions to move water across membranes and into secretions may develop obstructive plugging because of increased concentrations of macromolecules and the consequent failure to clear secretions. Studies using pancreatic secretions from patients with their pancreatic dysfunction well controlled strongly support this hypothesis.²

Pancreatic manifestations

The earliest characteristic morphological feature of the pancreas in cystic fibrosis is the accumulation of secretory material within ducts and ductal obstruction. Subsequent tissue damage, presumably from acinar release of lytic enzymes, leads to the progressive loss of functioning acinar tissue, fibrosis, and fatty replacement, the hallmarks of pancreatic disease in cystic fibrosis (fig 2). The degree of pancreatic destruction is highly variable, accounting for the differences in clinical

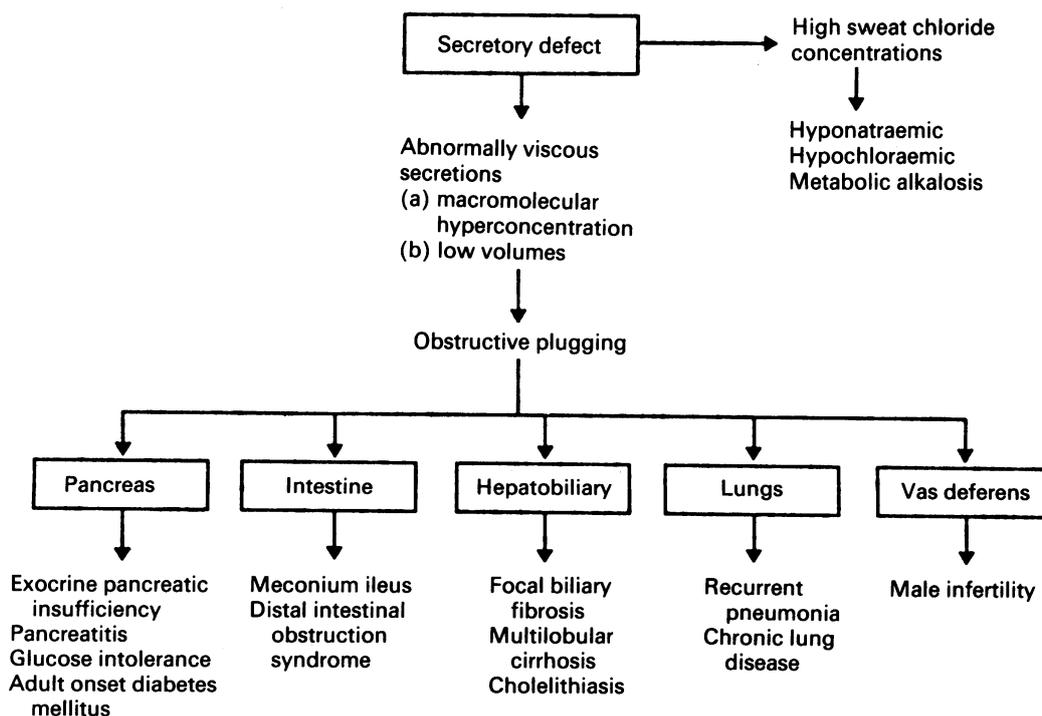
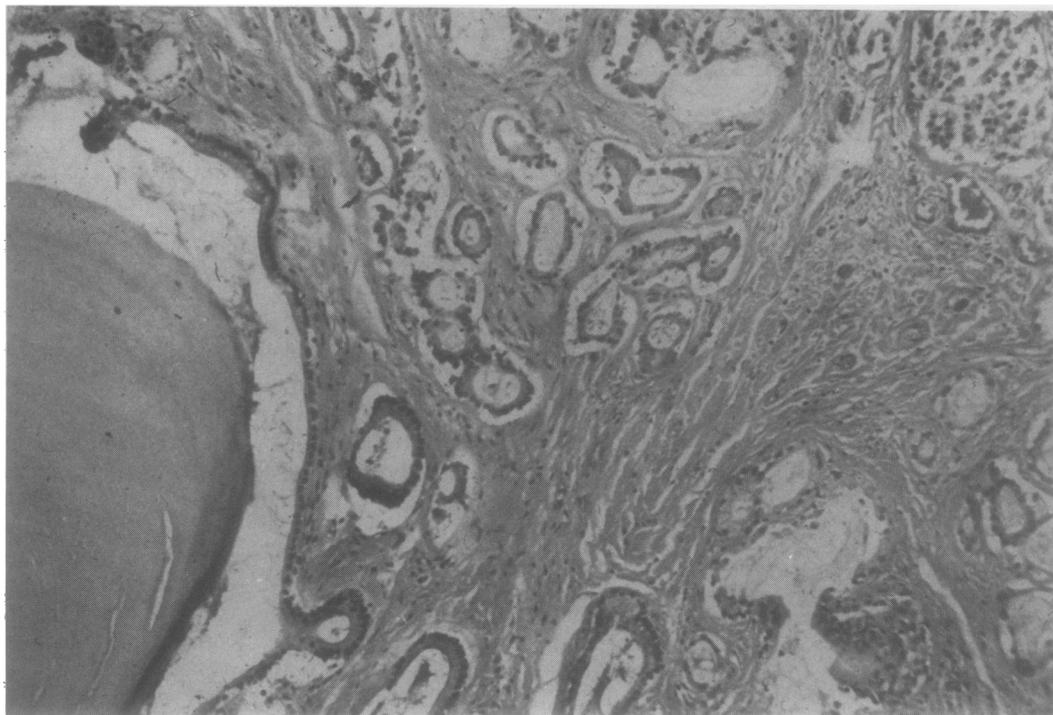


