NUTRITION IN CYSTIC FIBROSIS

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CONTENTS

INTRODUCTION

Cystic fibrosis (CF), an hereditary idiopathic disease of exocrine gland secretion, is the most frequently seen lethal or semi-lethal genetic disease of Caucasians and is transmitted as an autosomal recessive trait with an incidence of between 1 in 2000 (Caucasians) and 1 in 90000 (Orientals) live births (Cutting, 1990). Recent advances in recombinant-DNA probe techniques, have enabled the localization of the CF gene to chromosome 7 (Koshland, 1989). The disease has variable clinical manifestations related to the fact that there are about fifty mutations, although a common gene defect at Δ508 accounts for about 70% of cases.

Clinically CF is characterized most commonly by recurrent pulmonary infections, pancreatic insufficiency with maldigestion and malabsorption and excessive losses of sweat electrolytes. Although the biochemical basis for the disease is not fully characterized, present evidence suggests an inherent defect in anion transport by epithelial cells of

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exocrine glands related to an abnormal gene product called the CF transmembrane regulator (Riordan, 1990). In the pancreas, this appears to result in the production of viscous secretions which result in blockage of the pancreatic ducts leading to fat and protein malabsorption.

Until the 1950s, survival except in rare instances, was short. The discovery of involvement of the sweat glands by Di Sant'Agnes *et al.* (1953) led to the diagnostic sweat test (Gibson & Cooke, 1959). Since then, because of earlier diagnosis and improved treatment, there has been a considerable change in the outlook of the disease such that many clinics now report a median life expectancy of far greater than 20 years (Corey, 1980). Thus, although CF has historically been a paediatric disease, there are now increasing numbers of patients surviving into adulthood. Despite these advances in the clinical management of CF there remains a high morbidity and mortality rate amongst children and young adults. Recent improvements in our understanding of the basic biochemical defect and in our knowledge of the genetic basis for the disease (see Tsui *et al.* 1990) have led to the capability for carrier identification and prenatal diagnosis and in the future may lead to therapy for the underlying disorder (Crystal *et al.* 1990). However, in the absence of specific treatment for the underlying defect, treatment in the immediate future will remain empirical, aimed at prevention and treatment of the progressive clinical manifestations of this disease.

The two major factors adversely affecting prognosis are progressive lung disease and malnutrition. Relative underweight is a major factor affecting survival (Kraemer *et al.* 1978) and patients dying of CF have marked nutritional failure in the 1–2 years before death. Optimal nutritional management would, therefore, seem crucial in terms of growth, quality of life and long-term outcome (Mueller, 1990).

The purpose of the present review is to survey the nature and causes of the nutritional deficit in CF, to explore their consequences and to suggest strategies for their prevention and treatment (for earlier reviews, see Dodge, 1983, 1986; Shepherd *et al.* 1984; Gerson *et al.* 1987; Shepherd & Cleghorn, 1989).

CLINICAL FEATURES OF MALNUTRITION IN CF

A wide range of nutritional deficits, varying in their deleterious effects, occur in CF (Table 1). The major consequences of malnutrition in CF include nutritional growth retardation, delayed puberty, and specific deficiencies of protein, essential fatty acids, vitamins and minerals. There seem also to be adverse effects on lung growth and the course of pulmonary disease. Studies of body composition of CF patients have indicated deficits in total body mass and body fat (Miller *et al.* 1982; Johnston *et al.* 1988) as the median age of patients increases; nutritional support is becoming crucial because of the greater incidence and consequences of malnutrition in older patients.

Infants with CF are generally born with appropriate growth characteristics for their gestational age, although one report (Dodge & Yassa, 1980) has suggested that the genetic abnormality in CF may have an adverse ante-natal effect on nutrition. Certainly if the CF infant is not treated, failure to thrive, growth failure, wasting and gross motor delay are common early signs. Secondary hypoproteinaemia with associated generalized oedema have been seen to occur if the infant has been fed on a reduced usable protein source, such as soya milk, or on a relatively low intake of protein, as in breast milk, although a recent report indicates that breast milk with supplementation adequately supports growth in CF babies (Walker, 1990). Anaemia can result from haemolysis due to vitamin E deficiency and/or from a low iron-binding globulin concentration resulting from protein energy

Table 1. *Clinical features of malnutrition in cystic fibrosis (adapted from Shepherd & Cleghorn (1989))*

