Energy balance and growth in cystic fibrosis

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Introduction

Growth is a non-specific term that is used to describe a constellation of changes associated with the elaboration of form and function[1]. It is a process that has been identified as being canalized and target seeking (ie genetically determined). During growth the changes in form are most readily identifiable as an increase in linear stature and mass, but also include more subtle variations in the composition of the body and changes in the relative size of the different organs and tissues. The co-ordinated development and refinement of function may be more difficult to quantify than changes in size and are not as clearly characterized. Although growth appears to be a continuous process, there are a range of factors, dietary, environmental and pathological, which may impede, slow down or even reverse some or all aspects of growth.

As growth in terms of an increase in mass represents an increase in the net energy content of the body, energy must be made available in excess of that required to cover the maintenance energy needs for the synthesis of new tissue as well as the energy that is deposited in new tissue. Similarly, where growth represents an elaboration and refinement of form there is an energy cost associated with the process of remodelling. Therefore, in addition to the provision of specific nutrients required to form the new tissue, the amount of energy available from the diet will ultimately limit growth, both in terms of form and function.

Chronic undernutrition with significant weight retardation and linear growth failure are widely recognized features of CF. Patients with CF have been reported to have poor weight for height[2], delayed puberty[3] and the eventual size and nutritional state of those surviving to adulthood is commonly below average[4]. In reviewing the literature, Durie and Pencharz[5] concluded that most growth problems in CF may be attributed to a dietary inadequacy, in particular unfavourable energy balance, rather than to an inherent factor of the disease itself. Whilst the cause of this dietary inadequacy remains unclear, many authors have demonstrated an association between the severity of malnutrition and the decline in pulmonary function, which in turn adversely affected overall survival[3,6]. Whether prevention of malnutrition and growth failure will ameliorate the rate of progression of lung disease and improve survival has yet to be demonstrated. Care must be taken before attempting to determine the direction of causality (ie is there a direct effect of the specific membrane defect in CF that causes poor nutrition or is malnutrition a natural consequence of the advancing pulmonary lung disease?) as this fails to take account of the complex inter-relationship between the disease process, infection, lung disease and malnutrition.

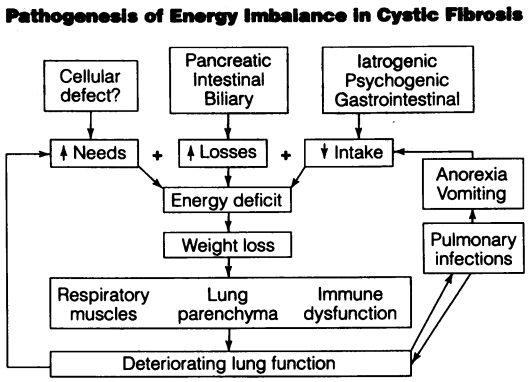

Figure 1. Interdependent factors which may give rise to progressive energy deficit as lung function deteriorates (reproduced with permission from J R Soc Med *1989, suppl. 16)*

Durie and Pencharz[5] recently proposed a model to explain the aetiology of the energy deficit in CF and defined the web of interdependent variables which may give rise to chronic malnutrition and growth failure in patients with CF (see Figure 1). Three factors are ultimately responsible for the development of an energy deficit sufficient to limit growth or cause weight loss: poor dietary intake, increased faecal losses through maldigestion and/or malabsorption or increased needs. In the majority of patients with minimal or moderate pulmonary disease, particularly those younger patients who have received continuous care in dedicated CF clinics from diagnosis, normal growth velocity and nutritional status can be maintained by voluntary intake of dietary energy and routine pancreatic enzyme replacement therapy until severe lung disease supervenes[7]. As lung disease worsens, most commonly in older adolescents and young adults, a variety of factors interact to cause an energy deficit and malnutrition which in turn contributes to a progressive deterioration of lung function. Thus, a vicious cycle is established leading inevitably to end-stage pulmonary failure and death.

Energy intake

It is widely accepted that the energy intake of patients with CF should be greater than that consumed by those healthy individuals without the disease. Although only a crude estimate, the suggestion that patients with CF require 120-150% of the recommended daily allowance (RDA) is often cited as a dietary goal or target[8-10]. In theory, additional energy would need to be consumed in order to cover the greater faecal energy losses in CF, although faecal energy losses would clearly vary between individuals

and also with the extent to which pancreatic enzymes may normalize maldigestion. Similarly, if the energy needs of the individual are raised, greater amounts of dietary energy should be consumed, although this may also vary both between individuals and within a given individual over time.