Figure 1 Pathogenesis and clinical manifestations of cystic fibrosis. Reproduced by courtesy of Medicine (North America).

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Figure 2 Characteristic morphology of the pancreas in cystic fibrosis, showing accumulation of material within the duct causing obstruction, with surrounding loss of acinar tissue and fibrosis.



presentation and severity of pancreatic manifestations (table).

PANCREATIC INSUFFICIENCY

About 85% of patients with cystic fibrosis have such severe loss of pancreatic acinar tissue that inadequate secretion of digestive enzymes causes malabsorption. These individuals present with large, bulky, greasy stools and poor weight gain or frank weight loss. They may develop manifestations of fat soluble vitamin deficiencies. Taurine, bile salt, and essential fatty acid deficiencies secondary to malabsorption may contribute to their poor state and in the long term reduce survival.

Pancreatic insufficiency can be diagnosed by assessing fat absorption or on the basis of the degradation of specific markers, such as bentrimide or fluorescein dilaurate.³ The assessment of fat absorption remains the gold standard and requires a fat balance study of at least 72 hours for determining stool fat output as a percentage of dietary fat intake. Direct assessment of the secretory capacity of the pancreas, though far more invasive and difficult to perform, offers the advantage of increased sensitivity. This latter method has shown the pancreas of patients with pancreatic insufficiency to have less than 2% of the normal secretory capacity.⁴

Successful management of pancreatic insufficiency is often achieved by supplementing the diet with commercial preparations of pancreatic enzymes. Enteric coated enzyme preparations are more effective and require fewer pills because the enzymes are not inactivated by gastric acid. Patients occasionally need pharmacological inhibition of gastric acid secretion with H₂ antagonists or buffers, or the use of prostaglandin analogues⁵ to attain optimal digestion and absorption. This is probably because they have a combination of

gastric acid hypersecretion⁶ and substantially diminished bicarbonate secretion.⁷

PANCREATIC SUFFICIENCY

About 15–20% of patients with cystic fibrosis retain sufficient functional acinar tissue to digest and absorb nutrients normally and they do not require pancreatic enzyme supplementation. They have a far better overall prognosis than patients with pancreatic insufficiency⁸ and do not usually develop some of the other gastrointestinal complications, such as hepatobiliary disease and the distal intestinal obstruction syndrome. These patients are not homozygous for the most common abnormal allele, $\Delta F508$.⁹ Nevertheless, they do manifest many of the characteristic clinical features of cystic fibrosis, and because of their more limited disease have allowed us to learn much about the primary pathophysiology of the pancreatic lesion in cystic fibrosis.

