A rational approach to the nutritional care of patients with cystic fibrosis

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Introduction

For many years, chronic undernutrition with significant weight retardation and linear growth failure, has been recognized as generalized problem of most large patient populations with cystic fibrosis (CF). Despite acknowledgment of its seriousness, chronic malnutrition was felt to be an inherent consequence of the disease; others argued that malnutrition was a natural consequence of physiological adaptation to advanced pulmonary disease. A number of early studies of CF patients, however, showed a good correlation between the severity of malnutrition and an accelerated decline in pulmonary function which in turn adversely affected overall survival[1,2]. Many authors have speculated that these two factors are causally associated, but it is not clear whether prevention of malnutrition and growth failure will ameliorate the rate of progression of lung disease and improve survival. In recent years there has been renewed interest in evaluating the multiple interdependent variables giving rise to chronic malnutrition and growth failure. In a number of CF centres, nutritional support is now viewed as an integral part of the care of the patients with cystic fibrosis and aggressive programmes have been instituted to prevent malnutrition.

It is now recognized that most growth problems in patients with CF are due to unfavourable energy balance rather than to an inherent factor of the disease itself. Roy *et al.*[3] drew attention to a number of reports from the Cystic Fibrosis Clinic in Toronto indicating that by far the majority of CF patients attending the Toronto clinic closely conformed to the normal distribution for growth[4,5]. Cross-sectional growth data from the Toronto clinic showed a normal distribution of height percentiles in males and females. In females, however, particularly after adolescence, weight distribution was skewed towards the lower centiles, but this was less evident than similar data obtained from other centres. In a comparative study of two CF clinic populations of similar size and age distribution (Toronto and Boston), Corey *et al.*[6] found a marked difference in median age of survival between the two centres (Table 1). Median survival in Boston (21 years) was markedly worse than in Toronto (30 years); furthermore, after 10 years of age there was a dramatic separation in survival curves between the two centres. Pulmonary function was no different in the two clinic populations. Patients in the Toronto clinic, however, were taller than those in the Boston clinic, and males in Toronto were heavier. It is noteworthy that, with the exception of nutritional management of their patients, the general approach to patient care, particularly pulmonary care, was similar in the two clinics. It was suggested that the improved survival in the Toronto CF population could be attributed to superior nutritional status.

Table 1. Characteristics of cystic fibrosis clinic populations in Boston and Toronto (1982)●

	Boston	*Toronto*
Number of patients	499	534
Male/female (%)	57/43	58/42
Age: mean±SD (years)	15.9±9.6	15.2±8.3
range (years)	0-45	0-43
Median survival 50% (years)	21	30

●Adapted from Corey *et al.*[5]

A review of existing dietary practices in the two clinics revealed a striking difference in philosophy. Standard practice in Boston[7] closely resembled the traditional approach in most centres throughout the world. This approach involved prescribing a low-fat, carbohydrate-rich diet. It was reasoned that reduction in dietary fat would improve bowel symptoms and reduce stool bulk. Recognizing the problem of maldigestion and absorption of long-chain triglycerides many centres advocated use of artificial diets with protein hydrolysates and substitution of long-chain fat with medium-chain triglycerides (MCT)[8]. However, a series of reports showed no long term benefits to growth when protein hydrolysates and MCT were used as supplements or substitutes[9]. Fortunately, these supplements are now hardly ever used through reasons of cost, poor compliance and unpalatability. Too often, the net effect of a restrictive, unpalatable diet was to present young CF patients with tasteless choices and to exclude them from the many energy-rich foods that are part of a 'normal' Western diet. Chronic malnutrition from reduced energy intake appears to have been an unfortunate, yet deliberate iatrongenic effect in most CF programmes worldwide.

Since the early 1970s, the Toronto group advocated a calorically enriched diet by encouraging not restricting fat intake and encouraging additional enzyme supplements to enhance digestion[10,11]. Because fat is the most energy rich, economical and appetising energy source, patients were encouraged to eat larger portions than their peers; to add fat in the form of butter or untrimmed meat, and to have high calorie snacks between meals and before bed. Fat

malabsorption occurred, but with additional pancreatic enzyme supplements, net absorbed energy improved, resulting in better growth. It is gratifying that in recent years increasing numbers of clinics worldwide have accepted a similar philosophy for the nutritional care of their patients. Thus, it appears that the potential for growth among patients with CF closely resembles that of the normal population.

Pathogenesis of malnutrition

A variety of complex related and unrelated factors may give rise to the progression of energy imbalance in patients with CF. The net effect on growth potential varies considerably, according to marked differences in disease severity from patient to patient, and with disease progression. Specifically, energy imbalance results from three interrelating factors: increased energy losses, reduced energy intake and increased energy expenditure (Figure 1).

Energy losses

Fecal nutrient losses from maldigestion/malabsorption are known to contribute to energy imbalance. Only 1-2% of total pancreatic capacity for secreting enzyme is required to prevent maldigestion[12], and yet in the majority of CF patients a degree of pancreatic failure is present at diagnosis. In those who exhibit maldigestion, very good correlations exist between residual pancreatic function (colipase secretion) and fat malabsorption up to daily fat losses of approximately 40% of intake (Figure 2). Patients with documented steatorrhoea, therefore, appear to have small but varying degrees of residual pancreatic function and this observation at least partially explains why some patients with pancreatic insufficiency appear to digest nutrients better than others when given pancreatic enzyme supplements with meals. Other factors may contribute to the problem of maldigestion. In the absence of adequate pancreatic bicarbonate secretion[13], gastric acid entering the duodenum may lower intestinal pH until well into the jejunum. Pancreatic lipase is readily denatured below pH 2 and even if not denatured, enzymatic activity is considerably reduced at a low pH. Bile acids are readily precipitated in an acid milieu[14], and duodenal bile acid concentration may fall below the critical micellar concentration, thereby exacerbating fat maldigestion. Precipitated bile salts also appear to be lost from the enterohepatic circulation in greater quantities, which reduces the total bile salt pool and alters the glycocholate : taurocholate ratio. Oral taurine supplements have been reported to benefit some patients[15]. This tendency is exacerbated by the