Signs	Infancy	Childhood	Adolescence	Adult
Protein–energy deficit				
Growth retardation/ underweight	+ +	+ +	+ + +	+ + +
Delayed puberty			+ + +	+ +
Lean mass				
Pot belly, rectal prolapse	+	+ +		
Muscle wasting	+	+ +	+ +	+ +
Vital capacity			+	+ +
Fat stores	+ +	+	+	+
Hypoproteinaemia	+ +		+	+
Voracious appetite	+	+		
Anorexia		+	+ +	+ +
Specific deficiencies				
Anaemia (vitamin E, iron) deficiency	+(vitamin E)		+	+
Bruising/bleeding (vitamin K)	+ +	+	+	
Skin rash (EFA)	+			
Osteopenia (vitamin D)			+	+
Night blindness intracranial pressure (vitamin A)		+	+	+
Neurological disease (vitamin E) (ataxia, abnormal eye movements)			+	+ +
Salt depletion	+ + +	+ +	+	+
Magnesium depletion	+	+		

EFA, essential fatty acids.
+, does occur; + +, occurs commonly; + + +, a significant clinical problem.

deficit. Young infants with CF are often described as having a voracious appetite (Schwachman, 1975), although in reality objective measurements of intake often show an inadequate intake due to anorexia.

In childhood and adolescence the heights and weights of CF patients are often markedly skewed towards the lower centiles, but reports of the prevalence of underweight and growth retardation have varied over time and between clinics (Sproul & Huang, 1964; Berry *et al.* 1975; Dodge & Yassa, 1980). Whilst findings of Soutter *et al.* (1986) from a longitudinal study suggest that improvement in growth of a sample population of CF patients was related to the survival of more-well-nourished patients rather than to any marked improvement in growth among undernourished patients or those who were initially growth-retarded, marked improvements in growth and restoration to normal growth centiles has been achieved with active nutritional supplementation (Shepherd *et al.* 1980, 1986; Mansell *et al.* 1984; Levy *et al.* 1985; Parsons *et al.* 1985; O'Loughlin *et al.* 1986). These studies (Table 2), thus, clearly point to the probability that growth retardation occurring in patients with CF, may be reversed using specific management programmes.

Low weight for height is a relatively common finding in CF adults, particularly in females, and this is correlated (as in younger age-groups) with a greater severity of

Table 2. *Long-term nutritional rehabilitation of malnourished cystic fibrosis patients: summary of the literature*

Study	Administration	Duration (years)	Formula studied	No. of patients
Levy *et al.* (1985)	Gastrostomy	1·1	Elemental	14 treated, 14 retrospective controls
O'Loughlin *et al.* (1986)	Nasogastric	0·5	Elemental	8
Boland *et al.* (1986)	Jejunostomy	1·6	Non-elemental	10
Soutter *et al.* (1986)	Gastrostomy	1·0	Non-elemental	15
Shepherd *et al.* (1986)	Nasogastric, some jejunostomy	2·0	Semi-elemental	10 treated, 14 height-, sex-and FEV-matched controls
Pierce *et al.* (1990)	Nasogastric, gastrostomy	0·5	Nocturnal supplements	22
Steinkamp *et al.* (1990)	Gastrostomy	1·0	Semi-elemental	11

FEV, Forced expiratory volume (1) in 1 min.

pulmonary disease and diminished overall survival (Corey, 1980; Wells *et al.*, 1985). In the adult population group a greater percentage have pancreatic sufficiency than in younger age-groups. Both cross-sectional (Gurwitz *et al.* 1979; Wells *et al*, 1984; Soutter *et al.*, 1986) and longitudinal studies (Soutter *et al.* 1986) have indicated that the older the child the more marked the trend toward nutritionally induced growth failure. These studies have also indicated that, after the onset of puberty, there is an apparent greater decline in the weight-for-height deficit, particularly in girls. Longitudinal studies (Soutter *et al.* 1986) have also demonstrated that there are several distinctive growth patterns occurring among groups of patients with CF. The first are a group of patients who are relatively underweight for age at diagnosis and whose linear growth deviates gradually below the 3rd percentile towards the end of childhood, only to further deviate either subacutely or acutely during early adolescence. A second growth pattern observed is where patients maintain their weight and height percentile throughout childhood but with a small deviation during adolescence, perhaps occasionally punctured by a decrease in weight-for-age and with episodes of pulmonary infection. In these patients it is, therefore, paramount to provide adequate nutritional support.

Certainly malnutrition and declining pulmonary function in CF are an ominous combination which once established tend to be relentlessly progressive. However, the hypothesis that malnutrition has a direct adverse effect on pulmonary function through its effects on pulmonary muscle function is difficult to prove (Marcotte *et al.* 1986; Marks *et al.* 1986), and any relationship between nutritional therapy, muscle function and muscle morphology is still unclear (Table 3). Malnutrition may also impair the usual pulmonary defence mechanisms, thus predisposing patients to parenchymal lung infection. Some support for the causal link between malnutrition and declining pulmonary function comes from several recent studies of long-term nutritional rehabilitation in CF, indicating that improved nutritional status is associated with a reduction in the number of pulmonary exacerbations and at least a stabilization in pulmonary function status (Levy *et al.* 1985; Lester *et al.* 1986; Shepherd *et al.* 1986). In contrast, no improvement in pulmonary function following 1 month of parenteral nutrition was observed by Mansell *et al.* (1984), whilst the study of Morton *et al.* (1988) indicated that exacerbation of chest infections in

