Sir David Cuthbertson Medal Lecture

Understanding chronic malnutrition in childhood and old age: role of energy balance research

John J. Reilly

University of Glasgow Department of Human Nutrition, Royal Hospital for Sick Children, Dalnair Street, Glasgow G3 8SJ, UK

Undernutrition is commonly associated with chronic disease in children and the elderly. Overnutrition is also, but less commonly, associated with chronic illness. In most diseases malnutrition arises because energy intake does not match energy output. Traditionally, the focus of research has been on abnormalities in energy expenditure, in the belief that these factors were the main determinants of energy imbalance. Recent studies using the doubly-labelled-water method to measure total energy expenditure, combined with more complex study design, have suggested an alternative conclusion. In many chronic diseases patient behaviour, and particularly energy intake, is responsible for energy imbalance and malnutrition. Energy balance studies have therefore provided a useful foundation for the design of strategies aimed at preventing or managing chronic malnutrition. However, modifying patient behaviour is an ambitious undertaking which may not be within the scope of existing clinical nutrition services. A number of non-traditional models of managing chronic malnutrition in children and the elderly are promising. Increasing recognition of the value of systematic review will also provide improved strategies for prevention and management of chronic malnutrition.

Chronic illness: Critical illness: Energy requirements: Energy expenditure: Nutritional support: Doubly-labelled-water method

Background: undernutrition and overnutrition in chronic disease

It has long been recognised that chronic disease is associated with, and indeed causes, undernutrition. Undernutrition, in turn, increases susceptibility to disease. The elderly are at particular risk of undernutrition, largely because disease is common in older adults, and compromises maintenance of energy balance. Sick infants, and to a lesser extent children, are also particularly susceptible to negative energy balance and undernutrition. Infants and children are also especially vulnerable to the functional effects of undernutrition, because of the sensitivity of many developing biological systems. In a few chronic diseases overnutrition is a greater risk than undernutrition and, like undernutrition, adverse functional consequences are to be expected. In summary, undernutrition and overnutrition usually result from chronic negative or positive energy balance secondary to disease.

Both forms of malnutrition should be of concern because of their functional and clinical consequences. The principal aim of the present review is to consider the contribution which research on energy balance can make to improving the management of chronic malnutrition in children and the elderly.

Measurement of energy balance in disease states: rationale and applications

In essence, energy balance is both very simple and extremely important clinically. By definition, energy balance refers to the difference between energy (food) intake and the sum of the energy outputs (principally total energy expenditure; TEE). Positive balance means that the excess energy must be stored, negative balance means that the energy deficit must be made good by oxidation of body tissues, reduction in TEE and/or compromised growth (in...
infancy and childhood). Chronic energy imbalance is not an epiphenomenon, but must ultimately have adverse clinical consequences.

Historically, identifying the precise causes of energy imbalance in many diseases has been difficult. This difficulty arose in part because of the complex origins of energy imbalance in many diseases, i.e. a combination of disease effects on patient behaviour, energy intake, digestion or absorption and intermediary metabolism. A further serious difficulty was the inability to accurately measure TEE, the principal determinant of energy requirement. This situation led to a dependence on measurement of resting energy expenditure (REE) in disease states. Measures of REE alone are not very informative when trying to identify causes of energy imbalance, and many studies based exclusively on measurement of REE have produced misleading conclusions (Reilly et al. 1997).

The advent of the doubly-labelled-water (DLW) method has revolutionised our understanding of human energy balance. It has high accuracy, with a mean error of <2% (Speakman, 1998), is relatively straightforward for the subjects being measured, and measures TEE in free-living conditions. The fact that DLW measures TEE, rather than its individual components, makes it an extremely useful approach for assessment of energy needs; it is much more informative than the more traditional experimental approach of only measuring REE. While REE measurements are relatively easy to make, they are difficult to interpret, since any increase or decrease in REE as a result of disease need not be associated with an increase or decrease in TEE (Jebb, 1997; Gibney, 2000). The best-known clinical example of this problem is in adults with HIV infection, where it was assumed that increased REE caused undernutrition. In fact, TEE was low, not high, during periods of weight loss, indicating that undernutrition was the result of compromised energy (food) intake (Macallan et al. 1995). Similar conclusions have been reached in a number of chronic diseases of childhood which are characterised by abnormal REE and energy imbalance (Table 1). In old age there is also a good deal of evidence that TEE is low in disease, not high (Prentice et al. 1989; Reilly et al. 1995). Even in diseases of old age where increased REE has been observed TEE is consistently low (Toth et al. 1997; Toth & Poehlman, 2000).