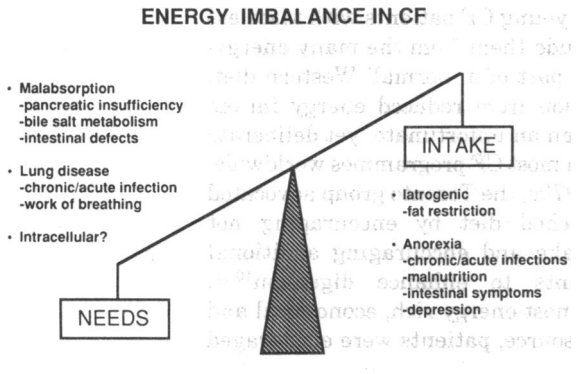

Figure 1. Factors producing energy imbalance in patients with cystic fibrosis (adapted from Roy et al.[3]*)*

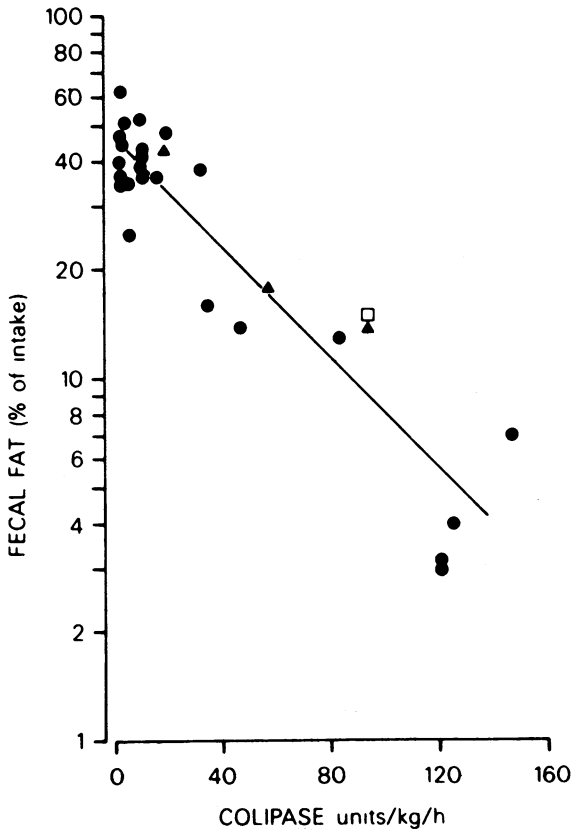

Figure 2. Comparison of fecal fat excretion (% of fat intake) with pancreatic colipase secretion in 28 patients with severe pancreatic dysfunction. Open circles; control subjects. Closed circles; patients with cystic fibrosis. Closed triangles; patients with Shwachman syndrome. Open square; patient with congenital pancreatic hypoplasia. (r=−0.92, P <0.001) Reprinted with permission from Gaskin et al.[12] Gastroenterology *86: 1-7, copyright 1984 by the American Gastroenterological Association*

binding of bile salts to unabsorbed protein or neutral lipid. Excessive mucus, with altered physical properties, may have a deleterious effect on the thickness of intestinal unstirred layer, further limiting nutrient absorption. Despite improvements in the enzymatic activity and intestinal delivery of ingested pancreatic enzymes, many patients continue to have severe steatorrhoea and azotorrhoea.

Energy intake

There has been very little documentation of actual energy intakes in patients with CF. It is widely accepted that energy intake should exceed normal requirements, and crude estimates have suggested that patients require 120-150% of the recommended daily allowance (RDA)[3]. However, when we accurately evaluated nutrient intakes in a group of healthy adolescents, we were surprised to learn that energy intakes were frequently in the range of 80-100% of RDA for age, body weight and sex[16]. Those with normal growth percentiles for height and weight did show higher energy intakes than the patients with growth retardation. Furthermore, other CF centres who have since encouraged more liberal attitudes to dietary fat intake have noted a corresponding improvement in energy intake and growth[17,18].

Some patients with cystic fibrosis are particularly prone to complications that limit appetite and oral intake. Oesophagitis is quite common in

patients with advanced pulmonary disease and is frequently associated with pain, anorexia and vomiting following bouts of coughing[19,20]. The distal intestinal obstruction syndrome (meconium ileus equivalent), an unusual form of subacute obstruction within the distal ileum and proximal colon[21], is particularly prevalent in adolescents and adults with pancreatic failure; it frequently causes recurrent, crampy abdominal pain and patients often find that the symptoms are exacerbated by eating. Other abdominal symptomatology, including extrahepatic biliary obstruction, cholangitis, advanced liver disease and severe constipation are less likely to be associated with decreased dietary intake.

Acute respiratory exacerbations are common causes of restricted oral intake, often resulting in acute weight loss. In patients with mild pulmonary disease, there is rapid catch-up in weight following improvement in respiratory symptoms, but in the terminal stages of pulmonary disease, chronic anorexia is a consistent feature. Further, patients with a severe chronic disease may be prone to bouts of clinical depression, which in the adolescent or adult may induce severe anorexia.

