Review article

Changing concepts of nutrient requirements in disease: implications for artificial nutritional support

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Since the introduction of parenteral nutrition in clinical medicine almost 30 years ago, there has been renewed interest in the nutrient requirements of disease, especially the changes associated with bypassing the gut. Here I shall discuss some of the latest developments, including the emerging specialty of nutritional pharmacology, which has extended the boundaries of nutritional science into other areas of medicine.

Energy requirements in critical illness

During the past two decades, the prescribed energy intake to critically ill patients receiving parenteral nutrition has decreased by up to twofold.[1] The early overprescription that occurred shortly after the introduction of parenteral nutrition was partly an over-reaction to severe malnutrition and rapid wasting in patients with prolonged intestinal failure. Three other major factors have contributed to our changing concepts.

Inappropriate methods

The energy requirements of disease were overestimated partly because measurements of resting energy expenditure were frequently made close to the time of peak hypermetabolism (typically, the first few days after trauma, injury, or burns) and then extrapolated to much longer periods (sometimes weeks) during which artificial nutritional support was required. They were also overestimated because the measurements were often done while the patients were being infused (either continuously or intermittently) with large amounts of nutrients, which increase resting energy expenditure by up to about 30%.[2] The recommendations of some professional organisations to provide more energy to take into account the effects of pyrexia (13% of basal metabolic rate per °C rise in temperature) is also inappropriate; the effect of pyrexia would already have been included in the measurement of resting energy expenditure if those measurements had been taken while the patient was pyrexial. It is also important not to account doubly for the energy cost of breathing, which may represent 20–30% of resting energy expenditure in patients with acute respiratory distress, compared with only 2–3% in normal subjects.[1]

Changes in clinical practice

Superficial necrotic tissue in patients with burns can be a source of bacteria, toxins, or both, which enter the systemic circulation and cause an increase in energy expenditure. The elective and early surgical removal of such tissue, which has largely replaced the practice of leaving it intact to form a scab, has contributed to the decreased energy requirement of patients with burns. In addition, the nursing of patients in some burn and intensive-therapy units at higher ambient temperatures than previously has contributed to the reduction in energy expenditure, especially in patients who are kept without clothes so that vital signs can be monitored.

Earlier diagnosis from the use of new techniques and more aggressive management of infections (eg, drainage of abscesses) has reduced both the magnitude and duration of hypermetabolism in various clinical settings. Patients (mean body-mass index 21 kg/m^2) in an intensive-care unit with systemic infections were reported to have a resting energy expenditure that was only 15% above the predicted basal metabolic rate of normal subjects, even though the measurements were made while enteral feeds were infused at a rate of 1·5 times the basal metabolic rate. One suggesion is that, historically, excess energy was provided to improve the poor nitrogen balance associated with biologically inefficient protein sources such as certain protein hydrolysates (now replaced by mixtures of L-aminoacids). However, several studies have shown that the commercial dialysed hydrolysates of casein or fibrin, which were in use in the late 1960s and 1970s, were generally well metabolised (5–10% urinary losses of aminoacids and peptides) and as effective as synthetic L-aminoacid mixtures in improving nitrogen balance.

Adverse effect of overfeeding

Excess carbohydrate and excess lipid have both been linked to hepatic steatosis and abnormal liver function. Lipid may also be deposited in the lung and impair diffusion of gases, and produce infusional hyperlipidaemia. Overfeeding with excess carbohydrate can lead to excess CO_2 production, which can precipitate respiratory failure in patients with poor respiratory reserve. An appreciation of these effects has restricted overprescription of energy.[1] Animal models of sepsis have shown that overfeeding can produce huge increases in mortality.[1,2] The relation between mortality and nutrient intake occurs both above and below the maintenance range of energy intake, possibly because hyperglycaemia, which follows increased nutrient intake, favours bacterial growth. Although the extent to which the observations in animals apply to man is uncertain, it is clear that in critically ill patients, hyperglycaemia becomes more common and blood glucose control becomes more difficult during overfeeding with high carbohydrate loads.

The overall trend to reduce the prescribed energy intake in patients with acute illnesses has been reinforced by direct measurement of energy expenditure by 24 h continuous indirect calorimetry—eg, in ventilated patients in intensive-care units or by tracer techniques. These techniques measure total energy expenditure, including its major component, basal metabolic rate, as well as thermogenesis (eg, induced by diet or drugs) and physical activity. Such studies[3–8] suggest that daily energy expenditure in adults is generally 1700–2500 kcal (30–35

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kcal/kg) (1 kcal is 4·184 J), irrespective of whether the patients are preoperative or postoperative,[3] receiving parenteral nutrition in hospital or at home,[6] or are in intensive-care units.[4,5-7] Even children with severe burns may expend either similar amounts or less energy than healthy children.[8]

Overall, it seems that the energy requirements of patients with disease are usually similar to or less than those of healthy subjects.[1] The basal hypermetabolism of disease[9] is often offset or more than offset by decreased physical activity. Furthermore, changing attitudes in some intensive-care units have meant that hypocaloric feeding is practised in the early stages of injury (eg, 1500 kcal/day for up to a week) to reduce to a minimum the risk of metabolic instability and its consequences. This form of nutritional support, while not preventing loss of lean or fat tissue, will limit it. An emphasis on repletion is given in the recovery phase.