Gastrointestinal manifestations of cystic fibrosis

	Relative incidence (%)
Pancreatic	
Pancreatic insufficiency	80–85
Pancreatic sufficiency	15–20
Pancreatitis	2–3
Abnormal glucose tolerance	30
Diabetes mellitus	1–13
Intestinal	
Meconium ileus	10–15
Intestinal atresias	?
Rectal prolapse	20
Distal intestinal obstruction syndrome	10–20%
Hepatobiliary	
Cholestasis in infancy	?
Fatty liver	15–40
Focal biliary fibrosis	25
Multilobular cirrhosis	2–5
Gallbladder abnormalities	45
Cholelithiasis	4–12

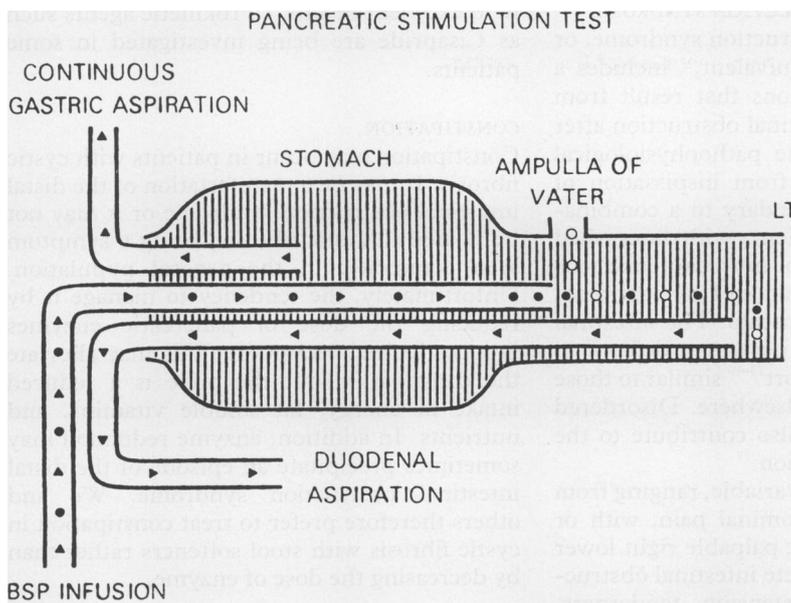


Figure 3 Diagrammatic representation of the technique of duodenal intubation, marker perfusion, and collection of stimulated pancreatic secretions used to assess quantitatively the secretory capacity of the pancreas. Basal phase 20 min; stimulation 60 min; intravenous cholecystokinin and secretin 0.125 U/kg/min. BSP—bromosulphalein as a marker infusion.

Normal fat digestion on the basis of a three day fat balance study or normal degradation of bentiromide or fluorescein dilaurate will identify pancreatic sufficiency, though these tests are not sensitive enough to be of further value. By the use of duodenal intubation, a marker perfusion technique, and standard exogenous pancreatic stimulation (fig 3) pancreatic function can be assessed quantitatively and with greater sensitivity. This method has shown a tremendous pancreatic reserve and a variability in residual pancreatic exocrine capacity in these patients, ranging from 2% to 100% of normal enzyme secretory capacity.^{3,4} Although some patients had normal or near normal enzyme secretory capacity, their ability to secrete fluid was defective by comparison with that of control subjects with similar pancreatic function. This accounts for the increased concentrations of proteins and poor clearance of secretions.² The defect in fluid secretion was due to diminished secretion of both chloride and bicarbonate ions⁷ and was consistent with abnormal epithelial anion transport in cystic fibrosis.^{10,11}

It is becoming clear that some patients with pancreatic sufficiency show progressive destruction of exocrine tissue and loss of function,¹² presumably from continuing or recurrent duct obstruction; these patients may eventually require enzyme treatment. The likelihood of developing insufficiency may be related to the degree of pancreatic reserve. Quantitative testing of residual pancreatic functional capacity may be a useful prognostic tool, indicating the likelihood of future pancreatic insufficiency.

PANCREATITIS

Among patients with pancreatic sufficiency recurrent pancreatitis may be a problem

because of duct obstruction and acinar release of enzymes. They often have a milder clinical course without all the features of cystic fibrosis and indeed the disease may not be diagnosed. Recurrent pancreatitis should be therefore an indication for sweat testing. About 15% of patients with cystic fibrosis who have pancreatic sufficiency may suffer from clinical pancreatitis.

DIABETES MELLITUS

Progressive pancreatic fibrosis ultimately disrupts pancreatic islet cell function. At least 30% of patients with pancreatic insufficiency will have an abnormal tolerance to glucose loads. Frank diabetes mellitus is less frequent and tends to occur later in the course of the disease. Its clinical presentation, diagnosis, and management are similar to the idiopathic adult onset form of diabetes mellitus.