Table 3. *Nutrition and pulmonary disease in cystic fibrosis*

Pulmonary disease is associated with
Energy expenditure
Protein catabolism
Protein synthesis during exacerbations
Nitrogen loss from sputum
Malnutrition is associated with
Decreased ventilatory drive
Impaired pulmonary muscle function
Decreased exercise tolerance
Airway obstruction (via altered prostaglandin metabolism)
Altered pulmonary immune response

CF patients receiving adequate nutritional intake is not a major contribution to protein malnutrition.

PATHOGENESIS OF MALNUTRITION IN CF

It seems likely that the nutrient deficit in CF results to a greater or lesser degree from a combination of increased requirements, inadequate absorption, and increased nutrient losses (Table 4). The concept that this disease is one of repeated energy-depleting insults occurring commonly on a background of chronic catabolic stress has recently been developed following studies of protein and energy metabolism (Shepherd *et al.* 1988*a*) and it follows that from such a combination of factors (Table 4) chronic undernutrition and growth retardation result.

Several models have been proposed for the aetiology of undernutrition in CF patients. The consensus view (Pencharz *et al.* 1984; Roy *et al.* 1984; Shepherd *et al.* 1984) is that negative energy balance in CF occurs in a situation where the patients' intake is insufficient, in the face of anorexia and/or inappropriate dietary modification, secondary to a combination of malabsorption, nutrient losses and perhaps primary and secondary increases in total energy expenditure.

INADEQUATE ENERGY INTAKE

Although many studies describe voracious appetites in children with CF, in reality, objective measurements of intake often show inadequate energy supply compared with recommended daily allowances (RDA). Where a voracious appetite is observed, these patients are usually attempting to compensate for increased requirements and excessive losses. To achieve an adequate absorbed protein–energy intake in CF, daily intakes greater than RDA by approximately 120–150% are usually necessary. Even under circumstances of a policy of encouragement to ingest in large quantities a normally balanced diet from the time of diagnosis, some patients, perhaps as many as 25% of patients, still achieve inadequate intakes due to a combination of anorexia and physical and psychological problems.

Poor appetite may be due to malnutrition *per se* (Hansen *et al.* 1971), but patients with CF are particularly prone to develop other complications that may limit appetite and oral

Table 4. *Aetiological factors in altered nutrient balance in cystic fibrosis (Adapted from Wells et al. (1985))*

↓ Absorbed intake	↑ Requirements
Anorexia	Nutrient losses
Chronic disease	Sweat
Pulmonary exacerbation	Sputum nitrogen
GE reflux	
Liver disease	Energy expenditure
	? Related to basic defect
Diet restriction	Pulmonary disease
e.g. Fat	Infection
-Food fads	Hypoxaemia
-Peer pressure	Work of breathing
Malabsorption	Altered metabolism
Pancreatic	Protein catabolism
Bile acid deficiency	Liver disease
Mucosal factors	Endocrine factors
Intestinal reaction	(insulinopenia)

GE, gastro-oesophageal.

intake. For example, gastro-oesophageal reflux is being recognized more frequently, perhaps related to the severity of the lung disease and the common use of medications which exacerbate reflux-causing oesophagitis. In addition, other gastrointestinal complaints such as the distal intestinal obstruction syndrome, pancreatitis, biliary tract abnormalities, pulmonary infection and liver disease may be associated with poor appetite.

MALABSORPTION

Malabsorption in CF occurs mainly as a result of the maldigestion of food secondary to pancreatic insufficiency. Other factors such as mucosal absorptive abnormalities, altered bile acid metabolism and, in some cases, short bowel syndrome following surgery for meconium ileus may also contribute to varying degrees. Malabsorption is rarely completely corrected by enzyme therapy and a consistent nutrient loss of between 10 and 20% of ingested fat, protein, fat-soluble vitamins and other nutrients may occur every day of a CF patient's life (Durie *et al.* 1980; Gow *et al.* 1981).

Pancreatic insufficiency, which occurs in 85% of CF patients, overshadows all other factors which influence the absorption of nutrients in CF. The major exocrine deficiencies involve trypsin, with poor hydrolysis of protein into peptides and amino acids, and lipases, with poor hydrolysis of long-chain fatty acids from dietary triacylglycerols. Malabsorption of fat-soluble vitamins and of some minerals accompany the fat maldigestion. Diminished bicarbonate and water secretion from the pancreas is probably fundamental to the exocrine deficiency, and diminished alkaline secretions in the small intestine in addition to the observed excess of gastric acid secretion result in an acid duodenal environment. Protein absorption has only received limited study in CF. Faecal nitrogen loss is very high in untreated patients (Forstner *et al.* 1980), and in treated patients (Gow *et al.* 1981) very variable faecal N losses are observed, although they are generally reduced by appropriate pancreatic enzyme supplementation (Gow *et al.* 1981). Without supplements, stool N output seems to be increased three- to fourfold above normal, but how much this is a

reflection of antibiotic therapy or increased transit time, and how much is related to the degree of protein digestion is unknown. The defect in N absorption is less severe than that of fat absorption (Forstner *et al.* 1980).

