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# Symposium on 'Cystic Fibrosis'

## Nutrition in cystic fibrosis: a historical overview

BY JOHN A. DODGE
*Department of Child Health, The Queen's University of Belfast, Grosvenor Road, Belfast BT12 6BJ, Northern Ireland*

### A BRIEF HISTORY

When the great Swiss paediatrician Fanconi, with two colleagues (Fanconi *et al.* 1936), reported an association between congenital cystic pancreatic fibrosis and bronchiectasis in 1936, and Dorothy Andersen, a New York pathologist subsequently termed the disorder 'cystic fibrosis of the pancreas' in 1938, there were probably no more than a few hundred such patients in the United Kingdom. Nevertheless, cystic fibrosis (CF) is now widely recognized as the most common of the severe autosomal recessive conditions in this country, with an incidence of about 1:2000–3000 live births and a population carrier rate of between 4 and 5% (British Paediatric Association Working Party on Cystic Fibrosis, 1988). The abnormal gene has clearly been around for a long time. The reason why the condition was not recognized until little more than 50 years ago was because the majority of affected individuals died in early childhood often from pneumonia, in the era before antibiotics. In 1991, with steadily improving management, current survival is estimated at about 25 years. The total CF population is approaching 6000, and increasing at the rate of approximately 130 per annum, and by the turn of the century the CF population will be approximately equally divided between children and adults (UK Cystic Fibrosis Survey, 1991, unpublished results).

As one would expect, the pancreatic abnormalities which are a hallmark of the pathology usually lead to impaired digestion and, hence, absorption of nutrients, particularly fat and protein. Both general malnutrition and deficiency of specific nutrients may, therefore, be expected in the untreated patient. It is believed that the first lesions in the pancreas follow obstruction to small ducts, with retention of secretions and gradual destruction of the acinar tissue. The sequence of cyst formation, attempted repair with increasing fibrosis, and distortion of the architecture leads to pancreatic exocrine insufficiency when more than 90% of function has been lost. This process begins *in utero*, and symptoms of pancreatic insufficiency are often present from birth. The symptoms include greasy offensive stools and failure to gain weight even in the presence of a good appetite. When pancreatic destruction is far advanced, diabetes mellitus may also appear as a result of islet cell obliteration.

The other cardinal feature of CF is an increased susceptibility to respiratory infection which becomes chronic and progresses to dilatation of the bronchi (bronchiectasis) and

increased fibrosis in the lung tissue between them, rather similar to the pathological changes in the pancreas. Indeed, the lung disease is believed to develop in broadly the same fashion, with early obstruction to the smallest airways by sticky mucus, which then becomes colonized with bacteria. The characteristic symptom of lung disease in infancy is a repeated irritating cough which represents the child's attempts to clear the retained secretions, and against this background acute episodes of pneumonia are common. Of course, these infections make further nutritional demands on a young patient who may already be malnourished, and may be an even more important determinant of nutritional status than the presence or absence of pancreatic insufficiency.

Up to 20% of infants with CF present with the condition known as meconium ileus. This is also an obstructive phenomenon in which the small intestine is blocked with tenacious meconium, and may even perforate, usually after twisting of a loaded loop of bowel so that the local blood supply is cut off causing gangrene of the intestinal wall. Intestinal obstruction in the newborn is a surgical emergency, and formerly carried a very high mortality, but with modern surgical techniques the majority survive this initial illness to face the other problems of life with CF.

The treatment of a typical CF patient includes attention to both the digestive and the respiratory aspects of the disease. The basic principles of nutritional management include a high-energy, high-protein diet with vitamin supplements, and the administration of varying amounts of pancreatic extract with each meal. Management of the respiratory problems is based on regular physical therapy and lung drainage procedures, and perhaps a programme of exercise, designed to help the patient cough up any retained secretions. Treatment must be given at least two or three times daily, and requires about 0·5 h each time. Any evidence of respiratory infection is treated vigorously with courses of antibiotics, and may require quite long periods in hospital. Young children often take antibiotics continuously during the first few years of life.