Intestinal manifestations

The major intestinal manifestations are the result of partial or complete obstruction of the intestinal lumen. Obstruction may occur in utero or at any time during the patient's life. Intestinal presentations of cystic fibrosis, all of which are indications for sweat testing, include meconium ileus, meconium peritonitis, intestinal atresia, unexplained intestinal obstruction, and rectal prolapse.

MECONIUM ILEUS

Meconium ileus is the earliest manifestation of cystic fibrosis, occurring in 10–15% of patients. It may present in utero with polyhydramnios or within 48 hours of birth as a small intestinal obstruction with thick inspissated meconium. Classically, the newborn infant fails to pass meconium and develops progressive abdominal distension and bilious vomiting. Abdominal radiographs show distended small bowel loops, absent or scarce air-fluid levels, and bubbles of gas and stool trapped throughout the small bowel. A barium enema reveals an unused "microcolon." If the meconium ileus is complicated by intestinal perforation in utero, the result is meconium peritonitis, associated with ascites, adhesions, and intra-abdominal calcification. Other associated intestinal complications include intestinal volvulus and jejunal and ileal atresias. Although none of these findings is pathognomonic of cystic fibrosis, all are strong indications for sweat testing as 30% of infants with meconium ileus with or without peritonitis and 15–20% with intestinal atresias will have cystic fibrosis.

In uncomplicated meconium ileus non-surgical relief of obstruction may be achieved with water soluble hypertonic enemas (Gastrografin or Hypaque) administered under fluoroscopic control. This is contraindicated in the presence of perforation, peritonitis, or evidence of volvulus or atresia. In these cases, or with failure of non-surgical manoeuvres, operative intervention is mandatory. The prognosis of infants with meconium ileus, once past the neonatal period, is no different from that of other patients with cystic fibrosis.

DISTAL INTESTINAL OBSTRUCTION SYNDROME

The distal intestinal obstruction syndrome, or the "meconium ileus equivalent," includes a range of clinical conditions that result from partial or complete intestinal obstruction after the neonatal period. The pathophysiological features probably arise from inspissation of intestinal secretions secondary to a combination of pancreatic insufficiency with diminished proteolytic degradation of mucoproteinaceous secretions and poor clearance of concentrated, dehydrated intestinal contents. The intestinal mucosal epithelial cell possesses defects in chloride and fluid transport¹³⁻¹⁶ similar to those seen in epithelial cells elsewhere. Disordered intestinal motility may also contribute to the occurrence of this condition.¹⁷

Presentation is highly variable, ranging from recurrent cramping abdominal pain, with or without an asymptomatic palpable right lower quadrant mass, to complete intestinal obstruction with abdominal distension, tenderness, and vomiting. It is often difficult to differentiate from the far less common conditions requiring surgical intervention, such as appendicitis, appendiceal abscess, intussusception and caecal neoplasm. The detection of large amounts of faecal material in the right lower quadrant by abdominal radiography or Gastrograffin enema, abdominal ultrasound, or computed tomography and resolution with treatment for the distal intestinal obstruction syndrome may help diagnostically.

Surgical intervention is rarely required. Medical management consists of increased amounts of pancreatic enzyme replacement; stool softeners such as mineral oil, psyllium hydrophilic mucilloid, and fibre; Gastrograffin and other enemas; and, in the past, oral or rectal *N*-acetylcysteine. In the absence of complete intestinal obstruction, balanced isotonic electrolyte solutions for gastrointestinal lavage are administered orally or by nasogastric infusion

with excellent results.¹⁸ Prokinetic agents such as Cisapride are being investigated in some patients.

CONSTIPATION

Constipation may occur in patients with cystic fibrosis. It may be a manifestation of the distal intestinal obstruction syndrome or it may not be related to cystic fibrosis, being a symptom seen commonly in the general population. Unfortunately, the tendency to manage it by reducing the dose of pancreatic enzymes induces fat malabsorption. This may alleviate the constipation but the price is a reduced intake of energy, fat soluble vitamins, and nutrients. In addition, enzyme reduction may sometimes precipitate an episode of the distal intestinal obstruction syndrome. We and others therefore prefer to treat constipation in cystic fibrosis with stool softeners rather than by decreasing the dose of enzyme.