Energy expenditure

Considerable data are emerging to suggest that patients with CF have increased rates of energy expenditure, but there is disagreement regarding the fundamental mechanisms. In 1984, Pencharz *et al.*[22], evaluated the relationship between heart rate and energy expenditure using an exercise cycle with graded workloads and simultaneous measurements of oxygen consumption and carbon-dioxide production using a closed-circuit indirect calorimeter and heart-rate telemetry. Subjects were malnourished and were receiving nutritional rehabilitation by continuous nasogastric tube feeding with a semi-elemental diet. Absorbed energy intake was calculated by subtracting stool energy content from the energy content of the feed. The energy needs of the patients were shown to be 25-80% higher than healthy individuals of the same age, sex and size. It was hypothesized that energy expenditure increased due to increased work of breathing in patients with advanced lung disease. Consequently, a patient with advanced lung disease might not be able to ingest sufficient calories to meet energy needs, resulting in energy imbalance and weight loss. In a subsequent study by the same group, resting energy expenditure was measured by continuous computerized open-circuit indirect calorimetry in 71 patients (8.9 to 35.5 years) who were not suffering from an acute respiratory infection[23]. Nutritional status and pulmonary function were studied simultaneously. Resting energy expenditure was found to be above normal (range 95-153%) of predicted values for age, sex and weight, and was negatively correlated with pulmonary function and nutritional status (percentage of body fat). In addition, in agreement with previous observations of others[2], pulmonary function was positively correlated with nutritional status. These findings have since been confirmed by Buchdahl *et al.*[24] who demonstrated that patients with CF had resting energy expenditure of 9% above body weight and 7% above lean body mass, respectively, in comparison with healthy controls. Although patients with severe pulmonary disease tended to have higher energy expenditure, increased levels of energy expenditure were also seen in those with normal pulmonary function and in 4/5 patients with above average weight for expected age.

This observation is of great interest because laboratory studies have suggested that the primary CF defect might be associated with an energy-requiring mechanism at the intracellular level, possibly within mitochondria. Feigal and Shapiro[25] measured O_2 consumption in cultured fibroblasts from CF homozygotes and heterozygotes. The rate of O_2 consumption exceeded control fibroblasts by 2 times in homozygotes and 1-1/2 times in heterozygotes. Subsequent studies in CF nasal epithelium showed oxygen consumption exceeded control tissue by 2-3 fold[26]. In this regard, Shepherd *et al.*[27] investigated total energy expenditure using the doubly-labelled water method in clinically well, appropriately nourished CF infants without clinical evidence of lung disease and data was compared with studies in healthy infants. This methodology measures total energy expenditure in unrestricted subjects. CF infants evaluated by this method had 25% higher rates of energy expenditure in comparison with data obtained by the same method in 16 healthy infants matched for age and body weight. These exciting preliminary observations require further confirmation and detailed analysis of potential confounding factors.

Pathogenesis of an energy deficit

A model is proposed to explain the etiology of the energy deficit in the CF patient (Figure 3), and defines the web of interdependent variables which may give rise to chronic malnutrition, and growth failure in patients with CF. It must be re-emphasized, however, that in the majority of patients with minimal or moderate pulmonary disease normal growth velocity can be achieved by consuming adequate diets, thus compensating for the three fundamental factors responsible for an energy deficit (Figure 1). Expressed differently, the majority of patients with CF can maintain normal growth velocity and nutritional status by voluntary intake of calories until severe lung disease supervenes[6]. We and others have speculated that malnutrition and decline in pulmonary function are closely interrelated, but the cause-effect relationships remain to be proven. As lung disease worsens, most commonly in older adolescents and young adults, a number of factors come into play which might predisopose to an energy deficit and malnutrition. There may be an increase in frequency and severity of pulmonary infections which in turn induce anorexia. Chest infections often given rise to vomiting

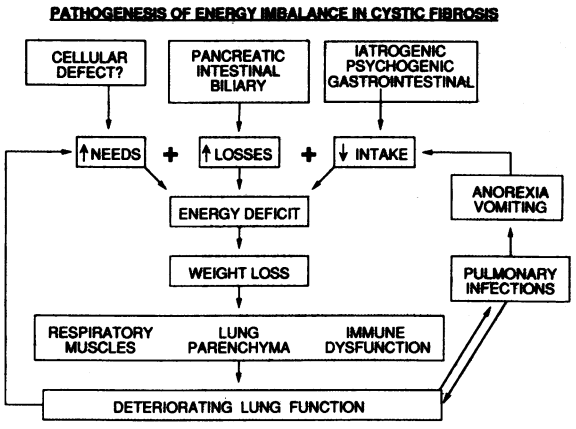

Figure 3. Interdependent factors which may give rise to progressive energy deficit as lung function deteriorates

which may further reduce intake. These factors, in combination with additional energy needs from increased work of breathing, may induce an energy deficit. Weight loss will result, initially producing a significant loss of adipose tissue, but with time there is a marked loss of lean tissue, with muscle wasting. Respiratory muscle wasting would adversely affect respiratory motion and coughing, resulting in further deterioration of lung function. Malnutrition is known to adversely affect lung elasticity[28] and a variety of aspects of immune function[29]. All these factors would, therefore, contribute to progressive deterioration of lung function. In essence, a vicious cycle is established, leading inevitably to end-stage pulmonary failure and death.

Deficits of essential nutrients

Deficits of essential micronutrients can arise as a result of primary malnutrition, but are commonly due to secondary features of the disease[30]. By way of example, CF patients with pancreatic insufficiency frequently malabsorb fat soluble vitamins and this places them at risk of developing clinical signs and symptoms of deficiency.