Although the inherited nature of the condition became clear within the first few years after its identification, the nature of the underlying defect was not immediately apparent, nor was it clear why lung and pancreatic disease should be associated. Farber (1945) recognized the sticky nature of the mucous secretions in the respiratory and alimentary tracts, and proposed the name 'mucoviscidosis'. di Sant'Agnese *et al.* (1953) discovered that the sweat of affected patients was very salty, and suggested that many or all exocrine gland secretions could be abnormal. This discovery of increased salt content of the sweat explained the folk wisdom of an old German saying that 'the child will soon die whose brow tastes salty when kissed'. The increased electrolyte content of CF sweat is the basis of the standard clinical test used in diagnosis. It was Quinton & Bijman (1983) who showed that the sweat abnormality was due to a decrease of chloride ion permeability in the sweat ducts. This defect in the passage of chloride has been found not only in sweat glands but also in respiratory epithelium and placental membranes, and it is assumed that the same abnormality of chloride transport is present in pancreatic ducts. The two main aspects of basic research into cystic fibrosis during the last decade have been in cell physiology and molecular biology. The cell physiologists have been attempting to discover why chloride transport is impaired, and concluded that the defect involved failure to phosphorylate a chloride channel found in certain epithelial tissues. The geneticists and molecular biologists, by observing linkages between CF and known genetic probes, discovered in 1985 that the gene was situated on the long arm of chromosome 7 (Eiberg *et al.* 1985). It took another 4 years of painstaking analysis

involving 'walking' and 'jumping' techniques to identify the gene, define its molecular structure, describe its protein product in terms of amino acid sequence and probable shape, and identify its most common mutation. The results of this work were published in three notable papers in *Science* in September 1989, by workers from Toronto and Michigan (Kerem *et al.* 1989; Riordan *et al.* 1989; Rommens *et al.* 1989). The gene product is a membrane-bound protein which has been named CF transmembrane regulator (CFTR), which appears to be one of a family of proteins involved in membrane transport of large molecules. In this case the protein either acts as a chloride channel or is closely involved in regulating chloride channel function. The most common mutation, known as delta F508 because a molecule of phenylalanine found in position 508 has been deleted, accounts for about 71% of CF mutations in this country (McIntosh *et al.* 1989), and when present in homozygous form appears to be associated with a severe form of CF. The other 25% of abnormal genes have other mutations, of which more than eighty have been described so far. Each of these other mutations is found in only a small proportion of CF patients and their families, but the large number of possibilities makes screening tests based on identification of a precise genetic abnormality very difficult if the whole range of known mutations has to be excluded. Current basic research is directed towards a more complete understanding of the mechanism(s) of CFTR function and dysfunction, and towards introduction of a normal gene using a virus vector, as well as to pharmacological methods by which the abnormal CFTR function can be either bypassed or rectified. Progress is rapid and exciting, but there remains a large population of patients with established disease. Moreover, because pancreatic damage is already well established before birth in the majority it is likely that the need for good nutritional strategies in CF will continue.

## GENERAL NUTRITIONAL PROBLEMS

The improved survival in CF has been accompanied by a corresponding improvement in nutritional status. Nowadays we do not often see the wasted young children characteristic of CF a generation ago. Even those infants and young children who are stunted and wasted at the time of diagnosis respond well to intensive nutritional rehabilitation, and to outward appearances may seem virtually normal for some years. Sooner or later, however, the disease begins to take its toll and weight gain, followed by height velocity, begin to slow down. The faltering of growth is often, but by no means always, associated with the first evidence of chronic pulmonary infection with *Pseudomonas aeruginosa.* Unless particular attention has been paid to maintenance of body-weight, most CF patients are underweight for their height by the time they reach adulthood. There is good evidence from North America that a strong emphasis on maintaining body-weight by nutritional means correlates well with improved survival, and the difference in mortality seen between different CF clinics with similar approaches to management of respiratory disease can be explained by differences in nutritional management (Corey *et al.* 1988). Whether normal growth in childhood, and the maintenance of a steady body-weight in adults, can be achieved depends on the balance between the energy requirements of the patient and his or her energy expenditure and losses being maintained in equilibrium (Fig. 1). Evidence for and against an increased energy requirement as an intrinsic part of the basic metabolic defect is presented elsewhere (O'Rawe *et al.* 1991), but is suggested by the observation that the mean birth weight of CF infants is approximately 0·5 standard