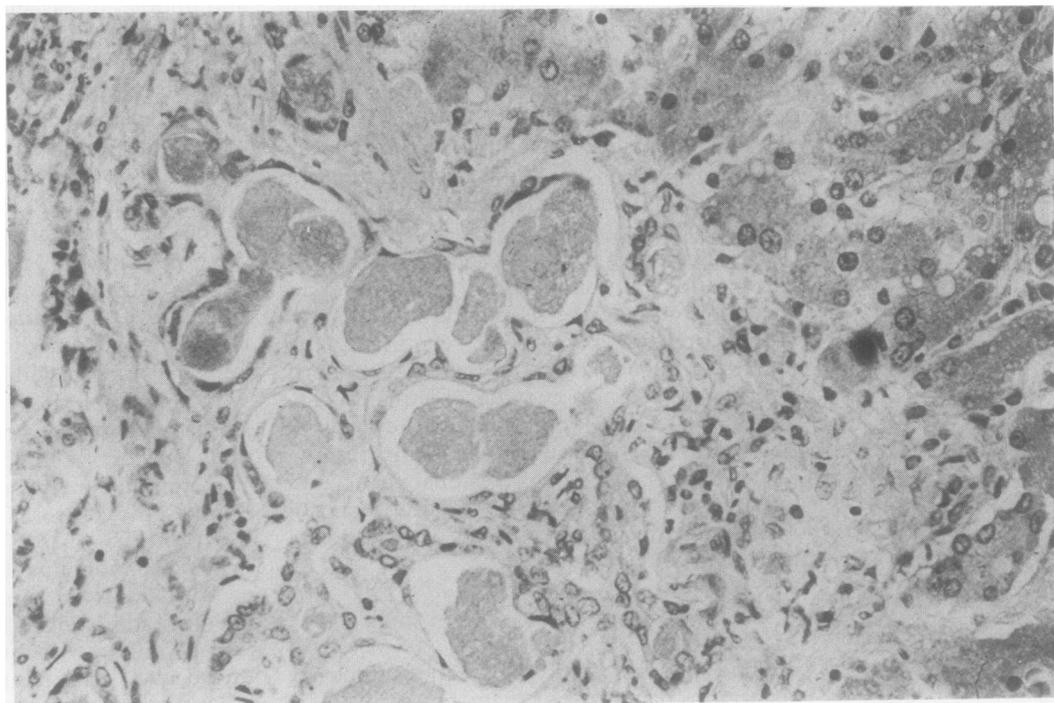
RECTAL PROLAPSE

Rectal prolapse occurs in about 20% of patients and may be the first manifestation of the disease. It is usually recurrent in the first few years of life, spontaneously resolves by 5 years of age, and often improves once treatment for pancreatic insufficiency is initiated. It rarely requires surgical intervention. Rectal prolapse may also occur in the absence of pancreatic insufficiency. In these circumstances attempts to diminish constipation or straining during bowel movements, or both, may be of benefit.

OTHER GASTROINTESTINAL PROBLEMS

Patients with cystic fibrosis may have other gastrointestinal problems, which may or may not be related to cystic fibrosis. Gastro-oesophageal reflux is extremely common and oesophagitis and peptic ulcer disease occur. There have also been reports of coeliac disease and Crohn's disease.

Figure 4 Characteristic morphology of the liver in cystic fibrosis, showing focal bile duct proliferation and accumulation of material within ductules.



PATHOLOGICAL, RADIOLOGICAL, AND FUNCTIONAL ABNORMALITIES

Features of the intestinal mucosa sufficiently characteristic to be diagnostic of cystic fibrosis include increased numbers of mucin filled goblet cells, dilated mucin filled crypts, and eosinophilic casts. Common radiological findings include thickened duodenal folds, nodular filling defects, and variable dilatation of intestinal loops. These findings probably have little clinical importance and should not be interpreted as signs of "duodenitis," ulceration, or inflammatory or infiltrative disease without further confirmation.

Selective intestinal absorptive defects in amino acids and bile acids have been reported, but remain to be confirmed; clinically important defects in the structure and function of the intestinal mucosa are not evident. Villous structure is intact, D-xylose absorption is normal, and intestinal lactase activity is normal or even increased. Lactose intolerance may occur, but its frequency reflects the normal ethnic and age related frequency in the population and it is unrelated to cystic fibrosis.

