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Sir David Cuthbertson Medal Lecture

Elucidating effective ways to identify and treat malnutrition

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There is a clear rationale for elucidating effective ways of identifying and treating disease-related malnutrition (DRM), given the physiological and financial consequences of this common condition and its treatability. Evidence indicates the efficacy of nutritional support methods (oral, tube and intravenous) in increasing total nutritional intake while having little effect on appetite, satiety, appetite mediators (e.g. leptin) and voluntary food intake. When used as the only source of nutrition, artificial nutrition can effectively maintain nutritional intake, and yet many patients find enteral or parenteral feeding alone is unable to relieve distressing appetite sensations, and unusual temporal patterns (including dissociation between hunger and desire to eat) occur. Despite the positive impact of these feeding methods on intake, controversy about whether nutritional support can affect patient outcome has remained. Systematic reviews and meta-analyses indicate that improvements in function and clinical (mortality, complication rates) outcome can occur in a number of patient groups (including hospitalised patients, the elderly, patients who have had gastrointestinal surgery, patients at risk of pressure ulcers). In order to target those patients who will benefit from nutritional support, and overcome the ongoing problem of poor detection and recognition of DRM, simple routine screening to identify risk followed by practical evidence-based treatment is recommended.

Appetite: Malnutrition: Nutritional support

Disease-related malnutrition (DRM) is a common condition that has physiological and financial consequences. There is, therefore, a clear basis for elucidating effective ways of its identification and treatment. Fig. 1 represents a conservative estimate of the expenditure on DRM annually in the UK (Elia *et al.* 2005). The physiological and psychological consequences are also well documented (Stratton *et al.* 2003b).

Many of the adverse effects of DRM should be reversible by appropriate, effective nutritional interventions. However, there has been reluctance to accept that in clinical practice increasing nutritional intake with various methods of nutritional support can improve the outcome of patients. A demand for an evidence base for this practice has arisen. Indeed, $>£350 \times 10^6$ are spent annually on artificial nutrition to treat malnutrition in the home setting alone in the UK (Fig. 1). In England prescription cost

analysis in 2003 indicates that approximately $£129 \times 10^6$ was spent on oral nutritional supplements and enteral tube feeds in the community (Department of Health, 2003). Thus, issues about the clinical efficacy of such commonly-used treatments for malnutrition need addressing. In addition, some consideration is needed of the mechanisms of action of effective nutrition support strategies, and in particular their impact on appetite, satiety and total nutritional intake amidst the problems of disease, injury and the associated anorexia.

Anorexia of disease and injury

The anorexia of disease and injury represents a failure of the homeostatic mechanisms involved in the control of appetite, food intake and body weight. Low energy and

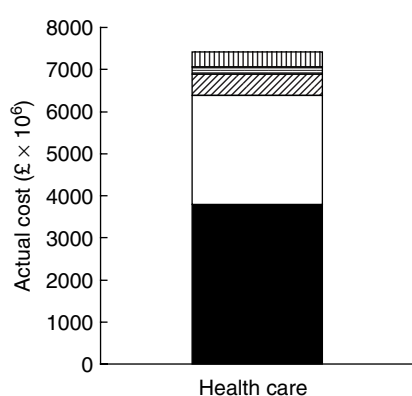


Fig. 1. Estimated annual expenditure on disease-related malnutrition. (■), Hospital inpatients; (□), long-term care; (▨), general practitioner visits (minimum values, >65 year olds only); (▩), hospital outpatients (minimum values, >65 year olds only); (▧), home artificial nutrition. (From Elia *et al.* 2005.)