INCREASED NUTRIENT LOSSES

The increased nutrient and energy requirements observed in CF could also result from nutrient losses other than from malabsorption or from altered nutrient metabolism or increased energy expenditure.

A less-well-recognized route of nutrient loss is via the sputum. Significant N loss from the sputum (up to 14% of total N losses) has been documented in some patients with CF (Holt *et al.* 1984). Whether or not these losses are significant protein-energy drain in these patients is uncertain, but studies of N balance in children with CF have determined total N loss to vary between 7 and 15 g N/d. The sputum losses documented above were up to 2 g N/d which underscore the possibility that such losses may represent an important component of total N loss. The contribution of sputum N losses to the protein–energy deficit was very variable depending on the severity of the lung disease, the presence of ongoing active infection and other factors. Thus, sputum N loss may need to be taken into account when assessing protein–energy needs of those patients with consistently high volumes of sputum loss.

The sweat gland abnormality in CF causes clinically significant losses of electrolyte which can result in dehydration, salt depletion and alkalosis, particularly in hot weather, if replacement therapy is not a routine part of management. However, it should also be noted that sodium is an important nutrient and even subclinical depletion can result in growth impairment if unrecognized.

A variety of other specific nutrient deficits have been reported in CF and include fat- and water-soluble vitamins and minerals. These are summarized in Table 5 and detailed reviews may be found elsewhere (Dodge, 1983, 1986; Shepherd *et al.* 1984; Gerson *et al.* 1987; Shepherd & Cleghorn, 1989).

ALTERED ENERGY EXPENDITURE AND NUTRIENT METABOLISM

There is increasing evidence which suggests that undernutrition and nutritional growth retardation in CF may not result primarily or solely from an inadequate amount of absorbed energy. There has been a growing interest in the relationships between alterations in energy expenditure, body protein turnover and turnover of other nutrients to malnutrition in CF, since the recognition of the apparent maladaptation to undernutrition (Miller *et al.* 1982), altered protein metabolism (Holt *et al.* 1984: Shepherd *et al.* 1988*a*), changes in essential fatty acid metabolism (Hubbard, 1983) and evidence for increased energy expenditure and basal metabolic rate in some patients (Shepherd & Cleghorn, 1989). This area of research is not well defined at present and a division of opinions exists as to whether the changes observed are secondary to abnormalities in intake or absorption, secondary to the effects of chronic lung disease, infection or hypoxaemia, or whether there is a primary abnormality in energy expenditure related to an energy-requiring basic defect. Studies along these lines have been directed so far into three main areas: energy expenditure, protein metabolism, and essential fatty acid metabolism, and discussion is confined to these.

Table 5. *Nutritional evaluation and management in cystic fibrosis (Adapted from Shepherd et al. (1984))*

Deficit	Evaluation	Management
Energy (E)	(1) Assess E balance nutrient intake (3 d), absorption (72 h stool fat and nitrogen) other E losses (e.g. sputum N) increased requirements (infection hypoxaemia, BMR)	Dietary counselling and high-energy supplements (complex sugars and fat to achieve 110–140% of absorbed E requirements) Enteral/parenteral supplements in selected cases. Optimal pancreatic enzyme therapy
	(2) Assess wt gain, growth body composition anthropometry (wt, height, skinfold) research techniques ($TB^{40}K$ analysis)	
Protein	(1) Assess protein stores Muscle mass(creatinine–height index) lean body mass (total body N and potassium), plasma protein and albumin and retinol-binding protein.	Provide adequate absorbed E High protein intake Protein hydrolysates
	(2) Research techniques for protein turnover: [^{15}N] glycine kinetics N balance, urine 3-Me-His excretion	
Fat	(1) Assess fat stores (subcutaneous fat fold)	Provide adequate absorbed E (avoid low fat diet)
	(2) Plasma EFA (linoleic acid)	Provide adequate unsaturated fats high in EFA Optimal fat absorption
Fat-soluble vitamins	A. Plasma vitamin A, Carotene	1000–2000 μg/d*
	D. Plasma 25 OHD	10–20 μg/d* + sunlight
	E. Plasma tocopherol	1000 μg/kg per d*
	K. Prothrombin time	50–100 μg/d (parenteral dose)
Water-soluble vitamins	Specific levels, especially during stress, antibiotic therapy	Give RDA unless deficient
	Vitamin B_{12} levels	
Micro- and macronutrients	Plasma electrolyte	Infants 1 g/d
Sodium chloride		Salt supplements for hot weather and physical activity (4–6 g/d)
Zinc	Plasma/hair Zn	
Iron	Serum ferritin/Fe studies	
Selenium	Plasma Sel	

EFA, essential fatty acids; 25-OHD, 25-hydroxycholecalciferol.