Water soluble vitamins

All water-soluble vitamins except vitamin B_{12} appear to be well absorbed, and there is no good evidence of clinically significant deficiencies in well nourished patients. Vitamin B_{12} absorption should be normalized with adequate pancreatic enzyme replacement therapy. Vitamin B_{12} supplementation is not necessary, apart from those patients with meconium ileus who have undergone extensive ileal resection and show biochemical evidence of vitamin B_{12} deficiency.

Fat soluble vitamins

Deficiencies of vitamins A, D, E and K have been repeatedly demonstrated at diagnosis[30,31]. In most instances, supplementation of fat soluble vitamins is instituted following diagnosis, but the recommended dose for each vitamin has not been adequately established and current routines vary considerably[31]. Optimal quantities and formulation of each preparation have been established on arbitrary grounds. There is little doubt, however, that supplementation with fat soluble vitamins is a necessary part of the nutritional care in CF patients with pancreatic insufficiency or severe liver disease.

Vitamin A: Clinically overt signs of vitamin A deficiency are rare. Increased intracranial pressure is an uncommon complication[33]. Treated patients appear to have high hepatic concentrations of vitamin A[34]. In fact, serum concentrations of vitamin A are frequently low in spite of supplementation, but levels usually correlate with serum concentrations of retinol-binding protein suggesting that malnutrition contributes to the deficiency[31,35]. It has been suggested that zinc deficiency may inhibit mobilization and transport of vitamin A, but biochemical evidence of true zinc deficiency is not commonly recognized[36].

Vitamin D: Vitamin D deficiency rickets and other clinically significant abnormalities of mineral and bone metabolism were infrequently reported in early studies of patients with CF[30,37]. Nevertheless, more recent studies have demonstrated that bone demineralization may be quite common. Mineral metabolism was assessed in patients with CF by quantifying active metabolites of vitamin D and radiographic bone mass in adolescents and young adults with CF and age-matched controls, living in two geographic regions with low and high sunlight exposure[38]. The levels of 25-hydroxycholecalciferol were lower in patients with CF than in the controls, and serum concentrations of the active hormone were significantly lower in the area of low sunlight exposure. Mean bone density in patients with CF was significantly below the normal American standards. It was concluded that seasonal sunlight exposure influenced the levels of vitamin D metabolites. Older patients with CF appeared to be at increased risk for developing abnormalities of mineral metabolism. This study suggests subtle deficiencies of vitamin D in patients who are deprived of sunlight, despite seemingly adequate ingestion of vitamin D. Frank osteomalacia has been reported in a black patient with CF and multilobular cirrhosis[39].

Protein-calorie malnutrition might well be a factor in these observations. Gibbens *et al.*[40] determined the prevalence of osteoporosis among patients with CF by evaluating vertebral bone density using a highly sensitive computed tomography technique. In comparison with age, race and sex-matched controls, the patients with CF had lower bone density, approximately 10% less than the controls. The decrease in bone density was not related to age, but a strong correlation existed between bone density and disease severity; poor bone mineralization was more common in patients with poor nutritional status.

Vitamin E: This powerful antioxidant protects nutrients such as polyunsaturated fatty acids and vitamin A from oxidation and has been shown to be extremely important in mediating prostaglandin synthesis[30]. The importance of bile salts in the absorption of vitamin E have been emphasized[41] and children with chronic cholestasis from a variety of causes rapidly develop clinical signs of neurological dysfunction. Signs of vitamin E deficiency are quite frequently noted in newly diagnosed infants with CF, who may have evidence of haemolytic anaemia[42]. Serum vitamin E levels are also frequently low in the absence of symptoms. Supplemental doses of alpha-tocopherol acetate appear to result in a biochemical response[31], but vitamin E tolerance tests in CF patients with pancreatic insufficiency do suggest poor absorption of this vitamin even with pancreatic enzyme supplementation. Clinical features of vitamin E deficiency have been reported in children and adults with CF; these include ophthalmoplegia, diminished reflexes, decreased vibratory and proprioceptive sense, ataxia and muscle weakness[43,44]. Axonal dystrophy and degenerative changes within the posterior columns have been demonstrated postmortem[45]. It should be noted, however, that the majority of patients with severe neurological disease appeared to have advanced hepatic disease, with focal biliary cirrhosis[43,44]. Since the prevalence of liver disease increases with age, this problem is likely to become more prominent as increasing numbers of patients survive into adulthood.

Vitamin K: Overt haemorrhagic manifestations of vitamin K deficiency may be seen in untreated individuals with CF[46]. Unexplained purpura,

intestinal blood loss, bleeding from an injection site or from a minor surgical procedure may be present in the newborn period or in infancy. Catastrophic, sometimes fatal intracranial haemorrhage can occur, but it is extremely unusual for treated patients with CF to have coagulation defects attributable to a deficiency of vitamin K. It must be remembered, however, that older children, particularly those on antibiotics or with advanced liver disease may be susceptible to secondary coagulation abnormalities even when supplemented with vitamin K.

Trace metal deficiencies

Plasma zinc levels appear to be low only in patients with moderate to severe malnutrition and levels correlate directly with plasma proteins, retinol-binding protein and vitamin A[48]. There is no obvious defect of zinc absorption or metabolism. Plasma levels of copper and ceruloplasmin may be elevated in patients with cystic fibrosis, but usually in proportion to the severity of pulmonary disease, possibly because ceruloplasmin is an acute phase reactant[48]. It has been proposed that cystic fibrosis is caused by an acquired deficiency of selenium and that a diet high in selenium and vitamin E could be of great clinical benefit. However, there is no reliable evidence to support the concept that selenium is of any clinical significance[49]. Symptomatic hypomagnesemia, with evidence of a positive Trousseau sign, tremulousness, muscle cramps and weakness, may develop in patients receiving aminoglycosides[50], and is reported to be a secondary complication in patients treated for distal intestinal obstruction syndrome with repeated oral doses of n-acetylcysteine[51].