Bypassing the gut

The unphysiological practice of bypassing the gut and delivering nutrients directly into the blood may not only have important adverse effects on intestinal structure (atrophy) and function (absorptive function, immunological function, and barrier function against translocation of bacteria and toxins), but also have important consequences for the requirement of trace elements.[10] The reason is that absorption of trace elements varies more than that of other nutrients, being as low as 1% for some (eg, 0·5–2·0% for chromium)[11] and as high as 75% or more for others (eg, fluoride, iodide, and selenium).[11,12] That the recommended intravenous intake of trace elements[9-13] varies according to the degree to which they are absorbed (figure 1) is therefore not surprising. However, when the gut is bypassed and excessive amounts of trace elements enter the circulation, there may be no effective way to increase their excretion. For example, the major tissue that regulates iron status is the gut, so excessive parenteral loads may lead to iron overload. A study of long-term home parenteral nutrition in children aged 1–18 years receiving as much as 0·1 mg iron per kg per day showed excessive deposition in the body, including the liver.[14]

The doses of manganese initially recommended for parenteral nutrition by various workers were high (1·0–2·5 mg/day) because of the erroneous belief that the absorption in healthy adults was as high as 50%.[13] In fact, under normal circumstances only 3–4% of the normal dietary intake of 2–4 mg is probably absorbed[11] (equivalent to only about 0·1 mg/day). In some countries, intravenous formulations contained excessive manganese (eg, 2·2 mg/day), which led to circulating manganese concentrations 5–10 times greater than normal.[15] Intravenous preparations containing as much as 5 mg/day are still marketed in some countries.[16] Although excess manganese can be excreted in bile (the major route of manganese excretion), many patients receiving parenteral nutrition have low bile secretion because of low oral fat intake. Therefore they may be at particular risk of manganese toxicity.

Toxic effects of manganese in man were first reported more than a century ago in manganese miners, who had excessive parenteral intake of manganese via the lungs. The syndrome of "manganese madness" was associated with psychological disturbances and parkinsonian-type symptoms. Later studies in primates showed that when

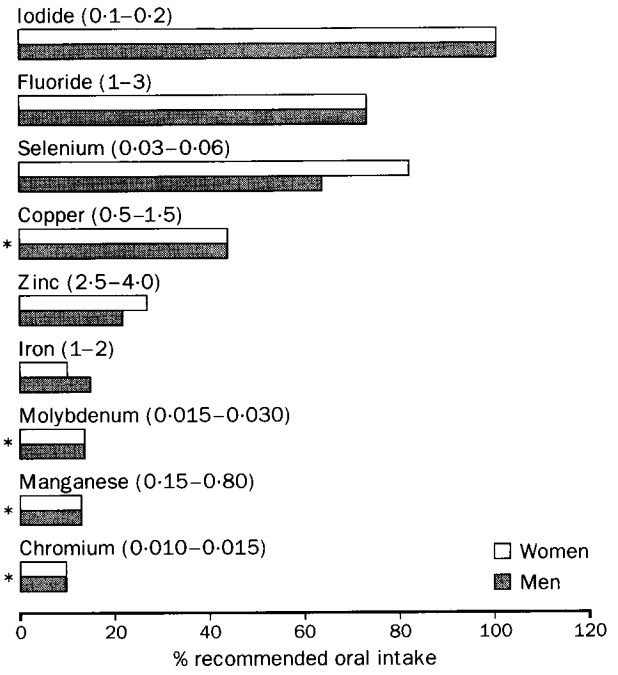

Figure 1: **Recommended daily intake of trace elements for intravenous use**
Recommendations for Cu, Zn, Cr, Mn to men and women based on the American Medical Association[13] and those for other trace elements on various workers. Recommendations expressed in mg/day (values in parentheses) and as percentage of oral recommended dietary allowance (RDA) for men (79 kg) and women (63 kg) aged 25–50 years.[11] Midpoint of recommended range for intravenous use was used in the comparisons with the single value for oral RDA for men and single value for women. *Trace elements for which there was too little information to establish a RDA for oral intake: therefore, midpoint of estimated safe and adequate oral intake used for comparison.

manganese was given parenterally, either through the lung or intravenously, it was specifically deposited in the basal ganglia of the brain where it caused depletion of dopamine.[11]

In some patients on long-term parenteral nutrition receiving only 0·33 mg/day of manganese and an uncertain amount in the fluids containing other nutrients, magnetic resonance imaging of the brain showed striking appearances of the basal ganglia (especially the globus pallidus and subthalamic nuclei[17,18]) that were similar to those observed in monkeys given excess manganese[10] and some patients with liver disease[11] (possibly because of impaired manganese excretion in bile). The discontinuation of manganese in one patient while all other nutrients in the parenteral nutrition solution remained unchanged was followed by a substantial improvement in the appearance of the basal ganglia within a year.[14] Unfortunately, although neurological symptoms were present in some of the patients (four of nine in one report) few clinical details are recorded,[18] which makes it difficult to assess the extent to which symptoms were due to the underlying disease or to the toxic effects of manganese.