BMR, basal metabolic rate; RDA, recommended daily allowance; 3-Me-His, 3-methylhistidine; $TB^{40}K$, total body ^{40}K content.

* Best administered in water miscible form.

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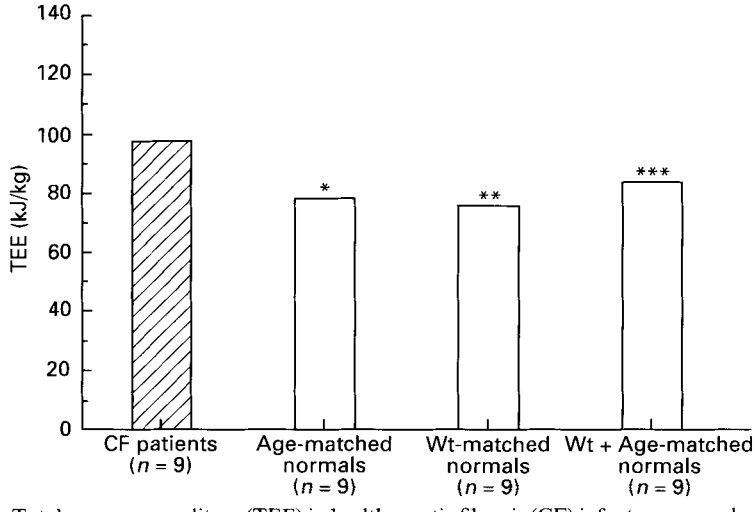

Fig. 1. Total energy expenditure (TEE) in healthy cystic fibrosis (CF) infants compared with age, weight and weight + age matched healthy control children (n 9 in all cases; SD 4%). Adapted from Shepherd *et al.* (1988*a*). Mean values for healthy control groups were significantly different from those for CF infants. * $P < 0{\cdot}05$; ** $P < 0{\cdot}01$; *** $P < 0{\cdot}001$.

Increased energy expenditure

An early study of basal metabolic rate in a small group of CF patients (Adeniyi-Jones *et al.* 1979) suggested that basal metabolic rate was elevated in malnourished CF patients with alterations of protein turnover. In a small group of stable but malnourished adolescents it has been estimated through indirect calorimetry and cumulative heart rate monitoring that the average energy requirement, excluding faecal losses, approaches 150% of RDA for subjects of similar age, sex, weight and activity levels (Archibald *et al.* 1981), findings confirmed in a similar group of patients by direct calorimetry (Vaisman *et al.* 1986). In addition it has been suggested that some drugs, such as bronchodilators, pulmonary infections or advancing respiratory insufficiency may also increase resting expenditure in many patients (Vaisman *et al.* 1987*a*). Conversely, since reasonable weight gain and growth appears to be achievable while consuming diets of 120% RDA (Parsons *et al.* 1983) it has, thus, been suggested that energy requirements of relatively stable CF patients may not be much different from those of the healthy population. However, recent studies using doubly-labelled-water techniques (Shepherd *et al.* 1988*b*), which accurately measure total energy expenditure in free-living humans, have documented significant increases in total energy expenditure, compared with controls, in a group of healthy well-nourished CF infants without any evidence of acute or chronic lung disease. These studies (Fig. 1), suggest that a primary abnormality of energy expenditure may exist possibly relating to an energy-requiring basic defect; whilst the findings of O'Rawe & Dodge (1990) suggest that those individuals with the common Δ508 mutation have a higher resting energy expenditure than those who have other mutations. Such a defect might also explain the observation of lower-than-normal birth weights in CF infants (Hsia, 1959). Further energy expenditure studies are required to document the metabolic cost of other energy-requiring processes, for example, chronic respiratory infection, increased work of breathing, and the requirements for catch-up growth seen in CF.