Iron deficiency anaemia with low serum ferritin is frequently seen in patients with advanced pulmonary disease[30], but may also be seen in the stable patient[52]. In patients with pulmonary insufficiency, polycythemia seems to occur less commonly than in other pulmonary disorders of comparable severity, suggesting that these patients have a relative anaemia even though haemoglobin levels are within the normal range. The precise mechanism of iron-deficiency anaemia is poorly understood, since there is no evidence of a defect of iron absorption or metabolism. Earlier reports showed increased iron absorption in children with CF not receiving pancreatic extracts, but these studies were probably carried out in children with depleted iron stores[53].

Essential fatty acid deficiency

In infancy, particularly prior to diagnosis, clinical features of essential fatty acid deficiency (EFAD) can occur with desquamating skin lesions, increased susceptibility to infection, poor wound healing, thrombocytopenia and growth retardation[30]. In older patients, who are adequately treated, overt clinical evidence of EFAD is extremely rare. Most patients with pancreatic insufficiency, nevertheless, have abnormal blood and tissue lipids[54]. Changes include decreased lineoleic and increased palmitoleic, oleic and eicosatetraenoic acids. Some reports suggest that these biochemical abnormalities reflect an underlying defect of fatty acid metabolism[55], while others have argued that the low plasma and tissue levels are due to increased metabolic usage and malabsorption in undernourished patients[56]. In a survey of 32 patients we found that low plasma essential fatty acid levels were confined to patients with less than 5% of pancreatic function[57] (Figure 4). The occasional report of patients with low levels and normal fat digestion may be due to the fact that some patients with 2 to 5% of pancreatic function do not have steatorrhoea. At present, there is no compelling evidence to suggest that supplementation with essential fatty acids have any major clinical benefits, but evaluation of subtle defects at the cellular level, attributable to membrane dysfunction or free-radical injury, remain to be adequately evaluated.

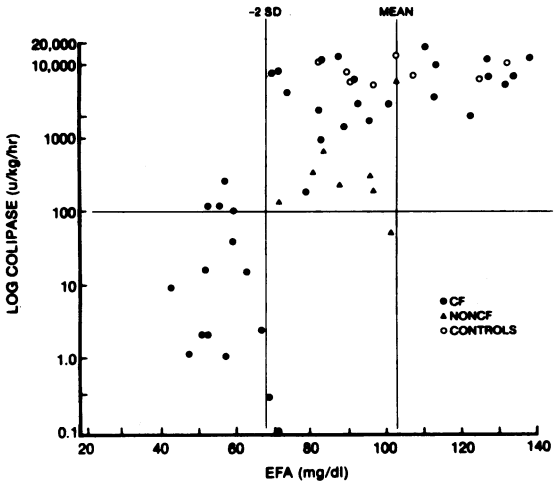

Figure 4. Comparison of pancreatic function (expressed as pancreatic colipase output (units/kg body weight/h) with plasma essential fatty acids in control subjects, and patients with cystic fibrosis (CF) and Shwachman Syndrome. Log colipase secretion reflects the range of pancreatic disease. Patients with colipase output between 100 units/kg body weight/h have pancreatic insufficiency with steatorroea. Only CF patients with pancreatic colipase output less than 5% of mean normal values showed evidence of essential fatty acid deficiency

Nutritional evaluation and therapy - a rational approach

Clinical

The nutritional support of patients with CF should be an integral part of overall care, and requires close clinical evaluation, monitoring of growth rates and appropriate dietary counselling (Table 2). At diagnosis, height, weight (percentiles), and anthropometry (skin folds, mid-arm circumference) should be carefully measured. During follow-up visits, careful monitoring

Table 2. Nutritional assessment

	At diagnosis	*Subsequent visits*
Growth	*Height/weight (percentiles)* *Arthropometry*	*Height/weight (percentiles)* *Arthropometry*
Diet	*Caloric intake by observation*	*Caloric intake by recall*
Digestion/ absorption	*•Fecal fat (% of intake)* *Bentiromide test* *Haemogram, iron stores* *PT/PTT* *Vitamins A, E, 250H-D* *Plasma proteins* *Plasma EFA*	*Stool microscopy (Steatocrit)* *Serum carotene* *Repeat initial measurements as indicated*

•If normal, pancreatic stimulation test

of growth should be instituted, preferably every 3-6 months. When patients receive an adequate diet, normal growth can be expected until advanced respiratory disease supervenes. Individuals failing to achieve normal growth velocity deserve careful evaluation - particularly young children with little pulmonary disease. Close involvement of a qualified, experienced dietitian is invaluable. Assessment should include careful evaluation of caloric intake and compliance with pancreatic enzyme supplements; additionally, assessment should include determining the adequacy of stool fat absorption (72-h fecal fat) and documenting fat and energy intake while continuing regular pancreatic enzyme supplements. Adjustments in the dose of enzymes, with or without the use of agents to improve digestion (histamine antagonists, bicarbonate, etc), may be used judiciously. Patients with mild pulmonary disease will often lose weight following an acute respiratory infection, but generally catch-up growth follows after recovery. Individuals suffering from recurrent abdominal pain due to distal intestinal obstruction syndrome often reduce caloric intake to control their symptoms; aggressive treatment may be necessary. In our experience, this is best achieved by intestinal lavage with a balanced electrolyte solution containing polyethylene glycol[58]. Similarly, signs of gastro-oesophageal reflux and oesophagitis[19,20] must be sought, and aggressive treatment instituted because severe symptoms will reduce caloric intake. Generally, patients with hepatic disease will grow normally, except in rare instances when hepatic decompensation supervenes.