Methodology available for measuring energy balance, and particularly measurement of TEE by DLW, has a number of other important clinical applications. The methodology has been used by our research group to: test hypotheses in relation to causes of energy imbalance (Reilly et al. 1996, 1998, 1999a; Bland et al. 2001); validate clinical methods, such as methods of dietary intake assessment (Reilly et al. 2001c); assess clinical algorithms for estimating energy needs (Reilly et al. 1999c).

### Energy balance studies in the elderly

Chronically- and acutely-sick elderly patients show a high prevalence of undernutrition, which increases with increasing dependency and disease (Morgan et al. 1986). Occasional studies of energy intake had suggested that in some diseases of old age energy intake was adequate, but assessments of energy intake alone (in the absence of measures of TEE) tend to be both inaccurate and imprecise. Use of the DLW method in the healthy elderly (Reilly et al. 1993) and chronically- and acutely-sick elderly (Reilly et al. 1992, 1995) revealed that energy requirements were exceptionally low in the sick-patient groups. Individuals with low levels of energy expenditure should, in principle, be prone to overnutrition not undernutrition. The apparently paradoxical association between low energy requirements and undernutrition is explained by the observation that it is inadequate energy intake which is usually the main cause of undernutrition in the elderly (Toth & Poehlman, 2000). The elderly may be particularly susceptible to negative energy balance. Some evidence suggests that elderly subjects have diminished capacity to adaptively ‘respond’ to a period of inadequate food intake, by failing to increase energy intake appropriately (Roberts et al. 1994).

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### Table 1. Studies of total energy expenditure (TEE) using the doubly-labelled-water method in chronic diseases of childhood

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Design</th>
<th>Conclusions</th>
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</thead>
<tbody>
<tr>
<td>Barden et al. (2000)</td>
<td>Sickle cell disease (SCD)</td>
<td>Patients (n 36) v. healthy controls (n 30)</td>
<td>Elevated REE, but not TEE, in SCD</td>
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<td>Stallings et al. (1996)</td>
<td>Spastic quadriplegic cerebral palsy (SQCP)</td>
<td>Patients (n 32) v. healthy controls (n 32)</td>
<td>Reduced TEE in SQCP</td>
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<tr>
<td>Motil et al. (1998)</td>
<td>Retts syndrome (RS)</td>
<td>Patients (n 14) v. healthy controls (n 11)</td>
<td>Elevated REE, but not TEE, in RS</td>
</tr>
<tr>
<td>Reilly et al. (1998)</td>
<td>Acute lymphoblastic leukaemia (ALL)</td>
<td>Patients (n 20) v. pair-matched healthy controls (n 20) and v. estimated average requirements (EAR)</td>
<td>Reduced TEE in ALL, below EAR</td>
</tr>
<tr>
<td>Bland et al. (2001)</td>
<td>Obstructive sleep apnoea syndrome (OSAS)</td>
<td>Patients (n 11) before v. after surgery, and compared with pair-matched controls (n 22) and with EAR</td>
<td>Elevated REE, but not TEE, in childhood OSAS</td>
</tr>
<tr>
<td>Reilly et al. (1999a)</td>
<td>Cystic fibrosis (CF)</td>
<td>Fourteen children during acute exacerbation v. when stable and v. EAR</td>
<td>No elevation of TEE</td>
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<tr>
<td>Bronstein et al. (1995)</td>
<td>CF</td>
<td>Presymptomatic infants (n 18) v. retrospective controls (no. of controls not given)</td>
<td>No elevation of TEE</td>
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<tr>
<td>Shepherd et al. (1988)</td>
<td>CF</td>
<td>Clinically-stable infants (n 9) v. healthy retrospective controls (n 16)</td>
<td>Increase in TEE in CF, inconclusive</td>
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<tr>
<td>Tomeszko et al. (1994)</td>
<td>CF</td>
<td>Stable patients (n 25) v. healthy controls (n 25)</td>
<td>Elevated TEE in CF (?), dependent on genotype</td>
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</table>
In one of our studies of elderly patients admitted to hospital with acute illness TEE was very low, but simultaneous measurements of energy intake demonstrated that, despite low TEE, patients were in substantial negative energy balance (on average −1.3 MJ/d; Klipstein et al. 1995). This factor was of particular concern because these patients were typically undernourished on admission to hospital, and a further marked deterioration in nutritional status was observed during hospitalisation (Potter et al. 1995).