Despite the widespread belief that patients with CF exhibit voracious appetites, several studies have shown that the energy intake of patients with CF are frequently only within the range of 80-100% of the RDA for age, gender and body weight even when they are comparatively well and free from infection[5,11-16]. This failure to consume energy intakes in excess of 120% of the RDA has been attributed to many factors including anorexia, dietary dislikes and emotional problems. Other factors that will limit energy intake are the continued use of the traditional low-fat diet and poor dietetic support[9,13]. The use of unrestricted fat diets has now been advocated and it has been suggested that as much as 35-40% of the energy must be provided from fat if total energy intakes of more than 125% of the RDA are to be achieved[9,15].

In an attempt to examine these ideas more closely, we have recently measured the food intake of a group of 30 children (median age 8.8 years; range 5.3-16.0 years) attending our CF clinic which has an established programme of dietetic support which actively advocates the liberal consumption of fat in the diet. In addition to comparing the energy intake against the arbitrary benchmark of the RDA[17], we were particularly interested in determining whether the CF patients ate differently from a group of age and gender matched controls of normal body weight. Metabolizable energy intakes were estimated from 7-day records of weighed food consumption and analysed using a computerized food composition database.

The median energy intake of the CF group was 92% of the RDA, and only 7/30 CF patients consumed intakes that met the RDA for age/gender. Only three of the 30 CF patients reported energy intakes in excess of 120% of the RDA[17] (see Figure 2). This apparently low energy intake could not be attributed to consumption of a low fat diet as both groups consumed essentially the same diet which provided approximately 37% of the daily intake of energy in the form of fat. What should be noted, however, is that the CF patients reported energy intakes which were 34% greater than that reported by the control subjects when the energy intake was expressed relative to body weight (CF: 326 kJ/kg/day v C: 244 kJ/kg/day; median values; $P < 0.05$). Despite eating more energy than their healthy peers at the time of the study, 30% (9/30) of the CF group exhibited weights which were more than 2 SD below the median and 17% (5/30) exhibited heights which were more than 2 SD below the median. Those with normal growth centiles for height and weight tended to exhibit higher energy intakes than those patients with evidence of growth retardation.

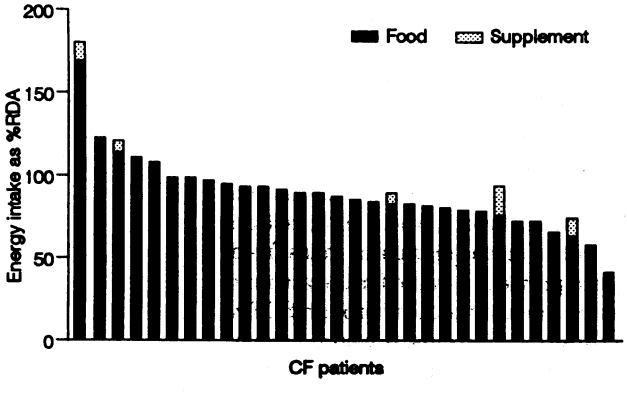

Figure 2. Energy intakes of patients with cystic fibrosis expressed as a percentage of the RDA for age, gender and body weight[17]

Therefore, even with regular dietetic support and a free diet, patients with CF may not consume energy intakes in excess of 120% of the RDA. The observation that these patients were eating relatively more energy than the group of healthy control children should not be overlooked. These children appeared to be eating to appetite as no patient reported any factor that would have limited food intake during the study. Considering the large amount of food already consumed, we are concerned to see whether it is possible to further increase energy intakes in these children. It is tempting to suggest that greater energy intakes could be attained by more active promotion of supplements as only five of the CF patients reported using dietary supplements during the study period. It should be noted however, that all patients had been regularly advised to use supplements and that considerable dietetic support had been given to the patient. Even in those patients using a dietary supplement, the contribution made by supplements to total energy intake was comparatively small (5-10%). In our experience, few patients persist with using dietary supplements for prolonged periods as part of their normal diet and food is often displaced by supplements so that only minor increases in total energy intake are maintained.