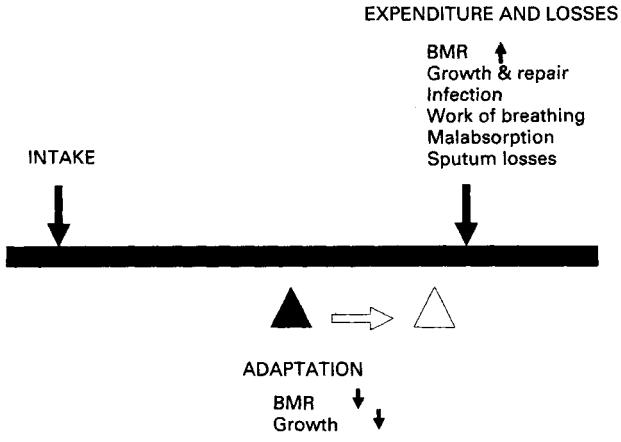


Fig. 1. Energy balance in cystic fibrosis. BMR, basal metabolic rate.

deviations below that of the general population. Biochemical evidence of malnutrition may be present within a few weeks of birth. In babies diagnosed by a neonatal screening procedure, low serum protein values were found as early as 2 months of age (Reardon *et al.* 1984; Mischler *et al.* 1991). In nine of sixty-six (13%) CF infants under 1 year of age in Denver, Colorado, protein–energy malnutrition was diagnosed on the basis of low serum proteins, oedema and anaemia. Eight of the babies were not taking pancreatin supplements. All nine had low zinc levels and six had *Pseudomonas aeruginosa* cultured from tracheal aspirates (Abman *et al.* 1986).

There are clearly important interactions between pancreatic disease and pulmonary infection. Malnourished children without CF but with a tracheostomy are more likely to be colonized with *Pseudomonas aeruginosa* than those who are well nourished. Malnutrition in rats is accompanied by decreased phagocytosis of *Pseudomonas*. Nevertheless, although malnutrition may predispose to pulmonary disease, it is the respiratory infection which is the main determinant of well-being and survival. In one study, children who presented with gastrointestinal features of CF had a good clinical course over the next 5 years regardless of the age at presentation. In contrast, those who presented with respiratory features frequently deteriorated (Kraemer *et al.* 1978). On the other hand, aggressive nutritional therapy may not only restore weight gain but also lead to fewer episodes of pneumonia (O'Loughlin *et al.* 1984). Although good nutrition will slow the rate of deterioration in lung function, damaged lung cannot be replaced. Established malnutrition produces a reduction in basal metabolic rate and in growth (adaptation). Growth velocity, and particularly weight gain, is the best clinical indicator we have to assess the adequacy or otherwise of food intake. Whatever the validity of recommended daily allowances (RDA) may be, normal growth velocity is often not achieved with energy and protein intakes below 120% RDA. This may be in part explained by continuing nutrient losses in the stools despite high intakes of pancreatin, and chronic infections may be another significant factor. The importance of respiratory

disease in determining nutritional status was emphasized by Kraemer *et al.* (1978), who showed that patients with predominantly respiratory problems were more likely to be underweight-for-height than those with only pancreatic disease. Such strict separation into exclusively digestive or respiratory inadequacy is usually difficult to achieve, and evidence from the Toronto clinic has shown that severe involvement of the pancreas is usually accompanied by severe involvement of the lungs, while those with normal fat absorption have a better respiratory prognosis (Gaskin *et al.* 1982). Further studies from Toronto suggest that pancreatic insufficiency, which correlates with severe lung involvement, can be explained by reference to the specific gene mutations (Kerem *et al.* 1990), but the severity of lung involvement can also be significantly modified by aggressive treatment. This is evident from the fact that the prognosis for CF has improved more than tenfold during a period when treatment has of necessity been directed at controlling symptomatic manifestations of the disease, rather than curing its basic genetic or metabolic nature.