The diet must be calorically adequate for individual needs. Since fat is the most economic and appetizing energy source it should be encouraged rather than restricted. The diet should be as normal for age and peer group as possible. Actual energy requirements of patients with CF are unknown but are estimated to be between 120 and 150% of the recommended daily allowance for age[3]. In this regard, although CF patients have been characterized as having voracious appetites, accurate records have revealed that energy intake is often very similar to that for normal children of the same age, sex, and stature and in some cases may even be reduced[16-18]. Dietary intake is closely related to an individual's self-esteem and general feeling of well being. It is, therefore, essential that patients who have nutritional difficulties receive psychological support; this is particularly important in adolescence and adulthood. Exercise programs aimed at improving physical capacity are considered to be important. Improved muscle mass may lead to a sense of accomplishment, and stimulate an interest in providing nutritional support for physical goals.

As a general rule, protein intakes of children with CF are more than adequate[16], but nitrogen balance may be particularly sensitive to insufficient total energy intake. Provided total energy intake is adequate, we recommend that protein intake equal the recommended daily allowance for age, sex and weight. The use of fat as a source of energy, which has been previously discussed in some detail, provides an excellent source of palatable, energy rich calories. The limited reserves of essential fatty acids in CF patients and the particular vulnerability of malnourished patients to essential fatty acid deficiency requires some specific attention. Although, there is no existing evidence to suggest that biochemical essential fatty acid deficiency has any major clinical impact, we do recommend a diet that contains adequate quantities of linoleic acid to maintain normal or close to normal fatty acid profiles. There is no known defect in the transport of monosaccharides and some investigators have even suggested enhanced glucose absorption. Despite the absence of pancreatic amylase in most patients, complex carbohydrates are generally well tolerated and are good sources of energy. Supplemented doses of fat soluble vitamins are indicated in patients with pancreatic insufficiency or severe hepatic-biliary disease; generally, two to three times normal intake is recommended.

Biochemical

Biochemical evaluation at diagnosis should include a careful assessment of nutritional status and pancreatic function (Table 3). We still recommend quantitative evaluation of fecal fat losses while accurately measuring fat intake, for documentation of steatorrhoea. Alternatively, recent modifications to the oral bentiromide test (N-benzyl-tyrosyl-aminobenzoic acid), provides a less costly and time-consuming approach for evaluating pancreatic function[59]. Poor substitutes include documentation of fat on stool microscopy, stool trypsin or chymotrypsin activity, serum carotene and vitamin A and E levels. Many of these tests are useful, however, for monitoring response to treatment on return visits. Serum levels of immunoreactive trypsinogen may be reduced in the older patient with pancreatic insufficiency, but only after the age of 7-8 years[60]. The most accurate method of assessing pancreatic function is the direct pancreatic stimulation test[12], which has been described separately (see p 2). This extremely invasive, time-consuming and difficult test should be reserved for the evaluation of patients with pancreatic sufficiency, or in those where the diagnosis of CF remains in doubt.

Routine biochemical measures of nutritional status, such as serum protein or albumin may be misleading. In the newly diagnosed infant, however, hypoproteinaemia and hypoalbuminaemia are a true reflection of the severity of malnutrition, and values usually revert to normal with nutritional rehabilitation. Plasma proteins with a short half-life such as retinol-binding protein and prealbumin, have been incompletely evaluated as markers of nutritional status in patients with CF. With advancing age, particularly in patients with severe pulmonary disease, albumin levels may be depressed, although elevated globulin may produce an increase in total protein concentration. The increase in globulin has been attributed to chronic pulmonary disease. The cause of decreased albumin levels in these patients is incompletely understood. Studies have shown normal albumin turnover rates and expanded plasma volume, suggesting that haemodilution may contribute. There appears to be an overall correlation between the severity of pulmonary disease and albumin concentration.

Specific nutritional considerations

The standard guidelines for the nutritional evaluation and support of patients with CF must be modified according to individual needs, the age of the patient and specific complications of the disease.

Table 3. Long-term enteral feeding of malnourished patients with cystic fibrosis

	Toronto[64]	*Ottawa*[65]	*Brisbane*[66]
Study design			
Patients (male/female)	14 (5/9)	10 (5/5)	10 (5/5)
Age - mean (years)	12.9	13.6	8.9
- range (years)	5-22	6-21	3-13
Enteral route	Gastrostomy	Jejunostomy	Nasogastric/gastrostomy
Supplement type	Semi-elemental	Intact	Semi-elemental
Duration (years)	1.1	1.6	1.0
Controls	Concurrent	Retrospective	Prospective
Patient characteristics			
Weight as % of height	82±10	80±9	No data●
FEV_1 (%)	47±15	No data	66±16
FVC (%)	53±13	64±18	84±12

● Expressed as Z-score

Infancy

Newly diagnosed infants may be profoundly anorexic and indifferent to food; hypoalbuminaemia, oedema and anaemia of infancy, particularly those under 3 months of age deserve special attention[30]. In addition, following surgery during the neonatal period for meconium ileus, active nutritional management is imperative. In these cases, a short course of parenteral or total enteral nutrition may be the only way to ensure adequate nutrition in the first few weeks of care. Albumin infusions may be indicated to reduce oedema. In general, however, patients improve rapidly with adequate attention to caloric requirements, vitamin needs and pancreatic enzyme supplementation; routine oral feeding with a standard age-appropriate formula becomes possible very quickly. Long-term use of protein hydrolysate, medium-chain triglycerides and polysaccharide supplements are rarely indicated. Infants who cannot maintain adequate growth with high-calorie standard nutrients hardly ever do better when given these supplements, unless they are artificially delivered by enteric tubes.