The potential dangers of overfeeding should also be recognized. It is possible to override the normal mechanisms governing appetite and food intake when patients are fed either nasogastrically or via total parenteral nutrition. Any substrate and co-factor consumed in excess of that required by the host imposes a metabolic demand. Under circumstances where the individual may be metabolically compromised (eg infection), the additional burden of excess substrate and co-factor may result in potentially dangerous sequelae[18]. Thus, the rationale behind feeding CF patients nutritionally complete feeds to a level of 120-150% of the RDA for energy demands careful and closer examination.

Energy losses

It has been estimated that approximately 90% of patients with CF develop pancreatic exocrine insufficiency which leads to the maldigestion of lipid, protein and carbohydrate[19]. Uncorrected, this maldigestion will severely limit the amount of energy available from the diet and in turn will contribute to an energy deficit sufficient to limit growth. Various forms of pancreatic enzyme replacement therapy (PERT) have been developed in an attempt to limit the extent of this maldigestion. The impact of PERT on clinical management of CF is considerable and has made a major contribution towards improved growth and nutritional status in CF.

Despite these advances, however, the extent to which PERT fully normalizes maldigestion in CF and the magnitude of faecal energy losses of patients on established PERT remains unresolved. In clinical practice, PERT is primarily directed towards the

symptomatic correction of steatorrhoea, abdominal pain relief and the reduction in stool frequency and the mass of stool passed each day. Of these, steatorrhoea would appear to be the most important clinical consideration and has frequently been used as an index of the extent of maldigestion. Using this empirical approach it is commonly assumed that when the gastrointestinal symptoms and steatorrhoea are improved, the amount of energy available from the diet would be normal. However, the extent to which stool energy losses are completely normalized in patients with CF on their habitual established PERT and the possible contribution that faecal energy losses may continue to make towards an energy deficit in CF has not been determined.

In an attempt to address these issues, we measured the faecal energy losses in 20 patients with CF aged 5-25 years on their normal established PERT in comparison to that observed in a group of 20 age and gender matched healthy controls[20]. The CF patients were taking between 11 and 43 capsules (mean 22) of Creon each day and had been using PERT in the form of enteric coated microspheres for at least one year prior to the study. All of the patients self-titrated their enzyme dosage against gastrointestinal symptoms and the nature and frequency of stools.

Although the gross energy intakes were similar for both the CF patients and control subjects, faecal energy losses were on average three times greater in the CF patients when compared to the control subjects (991 v 337 kJ/day; mean $P<0.001$) and were equivalent to 5-20% (mean 11%) and 3-4% (mean 3%) respectively of the gross energy intake. Thus, even when CF patients are on PERT and believe themselves to be comparatively asymptomatic, faecal energy losses remain substantially elevated and may be equivalent to as much as 20% of gross energy intake. This suggests that faecal energy losses may continue to contribute in part towards an energy deficit that may be sufficient to limit growth or cause weight loss.

Faecal lipid losses as an index of maldigestion must also be questioned as energy losses could not be simply related to the amount of lipid within the stool. Faecal lipid losses remained elevated in the CF patients in comparison to controls and were equivalent to 3-38% (mean 15%) and less than 4% of the lipid intake respectively. Differences in faecal lipid could only account for 19% of the variance of the differences in faecal energy in the patients with CF and less than half of the energy within the stool could be attributed to faecal lipid.

The collection and analysis of faecal material is both time consuming and unpleasant and the facilities for directly measuring faecal energy are not generally available in clinical practice. We have found, however, that there is a good relationship between the energy present in the stool and the wet weight of the stool for both CF patients and controls (see Figure 3). From the data available in this study, it would appear that 8 kJ of energy (2 kcal) is present in each gram of wet stool. With this information, an estimate of the extent of energy losses may be made by simply determining the weight of the stool passed each day. These results would also suggest that there is a need to reconsider the present approach to using faecal lipid to assess the efficacy of PERT. We would suggest that the routine measurement of faecal energy may provide a more accurate assessment of the extent to which PERT reduces energy losses in CF patients than the measurement of faecal lipid.