## SPECIFIC NUTRIENT DEFICIENCIES

Even before Fanconi (1936) and Andersen (1938) described CF as a distinct entity, Blackfan & Wolbach (1933) had reported a clinical and pathological study of vitamin A deficiency in infants. No fewer than six of the eleven infants examined at autopsy had extensive pancreatic lesions 'all identical and presumably representing a disease entity'. They concluded that the pancreatic disease might be responsible for failure to utilize vitamin A in the presence of an adequate intake, and noted that the same condition could occur without evidence of vitamin A deficiency. All six also had bronchiectasis and there can be no doubt that they were cases of CF. In an early paper, Dorothy Andersen (1939) reported that 20% of CF patients were deficient in vitamin A. It was subsequently shown that low levels of retinol-binding protein may be just as important as fat malabsorption in its aetiology. Even in the presence of low plasma vitamin A levels, a normal or increased liver concentration is found at autopsy, which suggests that there may be a problem in mobilization of vitamin A from the liver (Underwood & Denning, 1972). Among the clinical features described in CF are night blindness, conjunctival xerosis, dry thickened skin and abnormalities of bronchial mucosal epithelialization. Similar bronchial mucosal abnormalities are described in very-low-birth-weight infants with vitamin A deficiency and bronchopulmonary dysplasia. Andersen (1939) believed that the vitamin A deficiency may be a contributory factor to the clinical picture of CF, and it is possible that in the CF infant deficiency of vitamin A may predispose to bronchial infection, delay and prolonged normal healing after infection, and contribute to the loss of ciliary activity and loss of normal water homeostasis which are characteristic of both conditions. There is plenty of evidence that subclinical vitamin A deficiency appears early in the course of CF, and a study of thirty-six asymptomatic infants detected by newborn screening revealed deficiency in both vitamins A and E, and a significant proportion with low serum albumin, by the age of 6–8 weeks (Sokol *et al.* 1989). Indeed, xerophthalmia due to vitamin A deficiency was the presenting symptom in two infants with CF, and suggested the diagnosis (Brooks *et al.* 1990). Subclinical vitamin A deficiency may be detected by abnormal dark adaptation. Eight such patients were found in a series of forty-three aged between 8 and 44 years, and three of them also had conjunctival xerosis. Affected patients had lower levels of vitamin A and retinol-binding

protein than the others, and were more likely to have abnormal liver function tests (Rayner *et al.* 1989).

Deficiency of vitamin D, by contrast, is distinctly uncommon in CF patients. Contributory factors include malabsorption of vitamin D, malabsorption of calcium and phosphorus, and under-exposure to sunlight. In practice, the great majority seem to be able to produce enough vitamin D from sunlight, although blood levels of 25-hydroxycholecalciferol vary according to season and sunlight exposure (Reiter *et al.* 1985). Reduced bone density in patients with CF was described by Mischler *et al.* (1979). Frank rickets is rarely seen unless the patient has some co-existing (but perhaps related) problem such as severe liver disease.

Vitamin E deficiency, on the other hand, is almost always present in CF unless supplements have been given. Not only may it be detectable within the first month or two (Sokol *et al.* 1989), but it is sometimes the presenting feature, with haemolytic anaemia and jaundice in young infants. Some unsupplemented adults with CF may present with spinocerebellar degeneration and dysarthria, ataxia, weakness, absent reflexes and loss of proprioceptive sensation (Elias *et al.* 1981). Nerve conduction was delayed in eight of eighteen CF patients aged 5–25 years. These individuals were deficient in vitamin E and tended to be older and have poorer general condition than the remainder (Cynamon *et al.* 1988). Serum vitamin E levels were also found to be lower in CF patients with liver disease than those with normal liver function tests (Stead *et al.* 1986). Vitamin E deficiency is both more common and more marked than deficiencies of vitamin A and D, and may be related to reduced intralumen concentration of bile salts (Sitrin *et al.* 1987).

Deficiency of vitamin K also occurs occasionally. Contributory factors include malabsorption, decreased bacterial production of vitamin K in patients treated with antibiotics, decreased dietary intake and impaired liver function.

There is no reason to expect deficiencies of water-soluble vitamins unless the diet is very abnormal, but impairment of folic acid absorption by oral pancreatic extracts has been described in adults with chronic pancreatitis, although as far as I am aware no similar observation has been made in CF. The folate is believed to form insoluble complexes with pancreatin (Russell *et al.* 1980). Low levels of pyridoxal 5′-phosphate have been reported suggesting impaired pyridoxine metabolism in CF patients with reduced liver function (Faraj *et al.* 1986). Reduced absorption of vitamin $B_{12}$ can be demonstrated in all patients, perhaps because of failure of neutralization of gastric acid in the duodenum. Serum vitamin $B_{12}$ levels are usually normal, but one patient with a macrocytic anaemia has been described (Rucker & Harrison, 1973).