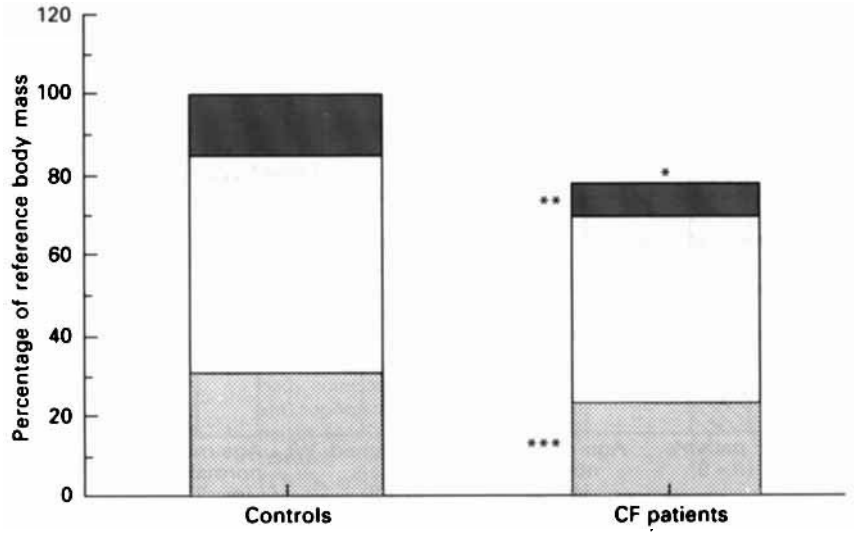

Fig. 2. Body compositions in seven cystic fibrosis children compared with reference values. Body fat (■) was determined by the method of Brook (1971) and lean body mass (muscle mass) (▨) from urinary creatinine excretion; values are means with their standard errors represented by vertical bars. Adapted from Shepherd *et al.* (1983). Mean values for healthy control group were significantly different from those for CF infants: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Table 6. *Whole-body protein turnover in cystic fibrosis (CF) infants in various clinical states and the effect of nutritional supplementation on stable but malnourished CF subjects*

Whole-body protein turnover was measured using a single-dose [^{15}N]glycine procedure (Adapted from Holt *et al.* (1985) and Shepherd *et al.* (1986))

		Malnourished CF patients		Effect of nutritional therapy	
	Normal subjects (*n* 10)	Acute exacerbation *v.* normal (*n* 8)	Stable *v.* normal (*n* 7)	1 month *v.* normal (*n* 10)	6–12 months *v.* normal (*n* 6)
Protein synthesis (S)	—	↓	↑	↑	—
Protein catabolism (C)	—	↓	—	↑	—
Net deposition (S – C)	+ve	0	0	+ve	+ve

Protein turnover and metabolism

Studies of body composition (Fig. 2), myofibrillar protein catabolism (Miller *et al.* 1982), and whole-body protein turnover (Table 6) in CF children have suggested that nutritional growth retardation is characterized by a protein–energy deficit resembling protein–energy malnutrition, and that in contrast to the normal adaptive response to protein–energy malnutrition these patients exhibit increased myofibrillar and total body protein catabolism. Since myofibrillar protein serves as a major body protein reserve and plays a role in energy provision in malnutrition it would appear that these CF patients are in a state

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of chronic catabolic stress, an hypothesis supported by studies of whole-body protein turnover using [^{15}N]glycine techniques (Adeniyi-Jones *et al.* 1979; Holt *et al.* 1985). During acute pulmonary exacerbations these patients exhibit a paradoxical decrease in whole-body protein synthesis (Holt *et al.* 1985) with a failure of net protein deposition (Table 6). More recent studies (Shepherd *et al.* 1988*a*) have indicated that the paradoxical decrease in whole-body protein synthesis during exacerbations occurs only in malnourished patients. In well-nourished CF subjects infection appears to increase catabolism without affecting synthesis. It is apparent that these metabolic derangements, if chronic or cumulative, may play a significant role in the development of nutritional growth retardation in this disease. In addition, they may play a functional role in delaying pulmonary recovery by adversely affecting pulmonary muscle function and respiratory drive. They emphasize the link between nutritional problems and pulmonary disease in CF and draw attention to the recurring protein–energy–depleting insult of pulmonary infection. As will be discussed, derangements of protein metabolism can be at least in part corrected by appropriate nutritional therapy (Shepherd *et al.* 1980, 1986, 1988*a*).

Abnormalities of essential fatty acid metabolism

Several reports describe abnormalities of essential fatty acid metabolism in CF. Most of the evidence suggests that there is increased turnover of essential fatty acids as well as deficiency (Hubbard, 1980; Lloyd-Still *et al.* 1981). Malnourished CF patients have reduced fat stores (Miller *et al.* 1982; Fig. 2) and most studies suggest that the essential fatty acid, linoleic acid (18:2 *n*-6) is deficient in up to 90% of non-supplemented patients (Congden *et al.* 1981) with decreases in palmitoleate (16:1) and oleate (18:1). These deficits result in part from malabsorption and from the low-fat diets which were prescribed in the past for CF patients. CF patients, both with and without exocrine pancreatic insufficiency, have been reported to have altered fatty acid composition. Moreover, if adequate energy and essential fatty acids are available then the deficiency can usually be easily corrected (Landon *et al.* 1981), suggesting an increased requirement for energy derived from fat sources. However, this does not entirely explain the apparent abnormalities in essential fatty acid metabolism seen in CF neonates (Robinson, 1976) or in heterozygotes (Burns & Dodge, 1982).