Hepatobiliary manifestations

The incidence of hepatobiliary problems in cystic fibrosis are listed in the table. The more frequent abnormalities have little effect on overall health and wellbeing. They include (1) obstructive jaundice in infancy, probably secondary to biliary plugging, which often resolves and is not necessarily associated with liver disease later in life; (2) hepatomegaly due to fatty change, which may be present even without appreciable malnutrition; (3) a non-functioning or "micro" gall bladder, unassociated with clinical symptoms.

The characteristic histological lesion in the liver in cystic fibrosis is focal biliary fibrosis, which is often present in symptomless patients with no biochemical evidence of liver disease. It is characterised by inspissated eosinophilic material in dilated ductules, bile duct proliferation, and variable fibrosis (fig 4). This probably

represents the hepatobiliary manifestation of the obstructive pathophysiology of this disease. A primary abnormality in hepatobiliary anion transport was suggested by evidence that patients with cystic fibrosis, regardless of the state of the pancreas, secrete significantly less bile salts than controls without cystic fibrosis.¹⁹ This might result in diminished flow and stasis of bile, and obstruction in the biliary tree. Decreased biliary chloride transport may have an important role but this has not yet been confirmed.

BILIARY STONES

Intrahepatic and extrahepatic biliary stones are one of the two clinically important hepatobiliary problems in cystic fibrosis. Their occurrence may be related to excessive intestinal loss of bile salts in patients with pancreatic insufficiency, causing the production of lithogenic bile. Symptomatic cholelithiasis should be managed as in patients without cystic fibrosis.

MULTILOBULAR BILIARY CIRRHOSIS

Cirrhosis is the second most severe and clinically important problem in cystic fibrosis. It may be the first manifestation of liver disease and be present despite only mild abnormalities of liver enzymes. Although cirrhosis rarely causes hepatocellular failure, it is associated with portal hypertension and oesophageal varices in 2–5% of patients.

The pathogenesis is not clear. It may result from silent progression of focal biliary fibrosis. It has also been proposed that it may be due to common bile duct stenosis secondary to pancreatic fibrosis and intrahepatic biliary tract abnormalities similar to sclerosing cholangitis (both of which occur in cystic fibrosis).^{20–21} This view remains to be confirmed. Unfortunately, no effective treatment is currently available, though experimental approaches, including supplementation with taurine or ursodeoxycholic acid or both, are being tried, to minimise putative toxic effects and enhance bile flow.

The management of hepatic failure, portal hypertension, hypersplenism, ascites, and variceal bleeding in cystic fibrosis is the same as that in those without cystic fibrosis. Sclerotherapy of oesophageal varices and hepatic transplantation have been accomplished successfully in patients with cystic fibrosis.

Nutritional manifestations

Patients with cystic fibrosis are at risk of nutritional deficiencies by three main mechanisms (fig 5)—namely, malabsorption, increased requirements to compensate for the effects of chronic lung disease and perhaps also to meet the increased needs arising from the basic metabolic defect of cystic fibrosis,²² and decreased food intake resulting from illness. All three factors contribute to the frequent development of both macronutrient and micronutrient deficiencies, which may be severe. The fact that energy and nutrient intake is insufficient to meet requirements accounts for the poor weight gain and growth; delayed

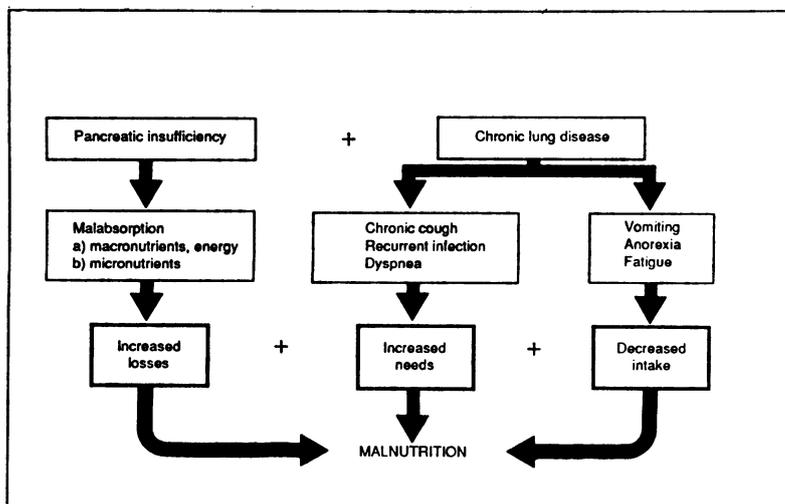


Figure 5 Pathogenesis of malnutrition in cystic fibrosis. Reproduced by courtesy of Medicine (North America).