From energy balance studies to treatment of undernutrition in the elderly

As noted earlier, the role of energy expenditure in undernutrition is negligible in most patients, and they become undernourished despite low energy needs, not because of high energy needs. Focus on energy intake as the principal determinant of undernutrition in chronic disease is therefore necessary, but this situation has required a paradigm shift. In clinical practice emphasis should be placed on strategies for supporting energy intake. In order to identify successful strategies it is essential to test the evidence base to consider the extent to which current clinical nutrition practices, such as enteral supplementation, are supported by unbiased generalisable empirical evidence. Such questions can be successfully addressed by systematic review, critical evidence appraisal and, where appropriate, meta-analysis.

An important meta-analysis of randomised controlled trials in enteral supplementation of adults was undertaken by Potter et al. (1998). This meta-analysis showed that enteral supplementation had positive effects on energy intake and indices of nutritional status such as body-weight change. These conclusions were deemed generalisable across many diverse clinical settings. This study provided a basis for enteral supplementation, but also identified important unanswered questions such as the effect of enteral supplementation on morbidity and mortality. It may seem surprising that questions of such importance in clinical nutrition are unanswered, but systematic review is very effective at highlighting what we do not know. In response to this meta-analysis, and our earlier evidence of undernutrition exacerbated by negative energy balance during hospitalisation, we designed a study to test the hypothesis that sip-feed supplements could improve morbidity and mortality in elderly hospital patients.

Sip-feeding is of course not the only available clinical option to support energy intake, but it is now firmly evidence-based. In some other diseases characterised by undernutrition research has also progressed from an understanding of the underlying mechanisms (such as the role of the inflammatory response in cachexia) to promising novel treatment strategies (Wigmore et al. 1997; Barber et al. 1999), and these strategies are now being tested using randomised controlled trials. A general model for improving clinical nutrition strategies is to use systematic review to explicitly identify what is known and what is not known, test for the underlying mechanisms of undernutrition if necessary and design treatments which target the underlying mechanisms. These treatments can then be rigorously tested by randomised controlled trials, the most appropriate means of obtaining unbiased evidence. Obtaining evidence from clinical studies is both difficult and time-consuming, but the examples described earlier show that it is possible.

Energy balance studies in children

Our research group has carried out investigations of overnutrition (obesity) in children with acute lymphoblastic leukaemia (ALL), the most common childhood malignancy. We have also investigated the causes of undernutrition in children with cystic fibrosis (CF), obstructive sleep apnoea syndrome and HIV infection. A detailed description of this work would go beyond the scope of the present review, so the aims here are to briefly summarise the research, to highlight lessons for clinical management of energy imbalance, and to identify research strategies and methods which exist to identify the causes of energy imbalance in chronic disease.

Energy balance and overnutrition in acute lymphoblastic leukaemia

At diagnosis undernutrition is relatively common in children with ALL (Reilly et al. 1999b), which may have important clinical consequences (Reilly et al. 1994; Weir et al. 1998). After diagnosis children with ALL gain weight rapidly, in excess of expected rates (Odame et al. 1994; Reilly et al. 2000). They maintain the excess weight or continue to gain weight excessively even after therapy has ended (typically 2–3 years post diagnosis). An extremely high prevalence of obesity is observed in survivors during childhood, adolescence and adulthood (Didi et al. 1995; Ventham & Reilly, 1999; Reilly et al. 2000). Children with ALL also have advanced ‘adiposity rebound’, an independent risk factor for adult obesity (Reilly et al. 2001b). Obesity is of increasing...
concern in ALL, as it is just one of a number of ‘late effects’ which are manifest as therapy for childhood cancer improves.