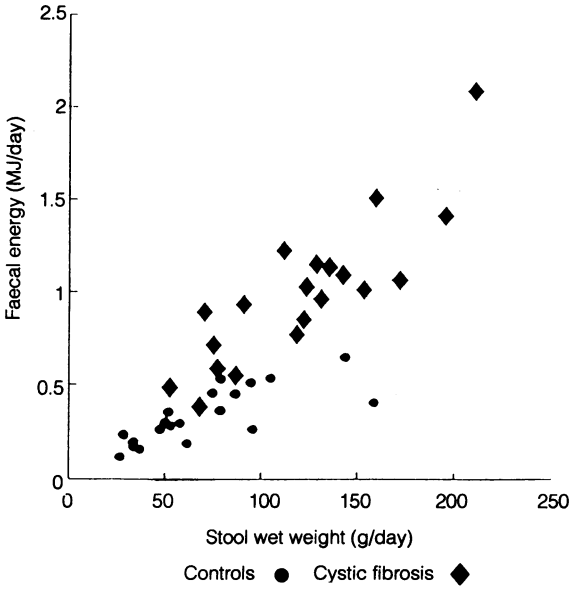

Figure 3. Stool energy losses versus stool wet weights for the control subjects and patients with CF. Regression line for CF values: Stool energy (kJ/day)=68.9+(stool wet weight g/day)×7.6; R=0.86; SEE=202 (reproduced with permission from Murphy et al. Arch Dis Child[20])

Further attention must also be directed towards determining the origin of energy within the stool. It is commonly assumed that all of the energy within the stool may be attributable to maldigested and malabsorbed dietary residue in CF. However, faecal energy losses could also be derived from endogenous secretions and cellular debris as well as colonic bacterial microflora[21,22]. Whilst it is not yet possible to state the relative contribution made by each of these components nor how they may alter with diet, disease or PERT, it is comparatively simple to measure the amount of bacteria within the stool using the method described by Stephen and Cummings[23]. Using this technique we estimate that bacterial microflora may account for approximately 30% of the total energy lost within the stool in both the CF patients and healthy children. Thus a major component of the stool (both as energy and lipid) is not simply maldigested and malabsorbed dietary residue, but bacterial microflora. Studies examining the source of substrate for this fermentation may give us insight on the way in which future developments of PERT might be best directed.

We have also been able to estimate the amount of energy that be made available to the host in the form of short chain fatty acids (SCFA: acetic, proprionic and butyric acids) through the fermentation of carbohydrate by the bacterial microflora[1]. It is possible to estimate the amount of carbohydrate that would need to be fermented to produce the amount of bacterial microflora observed within the stool as well as the total energy yield by that fermentation. Subtraction of the energy within the faecal microbial mass from this total energy yield provides a value for the amount of energy that may be made available through SCFA absorption. From these calculations, it would appear that colonic fermentation may provide additional energy equivalent to 7% of gross energy intake (range 3-13%). This would suggest that the colonic fermentation of carbohydrate affords the opportunity to recover, at least in part, some of the energy from

either unabsorbed starches and sugars or endogenous secretions that would otherwise be lost in the stool in children with CF. The contribution made by colonic fermentation may be relatively small when the gross energy intake is high. In contrast, for individuals on a marginal intake of energy or in whom requirements are elevated, the relative contribution will be greater and may be critical.

Another potentially important route by which energy may be lost from the body is through the expectoration of sputum - especially during chest physiotherapy or during an infectious exacerbation. It is not possible to determine the amount of sputum that is produced each day. Much of the sputum would be swallowed thereby allowing the opportunity to salvage the energy and nitrogen content of sputum through digestion or fermentation. We were particularly interested in determining the amount of energy that would be lost each day as expectorated sputum. All of the sputum that would normally be lost was collected over a two-day period in five patients with CF during a period of hospitalization as a result of an infectious exacerbation. Although the total volume of sputum collected each day appeared large, the total sputum energy losses averaged 35 kJ/day and was equivalent to less than 1% of gross energy intake. The greatest sputum energy losses observed was 274 kJ/day and was equivalent to approximately 5% of gross energy intake. Therefore, even though the amount of energy lost as sputum may be relatively small, sputum losses may also contribute to an energy deficit and may be particularly important where energy intakes are marginal.

Energy expenditure

Several authors have suggested that the energy requirements of patients with CF are increased on the basis of apparently greater rates of energy expenditure at rest. Vaisman and co-workers[24] demonstrated that resting energy expenditure (REE) measured by open-circuit indirect calorimetry was found to be greater than that predicted on the basis of age, gender and weight (range 95-153%) in a group of 71 CF patients aged 9-36 years who were not suffering from an acute respiratory infection. They noted that the extent to which REE was elevated above predicted values was negatively correlated with pulmonary function and nutritional status (as percentage body fat). These findings have been confirmed by others[25,26]. Closer examination of the literature reveals that the extent to which REE may be elevated appears to be greater in older CF patients than in younger patients with only mild to moderate lung disease and reasonable nutritional status. It should be noted, however, that even young patients with normal pulmonary function and above average weight for age may exhibit REE values which are greater than predicted for age, gender and weight.