nutrient intakes associated with disease and injury are well documented across patient groups, and they are typically the main causal pathway by which DRM develops (Stratton *et al.* 2003b). Although disease-associated increments in basal metabolism have previously been thought to be a major contributor to the development of DRM, these are largely offset by reductions in physical activity (Gibney *et al.* 1997; Jebb, 1997). There are many disease- and treatment-associated factors that negatively affect intake, including poor dentition, nausea and vomiting, mucositis, psychological factors and anorexia. The control of appetite in health is complex and involves metabolic, sensory, gastrointestinal, endocrine and other factors (Stubbs, 1999). In disease and following injury the situation is more complex, involving inflammatory mediators, cytokines and the influence of drug and other therapies (Plata-Salaman, 1996). Investigations of the anorexia of injury have included the role of two mediators of appetite: leptin, a satiety mediator; ghrelin, a stimulant of appetite. These studies have indicated that changes in circulating concentrations of both leptin (Stratton *et al.* 1997) and ghrelin (RJ Stratton, S Boyes, A Bucher and M Elia unpublished results) occur as part of the acute-phase response in the early post-operative period. Although these changes may be implicated in post-operative anorexia, hunger and food intake remain suppressed 5–7 d post-operatively despite circulating concentrations of these mediators returning to normal within 24 h (Stratton *et al.* 1997). Greater understanding is required to elucidate the many inter-related processes and mediators that influence appetite during disease and injury so that treatments, both nutritional and pharmacological, can be targeted appropriately.

Treatment of malnutrition: manipulation of appetite, satiety and intake

For the effective treatment of DRM strategies that can overcome the anorexia of disease and injury and that can increase nutritional intake are needed. In addition

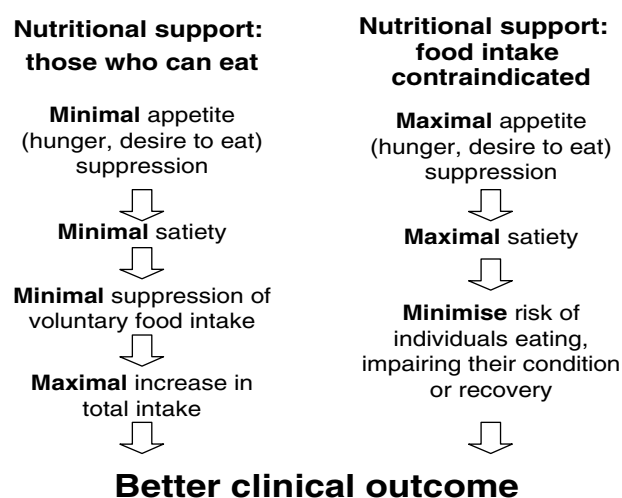


Fig. 2. Effective nutritional support strategies: impact on appetite.

to anorexia, there are also often other physical difficulties with oral intake to overcome in order to maximise nutrient intake. Effective nutritional support for those patients who can eat must have minimal effects on appetite and voluntary food intake and so maximally increase total intake and improve outcome (see Fig. 2). In contrast, for many patients with chronic disease (neurological conditions, obstructive malignancy, intestinal failure) oral intake may be contraindicated. Artificial nutritional support (enteral tube feeding or parenteral nutrition (PN)) may be the only means of feeding, often given for many months or years in the home environment (Elia & Stratton, 2005). In such cases it may be necessary to ensure that appetite is maximally suppressed by the form of feeding given, so that individuals are not tempted to eat, which would compromise their clinical condition or recovery (Fig. 2; Stratton & Elia, 1999b).

Effective nutritional support for patients who can eat

Improvements in nutritional intake are fundamental if nutritional support is to be effective in improving outcome in the patient with or at risk of malnutrition. Systematic reviews of the effects of oral nutritional supplements, primarily multi-nutrient liquid feeds, have assessed their impact on appetite, voluntary food intake and total intake (Stratton & Elia, 1999a; Stratton *et al.* 2003b). A systematic review of trials from the hospital setting (fifty-eight trials, *n* 3883; Stratton *et al.* 2003b) indicates the efficacy of oral nutritional supplements in increasing total energy and nutrient intakes in a variety of patient groups (e.g. patients with chronic obstructive pulmonary disease, the elderly, patients who have had gastrointestinal surgery, patients with fractured neck of femur, patients with liver disease). This effect appears to occur irrespective of whether patient groups are underweight (BMI < 20 kg/m²). Generally, liquid oral nutritional supplements have little suppressive effect on food intake, and in some cases (e.g. post-surgical patients) appear to stimulate appetite and food intake. Their effectiveness may be limited in some

patient groups during the peak acute-phase response (e.g. patients with chronic obstructive pulmonary disease) or severe malnutrition accompanying untreatable disease. Systematic reviews of trials from the community (108 trials, n 3747; Stratton & Elia, 1999a; Stratton *et al.* 2003b) in patients with chronic disease suggest that oral nutritional supplements can increase nutritional intakes and have little suppressive effect on voluntary intake, particularly in those patients who are underweight ($BMI < 20 \text{ kg/m}^2$). However, long-term use of supplementation may result in a wane in compliance, and total nutritional intakes can decrease.