We have systematically tested the underlying mechanisms of weight gain in ALL. Overnutrition in ALL is complex, and could arise from any one or a combination of factors related to treatment (e.g. ‘steroid effects’ on appetite), lifestyle (changes in habitual physical activity), or reduced REE (Venham & Reilly, 1999). By systematically testing hypotheses using modern techniques of energy expenditure measurement we have shown that REE is normal in ALL (Reilly et al. 1996), but that TEE, measured using DLW, is substantially reduced relative to controls before children become obese. In addition, TEE is predictive of subsequent weight gain (Reilly et al. 1998). This reduction in TEE secondary to reduced habitual physical activity in children with ALL confirms an important behavioural or ‘lifestyle’ component to the development of obesity in ALL. Some treatment effects also contribute. We recently demonstrated that the glucocorticoids used in ‘maintenance’ chemotherapy for ALL (5 d of steroid treatment with prednisolone or dexamethasone every 28 d) substantially increase energy intake (Reilly et al. 2001a). This response might not seem unexpected, but a literature review revealed almost no empirical evidence on the effects of corticosteroids on energy intake in clinical studies, and no evidence in children (Reilly et al. 2001a).

By systematically applying modern techniques of nutritional assessment (e.g. monitoring changes in BMI standard deviation score longitudinally) and energy expenditure (e.g. DLW), we have been able to both describe the natural history of obesity in ALL, and to identify its principal causes. The major remaining challenge is to test whether this knowledge can be used to design effective strategies for prevention of obesity in ALL. Patient behaviour (physical activity and inactivity) is clearly a component of the problem, and to modify the activity level of patients represents the most likely solution, since the scope for modifying drug treatment is limited.

**Undernutrition in cystic fibrosis: energy balance studies**

Despite a number of improvements in diagnosis and treatment of CF, undernutrition remains common (Morison et al. 1997). Undernutrition is widely believed to be due to chronic negative energy balance, but its origins appear to be complex (Reilly et al. 1997). CF has a number of features which might predispose patients to negative energy balance: energy intake may be compromised episodically or chronically (Scott et al. 1985; Stark et al. 1995); faecal energy losses are relatively high as a result of deficits in digestion or absorption (Murphy et al. 1991); REE is generally increased, although whether this increase produces an increase in TEE was open to question (Reilly et al. 1997). Recent studies by our own group and others suggest that TEE is normal or even low in most patients with CF (Table 1). This observation focuses attention on inadequate energy intake and control of faecal energy losses as more likely causes of undernutrition in CF, and as promising targets for treatment. The most productive means of identifying the causes of undernutrition in CF, and assessing their relative importance, has been to measure all components of energy balance simultaneously (Reilly et al. 1997), including TEE by the DLW method, and to study patients during periods of nutritional stress (Reilly et al. 1999a). The more traditional approach, in CF and other diseases, has been to measure only REE, and to study patients when they are well and clinically stable. The traditional approach has not been particularly informative, and the more complex approach, outlined in Table 2, is essential if mechanisms of negative energy balance and undernutrition are to be understood.

**Undernutrition in cystic fibrosis: from energy balance to treatment strategies**

The research described earlier suggests an important role for patient lifestyle in the management or prevention of undernutrition in CF. This role includes compliance with the diet prescription and pancreatic enzyme-replacement therapy. Several other lines of evidence support this view. First, our own studies have shown that in some patients the effect of poor compliance with therapy can have large effects in energy balance terms (Reilly et al. 1999a). Second, in both the UK and USA socio-economic status is a major determinant of clinical outcome (for example, see Schechter & Margolis, 1998), independent of access to medical care. Third, reduced doses of pancreatic enzyme-replacement therapy can actually improve growth and nutritional status, probably as a result of improved compliance with pancreatic enzyme-replacement therapy (Lowdon et al. 1998). The most convincing evidence comes from randomised controlled trials in which families of children with CF receive intensive therapy directed at achieving changes in patient behaviour (for example, see Jelalian et al. 1998). By teaching strategies which enable children and families to increase food intake and comply with therapy, nutritional status can be substantially improved in children with CF. This approach may be a useful model for improving nutritional status in other chronic diseases of childhood (Mackner et al. 2001). This research also implies that the more