One of the greatest difficulties in the interpretation of existing data has been the contentious issue of the selection of an appropriate control or reference group. In most studies, the results have been expressed as a function of predicted energy expenditure based upon age and body weight. This approach may be misleading as at any given age or weight, a patient with CF would be much leaner than a control subject (ie in CF a greater proportion of body weight is metabolically active tissue which would contribute a relative excess to the energy utilization of the individual). One would inevitably predict from this that a patient with CF would have a higher REE than expected, based upon a formula derived in individuals with a body weight and composition similar to that of the control subjects.

Table 1. Resting energy expenditure (REE) of patients with CF and healthy controls matched for body weight and lean body mass

	Cystic fibrosis (n=25)	*Control (n=25)*
Age (years)	13.5±0.9	9.8±0.5**
Body weight (kg)	33.5±2.4	32.8±2.0
Lean body mass (kg)	29.0±2.3	28.0±1.7
REE (kJ/day)	5444±328	4414±290*
WHO predicted REE (kJ/day)[17]	5023±174	5009±136
REE/predicted REE (%)	107±3	87±4**
REE (kJ/kg body weight/day)	167±5	138±7**
REE (kJ/kg body weight$^{0.75}$/day	395±10	325±16**
REE (kJ/kg lean body mass/day)	195±6	161±8**

Values are mean±SEM; *$P<0.05$, **$P<0.01$

In an attempt to overcome this important limitation, we have compared the REE of patients with CF against that of control subjects matched for lean body mass. In effect this means that we have to compare CF patients with much younger individuals to achieve comparable physical development. The REE of a group of 25 CF patients was compared with that of gender matched healthy controls of comparable body weight, lean body mass and predicted REE. This meant comparing the REE of CF patients against that of younger controls (13.5±0.9 v 9.8±0.5 years respectively; mean±SE; $P<0.01$). REE was determined by indirect calorimetry using a ventilated hood/mass spectrometer system in the CF group at a time when they were comparatively well and free from infection. The REE of the CF patients as a group was 22% greater than that of the control group irrespective of whether the REE is expressed in absolute values (eg MJ/day) or relative to body weight (see Table 1). These results add further weight to the view that REE may be raised in CF even when the patient is comparatively well. The raised REE cannot be attributed to differences in adiposity between the CF patients and controls in this study.

The heterogeneity of the disease state is also reflected in the considerable inter-individual variation in REE when expressed per unit fat-free mass within the group of CF patients (see Figure 4). Although as a group, CF patients exhibited REE values which were 22% greater than that observed of the control group, there are many CF patients with REE values that are comparable to that observed in the healthy controls. This would suggest that not all patients with CF have a greater metabolic demand for energy at rest.

A variety of mechanisms have been proposed which may result in an increase in energy expenditure at rest. These include the primary membrane defect in CF which may in itself result in a greater energy utilization within the cell[27,28], the increased energy cost of laboured ventilation, intercurrent infection,

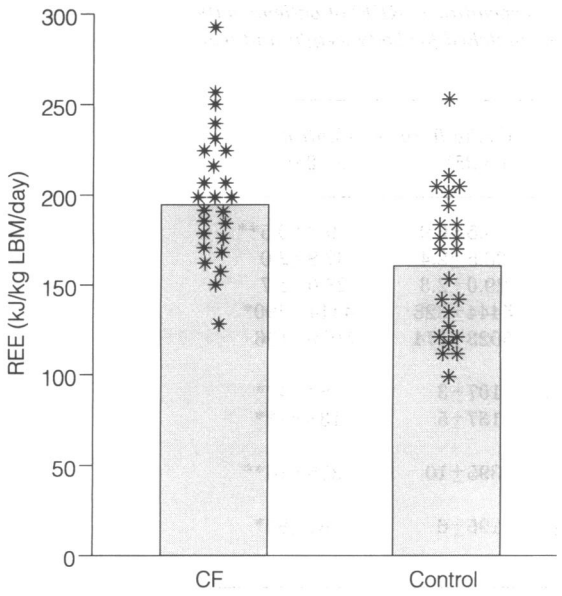

Figure 4. Individual values for resting energy expenditure (REE) expressed relative to lean body mass for control subjects and patients with CF