Similarly, enteral-tube feeding can effectively increase total nutritional intake. A series of placebo-controlled metabolic investigations of the effects of different tube-feeding schedules on appetite, food intake and appetite mediators has been undertaken in healthy subjects (Stratton *et al.* 1998a,b, 2000, 2003c). These studies have shown that enteral-tube feeding (equivalent to $1 \times BMR$ (6.9 MJ) daily for 3 d) does not markedly suppress hunger, satiety or voluntary food intake when given as a slow continuous infusion diurnally, nocturnally or over 24 h as compared with placebo feeds given for 2 d before and after tube feeding. In these studies tube feeding has been found to substantially increase total energy intake to approximately 20 MJ/d (Stratton *et al.* 1998b, 2003c). These findings cannot be explained by changes in various hormonal and metabolic mediators of appetite, including insulin, leptin, cholecystikinin, glucagon, metabolites (glucose, NEFA etc.), RQ or resting energy expenditure (Stratton *et al.* 1998b, 2003c; Stratton, 1999). However, the suppression of food intake is increased by bolus (instead of continuous) tube feeding or by extending the duration of feeding (Stratton *et al.* 1998a, 2000).

These experimental studies confirm the findings of a systematic review (121 trials, n 4090; Stratton *et al.* 2003b) that suggest that enteral-tube feeding can substantially increase total nutritional intake in a variety of patient groups, whether used in addition to food or as the only source of nutrition in those patients in whom food intake is contraindicated.

Effective nutritional support when oral intake is contraindicated

It may be necessary to ensure that appetite is maximally suppressed by artificial feeding if an individual's condition prevents them from eating (Fig. 2; Stratton & Elia, 1999b). However, studies of appetite in patients receiving artificial nutrition, both enteral and intravenous feeding (Stratton, 1999), have highlighted the inability of these unusual feeding methods to suppress hunger and provide satiety. It has been found that most medically-stable weight-stable patients (BMI 22.6 (SD 4.56) kg/m^2 ; n 16) receiving PN at home as the only source of nutrition are hungry (75%), and some are even distressed by hunger (44%). The majority (88%) have a desire to eat and 69% miss specific food items, despite the provision of adequate energy and nutrients to meet requirements and to ensure weight maintenance (Stratton, 1999). Other disturbances in appetite have also been noted in patients fed parenterally. Using visual analogue scales to assess hunger (from score