Similarly, deficiencies of minerals would not usually be expected as a consequence of pancreatic insufficiency, unless the diet is abnormal or the disease or its treatment imposes increased demands. There are important physiological interactions between Zn and vitamins A and E, and there is some evidence that CF children with impaired growth have lower plasma Zn levels than those of normal stature (Halsted & Smith, 1970). In a patient with severe retardation of growth and sexual development, plasma Zn levels were exceptionally low as a consequence of CF and nephrotic syndrome occurring together, which led to excessive loss of Zn in the urine. Treatment with large amounts of Zn resulted in spectacular growth and rapid sexual development (Dodge & Yassa, 1978). Treatment with aminoglycoside antibiotics causes loss of magnesium in the urine, and symptomatic Mg deficiency with tetany has been described in CF patients treated in this way (Green *et al.* 1985). Even in the presence of cyanosis, polycythaemia is uncommon

in CF and this may be due to a relative lack of iron. In other words, these patients are relatively anaemic and low Fe stores have been reported in such patients (Ater *et al.* 1983). Any such deficiency is more likely to be due to dietary inadequacy than malabsorption, and Fe absorption is reported as normal in children with CF and increased in those who have low Fe stores (Heinrich *et al.* 1977).

Deficiency of selenium causes different symptoms in different species of animals, particularly affecting the young. Se deficiency in the chick results in pancreatic atrophy thought to resemble CF, and similar observations have been made in sub-human primates. This led to a speculation that the clinical manifestations of CF might be due to Se deficiency (Wallach & Garmaise, 1979). Although several authors have confirmed that the mean plasma Se in CF patients is lower than that in controls (van Caillie-Bertrand *et al.* 1982; Neve *et al.* 1983; Dworkin *et al.* 1987), there has been no supportive evidence that Se deficiency contributes to the usual clinical picture of CF, and other authors have found comparable levels in patients and controls (Castillo *et al.* 1981; Lloyd-Still & Ganther, 1981). Like vitamin E, Se protects biological membranes against oxidation and deficiency of the two antioxidants may have a cumulative effect. The possibility that Se deficiency might have predisposed to gastrointestinal malignancy in some adult CF patients was raised by Stead *et al.* (1985). Nevertheless, the danger of Se intoxication is such that supplementation is not routinely advised, except in patients treated with total parenteral nutrition where myopathy due to Se deficiency has been described (Watson *et al.* 1985). The fact that plasma levels of Se in CF patients in Europe and North America are similar to those of healthy children in New Zealand, where there is no increased incidence of pancreatic insufficiency or CF, makes it unlikely that Se plays a primary role in CF.

In addition to individual deficiencies of vitamins and minerals which are evidently secondary nutritional problems in CF, essential fatty acid (EFA) deficiency has been proposed as a direct consequence of the underlying metabolic defect (Carlstedt-Duke *et al.* 1986). This followed the observation that arachidonic turnover in lymphocytes is increased. Deficiency of the arachidonic acid precursor, linoleic acid, has been widely observed in CF and biochemical evidence of EFA deficiency has been found in cord blood of affected newborns, and in infants diagnosed by newborn screening (Mischler *et al.* 1991). The administration of large amounts of linoleic acid and its derivatives has been claimed to produce both clinical benefit and in some instances a reduction of sweat electrolytes. In acute experiments involving CF volunteers, Navaro *et al.* (1989) showed that intravenous administration of lipid emulsion containing linoleic and oleic acids (Intralipid) had a marked effect on nasal potential difference, restoring it towards normal. This effect was transient and lasted for less than 1 h after the infusions. In a trial of evening primrose (*Oenothera biennis*) oil, which is rich in both linoleic acid and γ-linoleic acid, we found that treated patients showed little objective clinical benefit after 1 year of treatment, but there was an intriguing and consistent fall in sweat sodium (but not chloride) concentration which reverted to baseline levels when the supplements were discontinued (Dodge *et al.* 1990). This suggests that linoleic acid and its derivatives may indeed be directly involved in the regulation of electrolyte transport, and recent work from the United States has shown that both arachidonic and linoleic acids effectively inhibit chloride channel activity (Guggino & Hwang, 1990), while free arachidonic acid activates Na channels (Ausiello, 1990). Failure to remove arachidonic acid, or perhaps one of its metabolites, would, thus, keep chloride channels closed while stimulating Na pump activity, which exactly fits the physiological disturbance observed in CF.