Adolescence and adulthood

With close attention to energy needs and food intake, it is possible to maintain adequate energy balance for optimal growth in the majority of patients with CF, especially when lung function is not impaired. However, a number of affected adolescents and adults, especially females, will develop weight loss in association with advanced pulmonary disease (Figure 5). By definition, these patients have an energy imbalance since they seem not to be able to maintain adequate energy intake by voluntary means. A variety of short-term and long-term approaches to artificial nutritional supplementation have been undertaken in the hope that restoration of nutritional status might result in easier control of chest infections, ameliorate the rate of decline in respiratory function, and extend survival. High energy liquid dietary supplements are frequently advocated, and although their use may be successful in the very short term, no reliable information is available regarding their long-term efficacy. It is our impression that many of these energy-rich supplements are at best substitutes for normal dietary habits and do not result in long-term improvement in nutritional status. Patients with growth failure or weight loss, particularly those with deteriorating pulmonary function, therefore, may be considered as candidates for more invasive, artificial forms of supplementary nutrition. Existing short and long-term studies are critically reviewed.

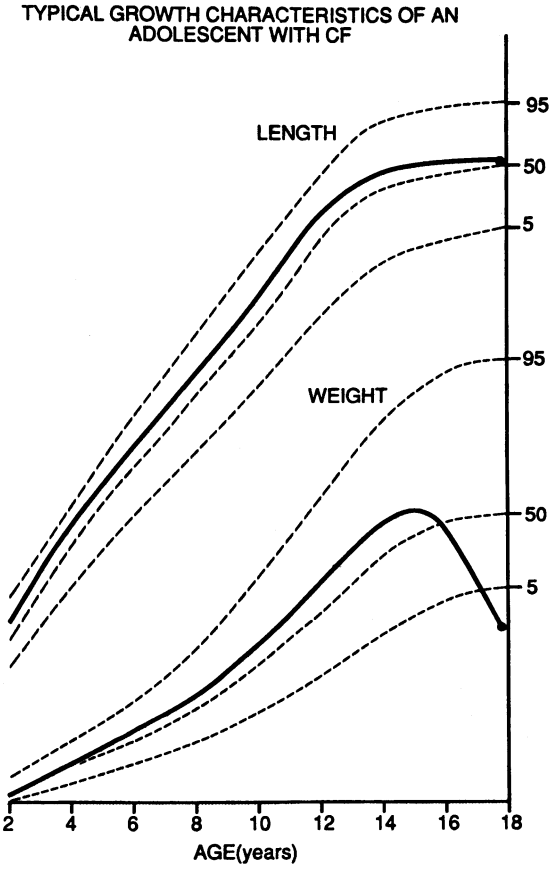

Figure 5. With adequate energy intake, most children with cystic fibrosis will grow normally to adolescence or adulthood, until severe lung disease develops. At this stage they appear to be unable to maintain adequate energy intake by voluntary means

Short-term studies

A number of short-term studies have used a variety of parenteral and enteral feeding techniques in an attempt to renourish malnourished CF patients. An early study by Shepherd *et al.*[61] evaluated 12 malnourished CF patients (mean age 5.43 years), 6 months before and 6 months after a 3-week period of parenteral nutrition. During the pre-treatment period, while

receiving 'conventional' dietary management, the patients had inadequate growth velocity, but 6 months after the short period of intravenous nutrition they appeared to exhibit continuing catch-up growth, fewer pulmonary infections, and a significant improvement in clinical score.

Unfortunately, other investigators have failed to show lasting improvement following short-term nutritional support, and the improved nutritional status in the patients included in Shepherd's study could best be explained by aggressive pulmonary management while patients were hospitalized. In addition, the very young age of the patients in question suggest that closer attention to voluntary nutrition may well have prevented the problem at the outset. Mansell *et al.*[62] who evaluated older malnourished CF patients (aged 10-17 years) also demonstrated improvement in nutritional status following a one-month period of supplemental parenteral nutrition when patients were given 120% of their energy needs. Immediately following supplementation bodyweight, triceps skin-fold thickness, and mid-arm muscle circumference increased significantly. Maximum inspiratory airway pressure also increased, suggesting improvement in respiratory muscle strength. However, none of the indices of lung function improved. One month following parenteral nutrition the patients were once again malnourished to levels similar to those before commencement of parenteral nutrition. In a study from Montreal[63], supplemental feeding by nasogastric tube was instituted while in hospital and continued at home for 4 weeks. Patients showed considerable weight gain, attributable to increased caloric intake, but the nutritional changes were transient and not accompanied by long-term improvement in growth or function. In a study from our centre, Pencharz *et al.*[22] evaluated body composition, nutritional status and energy needs of 6 undernourished adolescents and adults with CF. Lean body mass was preserved but there was significant wasting of adipose tissue. Following a brief period of nasogastric feeding with a semi-elemental diet, the effects of refeeding on body composition was reassessed. After refeeding, body weight, body fat and total body potassium all increased significantly but fat-free body mass and total body nitrogen did not change. All subjects were encouraged to continue nasogastric tube feeding at home, but none were able to continue for longer than 2-3 months. The majority of patients discontinued the supplemental feeding because of nasal irritation and coughing up the tube. Thus, based on the preceding studies it can be concluded that any nutritional benefits derived by brief periods of supplemental nutrition are short lived and not accompanied by any long-term improvement in growth or function.