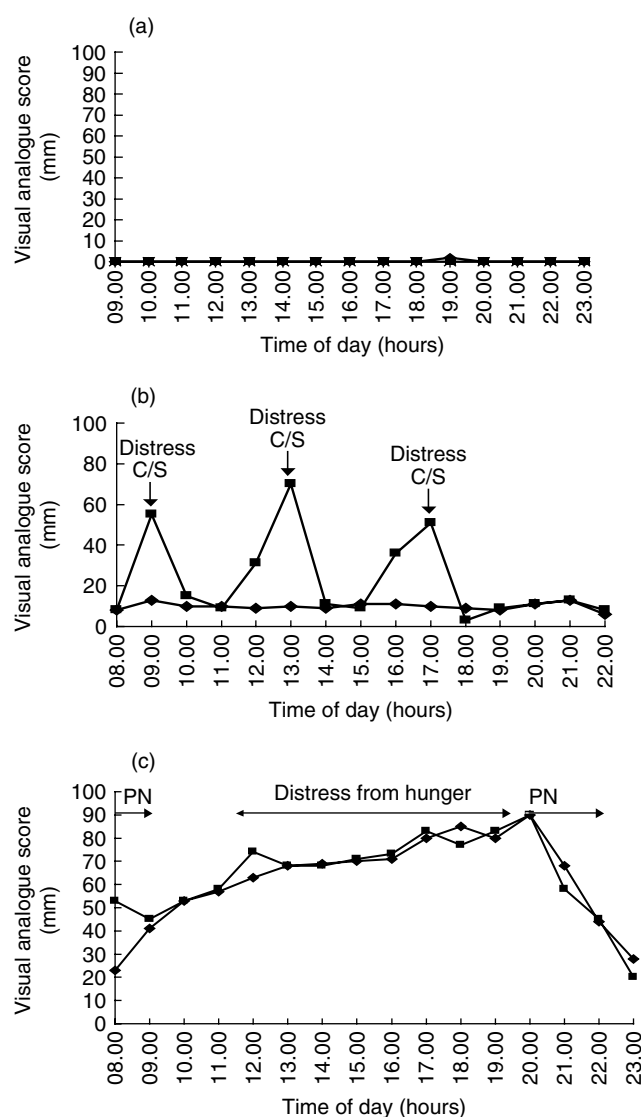


Fig. 3. Different diurnal patterns in hunger (◆) and desire to eat (■) in three patients (a–c) fed only parenteral (intravenous) nutrition. C/S, food ingested, chewed and spat out; PN, parenteral nutrition. (From Stratton, 1999.)

0 mm ('not at all hungry') to score 100 mm ('as hungry as I have ever felt'); Blundell, 1979), the range of mean daily hunger scores for patients at home (range 0–90 mm) and in hospital (range 0–100 mm) on PN has been found to be markedly greater than those of healthy subjects able to consume a normal diet (range 15–50 mm; Stratton, 1999). The temporal variation in appetite in patients receiving PN (Fig. 3; Stratton, 1999) has also been examined and found to differ widely and to be unlike that of a healthy subject eating *ad libitum* (Fig. 4). In one case (Fig. 3(a)) the patient (with small-bowel dysmotility syndrome and total gastrectomy, weight stable, with a BMI of 21 kg/m^2) was found to have no hunger or desire to eat at any time during her 11 months on PN. She had no wish to eat food following years of abdominal pain and vomiting, and only received PN overnight. In another patient (with total gastrectomy for gastric ulcer, weight stable, with a BMI

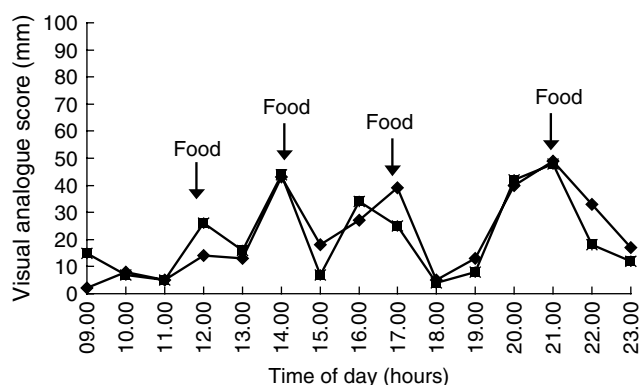


Fig. 4. Diurnal patterns in hunger (◆) and desire to eat (■) in a healthy subject eating *ad libitum*. (From Stratton, 1999.)

of 19 kg/m²) who was unable to eat and was fed overnight PN (3 years), there was an unusual dissociation between hunger and desire to eat (Fig. 3(b)). This patient had no hunger but regularly became distressed by a desire to eat. In order to relieve this distress she ingested food, chewed it and spat it out without swallowing (modified sham feeding), which effectively relieved the problem. Another patient (with Crohn's disease, colectomy and multiple fistulas, and a BMI of 20.3 kg/m²) described herself as being 'hungry all the time' after 1 month on PN, with distressing hunger pangs being the worst aspect of being fed intravenously. After the cessation of overnight PN she experienced increasing hunger and a desire to eat that became distressing by midday (Fig. 3(c)). This research highlights the need to develop ways of manipulating appetite in such individuals, perhaps by adapting artificial feeding schedules (although with PN this is difficult in practice), or by introducing safe chewing and spitting techniques (i.e. food is not swallowed or non-nutritive material is used; Stratton *et al.* 1999a,b) or similar methods to relieve distressing appetite symptoms in those patients fed long-term artificial nutrition in the absence of any dietary intake.