NUTRITIONAL CARE IN CF

The adverse effects of chronic pulmonary disease and intercurrent pulmonary infections on nutritional status, and conversely the adverse effects of malnutrition on pulmonary disease require an aggressive approach to nutritional management. Optimal nutritional therapy involves the maintenance of an adequate protein–energy balance. This requires detailed assessment, evaluation and advice from a nutrition support team. Maximizing absorption of nutrients is paramount to enable adequate intake, to prevent deficiencies and the complications of a malabsorptive state. It is also important to recognize specific risk periods which may necessitate increased nutritional support such as enteral or even parenteral hyperalimentation. Such periods may include acute pulmonary exacerbations or periods of rapid growth, for example, in early infancy and during puberty.

NUTRITIONAL EVALUATION

An important part of the routine management programme is the evaluation of nutrient intake. This involves regular assessment of dietary intake, assessment of nutrient and energy absorption, review of pancreatic replacement therapy, the recording of anthro-

Table 7. *Evaluation of nutritional status in cystic fibrosis*

Serial anthropometry
Weight, expressed as wt-for-age, wt-for-height, Z score
Height, expressed as height-for-age, Z score
Skinfolds
Skeletal age
Dietary absorbed energy intake
Dose/type/compliance of pancreatic supplements
Nutrient intake (3 d food record)
Faecal fat/nitrogen excretion (% of intake)
Specific deficiencies
Plasma linoleic acid and eicosotrienoic acid
Serum carotene, vitamin A
Plasma 25-OHD
Plasma vitamin E
Prothrombin time
Plasma electrolytes
Plasma zinc
Plasma iron and ferritin

25-OHD, 25-hydroxycholecalciferol.
Z score, statistical representation of the degree of undernutrition based on the degree of underweight $Z = (x-\bar{x})/S_{\bar{x}}$

Table 8. *Nutritional recommendations in conjunction with pancreatic supplements*

Energy	RDA × 1·5 (absorbed energy × 1·3)
Protein	RDA × 1·5
Fat	40% of energy
Essential fatty acids	5% of total energy
Fat-soluble vitamins	
A	1000–2000 μg as water-miscible form
D	1–2 μg/d
E	1000–3000 μg α-tocopheryl acetate
K	5 mg × 2 weekly (vitamin K)
Water-soluble vitamins:	
B group	RDA × 2
C	RDA × 2
B_{12}	RDA unless ileal resection
Sodium chloride (in hot weather)	Infants 1 g/d older patients 4–6 g/d
Zinc	RDA
Iron	RDA unless deficient

pometric data, biochemical evaluation for specific deficiencies (Tables 7 and 8) and a psychosocial evaluation where related to dietary intake. The frequency of detailed evaluation is dictated by the severity of the clinical status but should be at least biannually and more frequently if deviations occur.

Nutrient intake can be evaluated by using 3 d diet record, which should include both one weekday and one weekend day. In order that an accurate assessment of overall nutrient intake is obtained the patient or guardian should receive guidance in the recording of types of food eaten and the measurement of amounts. This, where possible, should be carried out with the aid of a dietitian. At this time a psychosocial evaluation should also be carried out to enable appropriate nutritional support to be given, recognizing that the increased nutrient requirements of CF patients will impose greater financial demands upon families.

Use of pancreatic supplements may be simultaneously recorded. If stool collections are also obtained for fat and N determinations then the net energy absorbed can be calculated (Parsons, *et al.* 1983). Body protein stores should be evaluated, as protein reserves in the body play an important role in energy provision in malnourished children and a deficiency of protein reserves indicates serious undernutrition. Commonly available measures include an assessment of lean mass by anthropometric measurement, an assessment of muscle mass by measurement of the creatinine height index, and measurements of serum proteins. Less widely available techniques such as measurement of whole-body potassium or body N and stable isotope techniques for measuring protein turnover and energy expenditure in CF (Miller *et al.* 1982; Holt *et al.* 1985; Shepherd *et al.* 1983, 1986, 1988*a*, *b*) have to date only been used in a research setting but are worthy of more widespread application. Unfortunately, the cost and technical complexity of such techniques is likely to preclude their wider use in the foreseeable future.

NUTRITIONAL CARE

It is usually possible in CF to promote normal growth and nutritional status, assisted by dietary counselling from a clinical dietitian, by manipulation of the diet and additional nutritional supplements (Bell *et al.* 1984). Typical nutritional recommendations for patients with CF are summarized in Tables 7 and 8.