Enlargement of the liver with fatty deposition is a common finding in children with CF. It is usually attributed to defective hepatic secretion of triacylglycerols as low-density lipoprotein resulting from diminished apo-lipoprotein synthesis. In a recent case report, Treem & Stanley (1989) describe an 8-month-old boy with CF where secondary carnitine deficiency led to a massively enlarged fatty liver. They postulated that decreased availability of carnitine may have led to decreased fatty acid transport into mitochondria, decreased ketogenesis by intramitochondrial oxidation of fatty acids, and the metabolic consequences of maladaptation to fasting. In a study of carnitine status in cord blood in CF, Lloyd-Still *et al.* (1990*a*), showed no significant differences between CF infants and controls in respect of total and free carnitine, but short- and long-chain acyl-carnitines were significantly lower in CF compared with controls, and they concluded that alterations in fat metabolism may be occurring *in utero* in CF. In a follow-up study, workers from the same unit found that a few CF infants had low carnitine levels at diagnosis which came into the normal range after 1 year of supplementation. They found no evidence for a major defect in carnitine metabolism in most infants with CF (Lloyd-Still *et al.* 1990*b*).

## PRINCIPLES OF MANAGEMENT

Human milk has the advantage over milk formulas that it carries its own bile-salt-activated lipase (*EC* 3.1.1.3). For sound nutritional as well as psychological reasons, therefore, mothers of CF infants are usually advised to breast-feed their babies whenever possible. This presents some practical problems with administration of pancreatin, and undoubtedly some breast-fed CF babies fail to thrive, either because of inadequate protein absorption or in consequence of early respiratory infections. A syndrome of hypoproteinaemia, oedema and anaemia has been observed in young infants fed in a variety of ways, but not if sufficient pancreatic enzymes have been given. For some time a 'home-made' milk formula originating in the Hospital for Sick Children London and colloquially referred to as 'cystic milk' was used in the UK. It was based on a mixture of a proprietary milk formula, dried skimmed milk and glucose polymer in equal parts and was effectively a high-energy low-fat formula (Francis, 1981). If a specialized formula is required, for instance following surgery for meconium ileus, Pregestemil, which contains medium-chain triacylglycerols and partially hydrolysed proteins has been widely recommended and is generally satisfactory. In the uncomplicated CF infant standard infant milk formulas are usually satisfactory provided that pancreatic extracts are given in addition.

At all ages, routine supplements of the fat-soluble vitamins A and D, which are usually packaged together with water-soluble vitamins, are necessary. As a rule of thumb, dosage is twice the RDA. Vitamin E supplements are not usually contained in the polyvitamin preparations and are now widely considered to be necessary. The diet itself should be high-energy, high-protein and have a normal fat content. The crude (and cheap) pancreatic extracts used for many years had limited bioavailability and were, therefore, often used in conjuction with a low-fat diet. This policy represented a double disadvantage to the patient, who not only ingested insufficient energy because of the fat restriction but also lost a significant proportion of the total through malabsorption. Modern pancreatic supplements consist of small granules (microspheres) which are individually enteric coated and disintegrate in the duodenum. Bioavailability is much

greater than with the old preparations, and this has allowed the dietary fat content to be brought up to normal. Although significant malabsorption of fat and protein may persist, it has nevertheless been possible, with good dietetic advice, to maintain normal growth velocities in patients willing to follow instructions. I have already commented on the need to treat respiratory infection vigorously, and would emphasize that this may be even more important than specifically nutritional management in preventing progressive malnutrition.

Sooner or later, as respiratory failure develops, the work of breathing becomes so great that tired, depressed and anorexic patients are no longer able to maintain nutritional balance by increasing their food intake. When this stage is imminent, high-energy supplements should be given. There is a wide variety of preparations available, which may be given orally, by nasogastric tube or through a gastrostomy. Clinical trials have demonstrated the short-term benefit of an aggressive approach to nutritional management, but such studies have usually been carried out in patients whose decline is far advanced. There is a growing consensus that nutritional intervention should be considered earlier in the course of the disease. Clinical experience combined with literature reports indicates that the patients who benefit most are those who are already reasonably well nourished (Allan *et al.* 1973; Yassa *et al.* 1978; Soutter *et al.* 1986).

In summary, although CF is a biochemical disorder and unlikely to be treatable by purely nutritional means there is no doubt that its course may be significantly ameliorated by wise and intensive dietary management.

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