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**Table 1. Recommendations for identifying causes of energy imbalance in complex disease states**

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<th>Methods</th>
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<tr>
<td>Measure all components of energy balance (REE, TEE, energy intake)</td>
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<td>Measure energy balance components simultaneously, in same patient</td>
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<td>Measure TEE using DLW where possible</td>
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<tr>
<td>Measure body composition appropriately, taking account of effects of disease on methodology</td>
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**Setting and design**

- Study patients during periods of clinical instability or nutritional stress
- Use longitudinal studies
- Consider multicentre studies to provide sufficient sample size, power and generalisability
- Consider using each patient as his (her) own control
- Choose appropriate controls or match for main determinants of energy expenditure

REE, resting energy expenditure; TEE, total energy expenditure; DLW, doubly-labelled water

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traditional medical model of prescribing medication and/or supplements, with a little patient education, is insufficient to prevent or manage undernutrition successfully.

Approaching the problem of undernutrition in CF from a cognitive or behavioural viewpoint, therefore, appears to be a successful evidence-based strategy. However, the cognitive or behavioural approach may not be readily generalisable, because it requires an intensive input of resources and access to health professionals not widely available, such as clinical psychologists. Nevertheless, recognising that patient behaviour can be central to managing malnutrition in chronic disease, and setting out to change patient behaviour, appears to be worthwhile, but requires a fundamental change in our approach to the treatment of many diseases. A number of other examples of the success of novel behaviourial approaches to nutritional treatment exist in diverse chronic diseases in both children and adults (for example, see Wright et al. 1998; Epstein et al. 2000; Jeffery et al. 2000).

An important systematic review concluded recently that traditional clinical approaches to managing undernutrition in children, such as enteral supplementation, are not evidence-based at present (Poustie et al. 2002). This conclusion not only questions our standard clinical methods, but clearly and specifically identifies important research needs, a similar outcome to the systematic review of enteral supplementation in adults (Potter et al. 1998). This absence of a sound evidence base to clinical practice is not unique to undernutrition, but also applies to childhood obesity (Reilly et al. 2002), and to paediatric practice in general (Smyth, 2001). However, not being uniquely disadvantaged in terms of our evidence base is little consolation; it still represents an important challenge to clinical nutrition research.

**Conclusions**

The advent of the DLW method has made it possible to definitively identify causes of overnutrition and undernutrition in chronic disease. The method is particularly effective when combined with simultaneous measurements of energy intake, REE and appropriate measures of body composition. Longitudinal studies which include periods of nutritional stress or weight loss are also particularly informative as to causes of weight loss. In many chronic diseases the underlying causes of malnutrition have now been identified as a result of applying modern energy balance methods. Chronic disease is rarely, if ever, associated with increased TEE. In most cases the evidence strongly suggests that patient behaviour in general, and energy intake in particular, is the main determinant of undernutrition or overnutrition. Even when patient behaviour is not the underlying cause of the nutritional problem, modifying behaviour is likely to be part of the solution. This approach is likely to require a major revision of the way in which we manage or prevent chronic malnutrition, with greater emphasis on the need to understand and modify patient behaviour.

Systematic review provides a powerful means of identifying the evidence base for clinical nutrition. It can usefully identify research needs and improve treatment strategies. Systematic review can also deal with the problem noted by Mark Twain: ‘It aint the things we know which are the problem, it’s the things we know that aint so’.

**Acknowledgements**

I am indebted to a great many collaborators and mentors. The work described here refers to a programme of research over 11 years, and so the number of colleagues, and funding bodies, who merit an acknowledgement is too great to list here. I thank them all.

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