It is well recognized, however, that conventional pancreatic supplements rarely completely correct the malabsorption, related to denaturation of foods by gastric acid and inappropriate duodenal pH, and recent interest has focused on methods of overcoming this problem (Cox *et al.* 1979; Durie *et al.* 1980; Gow *et al.* 1981). The development of pH sensitive enteric-coated microspheres to deliver exogenous enzymes represents major progress in the management of malabsorption in CF. The study of Gow *et al.* (1981) has clearly shown that near-normal absorption can be achieved with lower daily enzyme doses using such preparations. However, in some patients malabsorption is refractory and the use of semi-elemental diets may be warranted. There is demonstrated value of the use of peptide hydrolysates and medium-chain triacylglycerols in pancreatic insufficiency (Imondi & Stradley, 1974), although the potential benefits of these formulas have not been definitively tested in CF. Adjunctive measures which increase duodenal pH, such as misoprostol (Cleghorn *et al.* 1989) and cimetidine (Gow *et al.* 1981), have been shown to improve malabsorption in refractory individuals.

CF patients need a high-energy, high-protein and moderate-to-high-fat diet with extra salt in hot weather and extra vitamins and minerals. Palatable and nutritious readily available high-protein–energy foods should be encouraged provided replacement pancreatic enzyme therapy is adjusted. In older children commercial or home-made milk-based drinks with added energy sources such as protein-enriched powder, glucose polymers, fat emulsions or medium-chain triacylglycerol represent a good way of increasing total energy intake. Although it has been standard practice in the past for many CF clinics to prescribe low-fat high-carbohydrate diets (Dodge & Yassa, 1980; Pencharz, 1983), largely on aesthetic grounds because of steatorrhoea, it is now generally accepted that low-fat diets offer no benefits to CF patients, impairing total energy intake and contributing to essential fatty acid deficiency as well as nutritional growth retardation (Pencharz, 1983).

The importance of counselling and dietetic support cannot be overstated. To the non-CF sufferer advocacy of an unrestricted and unlimited diet may seem idyllic! However, when it is imposed as part of a treatment regimen and appetite may be suppressed, food and meal times can become a chore. The demands of an anxious parent to achieve adequate dietary intake can become burdensome to the CF child. This is most often seen in the toddler age-

group where behavioural problems associated with feeding become exacerbated and continue into the older child. Peer-group pressure, particularly at school, are other areas which may need careful monitoring and support. Children often find it difficult to take their pancreatic supplements in front of their class-mates in order not to appear different. This may result in non-compliance or not eating to avoid embarrassment.

Where an adequate nutrient intake cannot be sustained or weight gain is unsatisfactory short-term nutritional supplementation either via the parenteral or enteral route (Shepherd *et al.* 1980, 1983) can have significant benefits in terms of body protein accretion and normalization of abnormalities in protein turnover. In a controlled study in our clinic, short-term nutritional supplementation during management of pulmonary exacerbations (Shepherd *et al.* 1986) increased body protein synthesis and protein deposition was achieved; an improvement not observed in patients receiving standard therapy or tube-feeding. Strategic short-term nutritional intervention should be, thus, considered in management of pulmonary exacerbation especially in malnourished patients. In patients, who are unable to sustain normal growth and nutrition by the oral route, a sustained increase in energy and protein intake can be achieved by long-term tube-feeding (Levy *et al.* 1985; Boland *et al.* 1986; O'Loughlin *et al.* 1986; Shepherd *et al.* 1986). These studies have demonstrated significant benefits in terms of weight gain, growth, and pulmonary function. Protein turnover studies have shown evidence of increased protein synthesis in excess of breakdown with net protein accretion within 1 month of commencing treatment (Table 6). However, since a longer period is required before catabolism falls it appears that the likelihood of long-term benefits from nutritional supplementation are likely to occur only after prolonged periods of treatment. It does appear that the duration of supplementation should at least be until adequate catch-up growth has occurred, and adaptation to lower levels of protein turnover with reduced catabolism has resulted, but further studies are necessary to determine the duration of such aggressive therapy, which may for some patients be indefinite. Delivery of nutritional support must be convenient and comfortable for the patient. Use of gastrostomy feeding has enabled patients to receive feeds frequently without having the distress of re-passing nasogastric tubes. Gastrostomies can now be inserted using percutaneous endoscopic procedures which avoids patients having to undergo anaesthesia and lengthy operations.

FUTURE DIRECTIONS

Further advances in nutritional and absorptive therapy will come from greater study of energy expenditure in CF and from a greater understanding of the pancreatic pathophysiology in relation to the functions of the CF transmembrane regulator and the basic defect. It seems possible that specific therapy aimed at improving the transport defect either by corrective drug treatment or by gene therapy will be possible but is clearly some time away. In the meantime, better definition of age- and disease-related alterations in energy expenditure will help to target CF individuals at high risk for malnutrition and, furthermore, the development and routine application of early diagnosis by neonatal screening (Bowling *et al.* 1987*a*, *b*) should help to prevent the occurrence of the nutritional problems currently seen commonly in this disease.

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