Long-term studies

Since brief periods of nutritional supplementation of chronically malnourished CF patients did lead to a transient improvement in nutritional status, it became evident that long-term approaches to artificial supplemental feeding might achieve and maintain normal nutrition in patients who were unable to meet their energy needs. Further to this, it was felt that reversal of malnutrition may have a favourable influence on the course of pulmonary disease, and consequently upon survival.

As shown in Table 3, three major studies have approached the problem by using various forms of nocturnal enteral supplementation[64-66]. In a study from Toronto[64], patients were given nocturnal supplemental feeding of a semi-elemental formula given by gastrostomy tube for an average period of one year. The adolescent and adult patients were suffering from moderate to severe lung disease and all were markedly wasted or stunted. Gastrostomy tubes were placed endoscopically without incision and under local anaesthesia. A contemporary group of patients with CF (age, sex, nutritional, and pulmonary function-matched) derived from the clinic computerized data bank were pair-matched to the study group. In a second Canadian study, from Ottawa[65], 10 malnourished CF patients (mean age 13.6 years) with moderate to severe lung disease were provided with nocturnal supplemental feeding of an intact formula by a needle jejunostomy tube for periods of 10-36 months. Pancreatic enzyme supplements were added to the formula. Jejunostomy feedings appeared to pose no technical or medical difficulties. In the third study from Australia, Shepherd *et al.*[66] evaluated 10 undernourished CF patients (mean age 8.9 years) who are unable to maintain normal growth by oral means. These patients were followed during a one-year course of nutritional supplementation with a balanced-peptide or a semi-elemental formula delivered overnight by nasogastric or gastrostomy feeding. The patients were compared concurrently with height, sex, and pulmonary function-matched patients receiving conventional nutritional therapy. In all 3 studies, normal activity and regular meals were permitted during daytime hours.

Evaluation of these studies revealed that chronic enteral supplemental feeding resulted in a significant improvement in catch-up growth and positive changes in body composition (Table 4). Long-term benefits particularly the effects on pulmonary function and survival remain somewhat more controversial. In the two Canadian studies[64,65], the rate of deterioration of pulmonary function appeared to have been slowed in the supplemented group. In Shepherd's study[66], respiratory function deteriorated in the control group but appeared to actually improve in the patient group. However, Shepherd's patients were considerably younger and were suffering from less-compromised

Table 4. Effects of long-term enteral feeding in malnourished patients with cystic fibrosis

	Toronto[64]	*Ottawa*[65]	*Brisbane*[66]
Nutritional status			
ΔWeight (kg)	↑	↑	↑
ΔHeight (cm)	↑	↑	↑
ΔWeight as % of height (%)	↑	↑	↑
Total body potassium (g)	↑	No data	No data
Body fat (%)	↑	No data	No data
Mid-arm muscle circumference	No data	↑	No data
Protein synthesis	No data	No data	↑
Respiratory function			
Patients	Unchanged	Unchanged	Improved
Controls	Deteriorated	Deteriorated●	Deteriorated

●Compared with year before intervention

pulmonary function, in comparison with those in the two Canadian studies. It could be argued, that at early stages in the natural history of the disease, patients with mild pulmonary disease should be able to maintain normal growth velocity with conventional dietary therapy. On the other hand, it is possible that early aggressive treatment of the nutritional deficit might have a more beneficial effect on pulmonary disease.

Conclusions

There is no convincing proof that aggressive supplemental nutrition actually improves survival. Furthermore, although we are convinced that nutritional rehabilitation results in an improvement in patient well-being, the psychological impact of aggressive invasive means of supplemental nutrition have not been adequately evaluated. Other questions remain to be answered before invasive enteral techniques can be universally accepted for the routine management of malnourished patients with CF. These include appropriate clinical and psychological criteria for patient selection, and evaluation of the cost-effectiveness and complication rate of various approaches. No consensus has been reached regarding the appropriate formula type, or the optimal method of administration. Careful evaluation of the long-term benefits, particularly survival are necessary, but these are likely to be extremely difficult, if not impossible to conduct with conclusive results.

Prevention of growth failure should be a primary aim in the management of CF patients; obviously this would be best achieved without the necessity of instituting invasive approaches. In our experience, normal growth can be achieved in the vast majority of patients with rational use of a normal-high energy (high fat) diet from the time of diagnosis and with careful monitoring of progress (Table 5). With this approach, most patients will grow normally until advanced lung disease supervenes. It is usually at this point that severe malnutrition becomes a problem and one is forced into considering artificial, often invasive means of intervention. It is extremely doubtful, however, that any form of aggressive nutritional therapy has any impact on outcome during the terminal stages when the patient is either permanently hospitalized or in a practical sense bed ridden from cardiopulmonary failure[67]. Unfortunately, this is often the time when demands for nutritional intervention become most intense. Perhaps the most important role of the care-giver during this period, is to discourage aggressive artificial means of nutritional support and other examples of our technical versatility, which only add to the discomfort and frustration of the last days of life.

Table 5. Approach to nutritional treatment of patients with cystic fibrosis

Encourage good feeding habits early
In patients with growth failure
assess energy intake
assess absorptive function
assess for gastrointestinal complications which would reduce intake
evaluate psychological/family dysfunction
encourage voluntary supplements and/or modify enzyme therapy
Invasive methods of nutritional supplementation should be considered as a last resort, but *before* malnutrition and severe lung disease supervenes
In patients with end-stage pulmonary failure invasive methods will only prolong the agony of dying

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