Although research has been able to show fundamentally that nutritional support methods are effective at increasing total nutrient intake, are such increases in nutritional intake related to improvements in patient outcome?

Treatment of malnutrition: evidence-based practice?

A series of systematic reviews and meta-analyses have attempted to establish the evidence base for using enteral nutrition (oral nutritional supplements, tube feeding) in the treatment of malnutrition.

Systematic reviews (including a total of 287 trials (11 720 patients across many specialities) suggest that, compared with routine care, patients receiving multi-nutrient oral supplements or tube feeding have: a significantly lower mortality (meta-analysis of thirty randomised trials in a variety of patients; odds ratio 0.59 (95% CI 0.48, 0.72), $P < 0.001$); a significantly lower rate of complications, including sepsis, wound infections, pneumonia etc. (meta-analysis of twenty-seven randomised

trials in a variety of patients; odds ratio 0.41 (95% CI 0.31, 0.53), $P < 0.001$); a range of functional benefits, depending on the patient group, including improved skeletal and respiratory muscle strength, increased walking distances, improved wound healing, greater physical and mental health, and immune benefits.

Other meta-analyses in specific patient groups, e.g. the elderly (Milne *et al.* 2002; Stratton *et al.* 2003b) and patients who have undergone gastrointestinal surgery (Lewis *et al.* 2001; Stratton & Elia, 2005), have also identified marked improvements in clinical outcome (mortality or complication rates) with the use of enteral nutrition. In patients at risk of pressure ulcers a meta-analysis has shown significant reductions in the incidence of pressure ulcers with enteral nutritional support (five randomised controlled trials, n 1325; odds ratio 0.74 (95% CI 0.62, 0.88); Stratton *et al.* 2005).

The issue of the cost efficacy of nutritional intervention in the treatment of malnutrition is an area of research for which there is remarkably little data. A simple cost analysis based on randomised controlled trials from a systematic review (Stratton *et al.* 2003b) suggests that there could be marked cost savings per patient (£314–£5027) from the use of oral nutritional supplements, principally as a result of the reductions in the length of stay in hospital (Stratton *et al.* 2004a). More detailed retrospective analyses suggest cost savings with the use of oral nutritional supplements in the hospital and community settings (Elia *et al.* 2005).

Despite overwhelming evidence that malnutrition is a debilitating and common condition that can often be effectively treated, it is a condition that has typically been undetected and untreated. Routine and effective methods for identifying malnutrition are often not in place in clinical practice.

Identification of malnutrition: a new screening tool

In view of the prevalence and deleterious consequences of DRM and the potential for its effective treatment (outlined earlier), it seems pragmatic to introduce routine means of identifying DRM, at least in healthcare settings. This approach is endorsed by many national and international organisations, i.e. British Dietetic Association (1999), Department of Health, (2001a,b), Royal College of Physicians (2002), Council of Europe (2002), British Association for Parenteral and Enteral Nutrition (Elia, 2003) and European Society for Parenteral and Enteral Nutrition (Kondrup *et al.* 2003), that have highlighted the frequent under-reporting of malnutrition and hence the importance of routine identification using a simple screening tool. In the absence of screening, even simple nutritional information such as body weight goes unrecorded in patient's notes (McWhirter & Pennington, 1994).

A new and effective way of identifying malnutrition

In the UK a new screening tool to identify malnutrition (both undernutrition and obesity), the 'Malnutrition Universal Screening Tool' (MUST), has been developed