and stimulation of metabolism by sympathomimetic agents such as bronchodilator therapy[29]. Further support for the view that the membrane defect may provide a cellular basis for an increased energy expenditure at rest has recently been proposed by O'Rawe and co-workers (personal communication). They suggest that the specific genetic defect whereby a phenylalanine residue is deleted (Δ_{508} allele) may influence cellular bioenergetics. Patients who were homozygous for the deletion had a median energy expenditure at rest which was 25% greater than that predicted for age, gender and weight, whilst those patients without the deletion exhibited energy expenditure values which were only 2% greater than predicted. However, it should be noted that these are preliminary observations and need further investigation.

Various attempts have been made to specifically associate the extent to which REE may be increased with either lung function and disease, nutritional status and a specific gene mutation. However, such analysis fails to take into account the complex inter-relationship between such variables and the extent to which any one variable may contribute to energy expenditure will clearly differ both between individuals with CF and also within a given individual over time with progression of the disease. Only by establishing a large-scale multi-centre trial using standardized methodology such as that in progress in paediatric oncology (eg UKALL trials) will it be possible to gather sufficient information to identify the relative contributions that each of these factors may make to energy expenditure.

Even if energy expenditure at rest is increased in patients with CF, this does not necessarily mean that the total amount of energy expended each day, and hence energy requirement, is raised. This will depend on the extent to which the amount of energy expended in physical activity is altered in CF. It is not known whether the energy cost of activity is also increased and whether the total amount of energy expended each day is greater. Even if the energy cost of a given task were increased, the individual with CF may be less active, thereby reducing the total amount of energy expended each day. This reduction in energy expended in physical activity may be a compensatory mechanism to accommodate an elevated expenditure of energy at rest such that the total energy expenditure is the same as or lower than that observed in healthy control subjects. Encouraging the individual with CF to engage in physical activity may increase total energy expenditure thereby creating or exacerbating an energy deficit which would further limit growth or cause weight loss. Alternatively, the increased physical activity may lead to an improvement in appetite and nutrient intake. No attempts have been made to examine the impact of exercise therapy on energy balance or nutritional status in CF.

To date, only one study has been reported where attempts were made to determine whether the total energy expenditure is raised in CF. Shepherd and co-workers[30] measured total energy expenditure using doubly-labelled water in a group of clinically well nourished CF infants without evidence of lung disease. CF infants evaluated by this method had 25% higher rates of total energy expenditure in comparison with that observed in a group of healthy infants matched for age and body weight. Before these limited observations are taken to substantiate the view that energy requirements are increased in CF, it is important to recognize that the majority of energy expended by infants is at rest and the amount of physical activity will be minimal and that the doubly-labelled water technique for measuring total energy expenditure requires validation not only in growing children, but also in children with CF.

Conclusions

The rationale behind the current dietary recommendations for patients with cystic fibrosis requires careful consideration and refinement. Some patients with cystic fibrosis may find it increasingly difficult to satisfy the metabolic demand for energy because of poor appetite, sustained faecal energy losses and raised total energy expenditure. These individuals will exhibit alterations in both form and function unless the energy deficit is corrected. Others may have minimal faecal energy losses and a normal (or even lower) total energy expenditure, such that the energy requirements may be satisfied by the consumption of normal amounts of dietary energy. Attempting to apply a common dietary goal of 120-150% of the RDA to all patients with CF is clearly inappropriate. Over-zealous attempts to feed to that level irrespective of the metabolic demand and appetite of the individual is potentially harmful and must be actively discouraged.

Given the heterogeneity of the disease state, attempts must be made to characterize the nutritional requirements of patients with CF and examine the complex inter-relationship between the disease process, lung disease, infection and malnutrition. The demands of the growing child with mild to moderate lung disease are likely to be different from that of the child with infection and that of the adult with advanced lung disease. Such an approach could only be achieved through a co-ordinated programme of research using standardized methodology throughout the different CF centres in the UK. In this way, it would be possible to develop appropriate guidelines on feeding patients with cystic fibrosis that could be used simply and effectively in clinical practice.

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