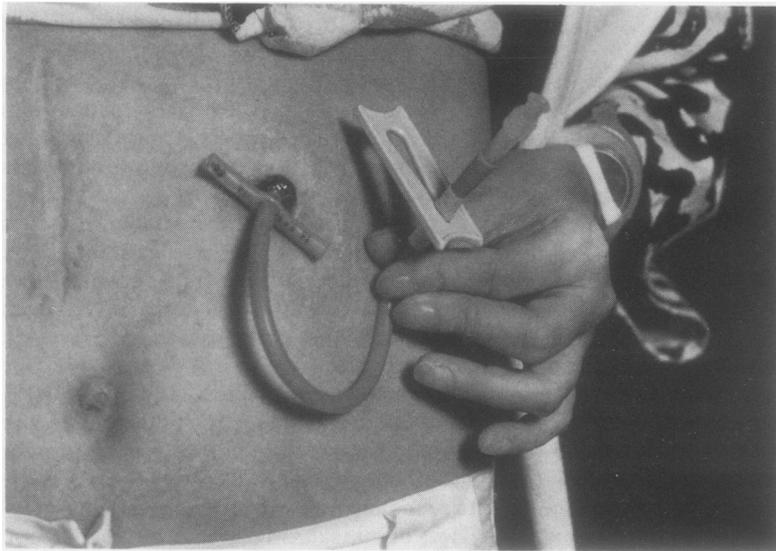


Figure 6 A patient with cystic fibrosis displaying the percutaneous gastrostomy tube. A small amount of granulation tissue has accumulated around the site; it can be removed by application of silver nitrate.

puberty; muscle wasting; and vitamin, mineral, essential fatty acid, and taurine deficiencies.

Standard management of malabsorption includes supplementation with pancreatic enzymes and fat soluble vitamins. Most clinics now recommend and actively encourage consumption of high energy, balanced diets rather than low fat diets, which tended to limit intake of energy and essential fatty acids. Oral liquid energy supplements are frequently encouraged to help patients meet their increased energy requirements, which have been estimated empirically at 120–150% of the recommended nutrient intake for age.

Over the past decade more aggressive approaches to nutritional management have been proposed and are becoming more generally accepted, including the use of total parenteral nutrition^{23–24} and night time enteral feeding of infusions of high energy formulae via a nasogastric tube,²⁵ a gastrostomy,²⁶ or a jejunostomy.²⁷ Nasogastric feeding requires the individual's sustained commitment for nightly insertion of the tube and removal the following morning, and it may be hampered by the presence of nasal polyps and congestion as well as frequent coughing up of the tube in patients with severe chronic cough. Despite the frequency of occult gastro-oesophageal reflux in cystic fibrosis, nasogastric tube feeds are usually well tolerated. Insertion of a jejunostomy tube has been used to avoid problems with reflux. Some centres insert percutaneous gastrostomy tubes (fig 6), without a general anaesthetic or laparotomy, and have had little difficulty with reflux. The provision of an additional 1000–2000 calories a day using elemental, semi-elemental, and polymeric products by any of these routes has been successful in achieving improved weight gain. Unless a polymeric formulation is used, pancreatic enzyme supplementation is not required with these feeds.

On theoretical grounds, the improvement in nutrition should enhance respiratory muscle

strength and immunity, and may therefore have important long term effects on the state of the lungs and ultimately on prognosis. Retrospective cross sectional studies have already documented a correlation between good nutrition and improved lung function⁸ and survival.¹ Overnight feeding and improved nutrition have been associated with improved wellbeing, a slower deterioration of lung function,^{26 27} and a tendency to improved expiratory respiratory muscle strength.²⁸ With the advent of lung transplantation for cystic fibrosis the need to maintain and improve nutrition to optimise the perioperative and postoperative course has increased. Thus aggressive attention to the maintenance of good nutrition has become a major feature in the care of individuals with cystic fibrosis.

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