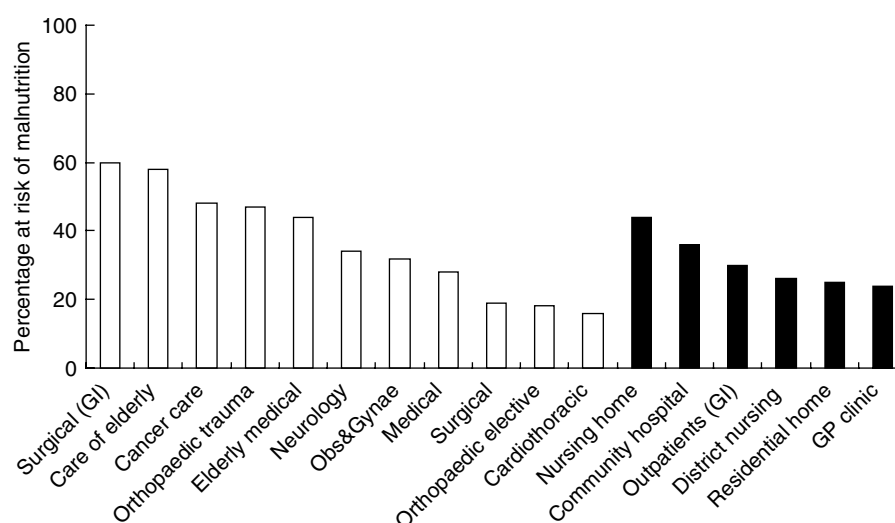


Fig. 5. Prevalence of disease-related malnutrition in hospital (■) and community (□) settings using the malnutrition universal screening tool. GI, gastrointestinal; Obs&Gynae, Obstetrics and Gynaecology; GP, general practitioner. (From Elia, 2003; Stratton *et al.* 2004b).

and validated according to published guidelines (Royal College of General Practitioners Clinical Guidelines Working Group, 1995; Department of Health NHS Executive, Public Health Division, 1998; British Dietetic Association, 1999; Scottish Intercollegiate Guideline Network, 1999; Shekelle *et al.* 1999). The tool has been developed for use by all healthcare professions by a multi-disciplinary committee (the Malnutrition Advisory Group of the British Association for Parenteral and Enteral Nutrition; Elia, 2003). MUST is for use in all adults, across specialties and healthcare settings, thus aiding continuity of care. Importantly, the tool is evidence-based and easy to use, even in those patients who cannot be weighed (Elia, 2003). MUST has concurrent validity (good to excellent chance-corrected agreement with many other published methods for the identification of malnutrition (e.g. subjective global assessment, mini nutritional assessment and screening; Stratton *et al.* 2004b); an important form of validity considering the lack of a 'gold standard' measure for malnutrition. The tool is reliable, with excellent inter-rater reproducibility (chance-corrected agreement 0.898–1.000, where a value of 1.000 indicates perfect agreement; Landis & Koch, 1977) and excellent reliability within the tool in the use of recalled and alternative measures *v.* measured values for weight, height and BMI (Elia, 2003; Stratton *et al.* 2003a). MUST also has some predictive validity, predicting increased mortality and healthcare utilisation in a variety of groups in both hospital and community settings, including increased general practitioner visits, hospital admissions, longer hospital stays and increased costs for those identified as at risk of malnutrition with MUST (Stratton *et al.* 2002, 2004b, 2004c; King *et al.* 2003; Wood *et al.* 2004). Screening with MUST has highlighted the prevalence of DRM across hospital specialties and in the community in the UK (see Fig. 5; Elia, 2003; Stratton *et al.* 2004b).

One outstanding issue that is still to be addressed fully is the impact of routine intervention with screening and the associated treatment regimen (a screening programme) on the outcome of all patients.

Summary

DRM is an expensive condition that is frequently left undetected and untreated. Thus, DRM requires prompt identification and treatment with effective practical cost-effective evidence-based methods. The evidence increasingly shows the efficacy of nutritional support in treating malnutrition. Nutritional support effectively increases total nutritional intake and has little effect on appetite, satiety and voluntary food intake. However, when used as the only source of nutrition, many patients find artificial nutrition (enteral or parenteral) is unable to relieve distressing appetite sensations. Nevertheless, improvements in clinical outcome and in function have been shown in a number of patient groups. In order to target those patients who will benefit from nutritional support or other dietary methods (e.g. counselling, dietary fortification), routine screening to identify malnutrition risk is necessary. A simple evidence-based screening tool used regularly is recommended together with a practical and evidence-based care plan for treatment in order to prevent and treat DRM, thus alleviating the clinical and cost implications of this common condition.

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