Nevertheless, the observations emphasise the importance of good physiological information about nutrient absorption and disposition before recommendations for parenteral nutrition are made, and before legislative approval of commercial products is given. Toxic effects of aluminium (encephalopathy and bone disease), observed in patients on renal dialysis, is another reminder of the possible danger of bypassing the

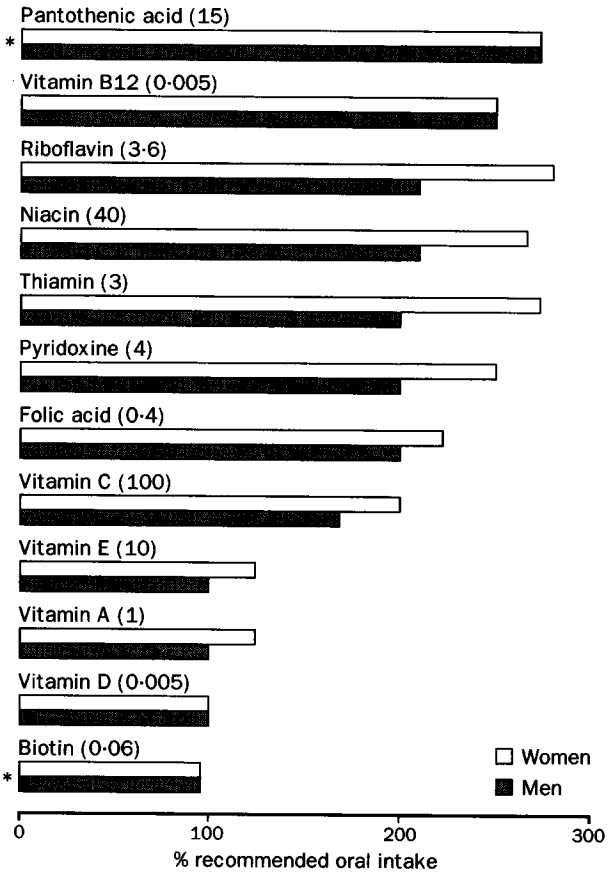

Figure 2: **Recommended daily intake of vitamins for intravenous nutrition**
Recommended intake of vitamins[21] for men and women expressed in mg/day (values in parentheses) and as percentage of oral recommended dietary allowance (RDA) for men (79 kg) and women (63 kg) aged 25–50 years.[11] *Vitamins for which there was too little information to establish RDA for oral intake; therefore, midpoint of range of estimated safe and adequate oral intakes used for comparison. Vitamin D as cholecalciferol (10 kg = 400 IU), vitamin E as α-tocopherol equivalents (1mg = 1 α-tocopherol equivalent) and vitamin A as retinol equivalent (1 mg = 6 mg β-carotene).

gut. Toxic effects of aluminium from the unintentional administration of aluminium in parenteral nutrition solutions or parenteral additives[19] have also been the cause of metabolic bone disease in some patients on long-term parenteral nutrition. Finally, the intravenous administration of chromium in doses that have not been adequately considered led to high circulating concentrations in both adults[15] and children[20] (eg, >20 times higher than controls).

Vitamin requirements

There is no formal general advice about vitamins for patients on enteral tube feeding, although the national recommendations for healthy individuals have frequently been adopted. By contrast, a committee of the American Medical Association has provided specific vitamin recommendations for patients on intravenous nutrition.[1,21] The recommended intake for most vitamins (figure 2), especially water-soluble vitamins, was increased (often 2–3 times above those recommended for oral intake in normal subjects) to cater for inadequate previous intake and the need for new tissue synthesis, and for the presumed increased requirements of disease. However, there was little supportive information about the effects of different diseases on vitamin requirements. The committee acknowledged that it was not possible to provide accurate scientific support for many of their recommendations.

Since then, there have been various important developments. First, the amount of vitamins infused into the patient may be less than half of that added to parenteral nutrition mixtures.[22,23] For example, many studies have shown that the loss of vitamin A during a 24 h infusion is 40–98%, depending on ambient temperature and light conditions. Sunlight causes rapid degradation of vitamin A (the most photosensitive vitamin) but fluorescent light does not; therefore a bag placed near a window during the day will deliver much less vitamin into the patient (eg, <10% of the original amount) than a bag placed away from a window. In addition, the plastic of polyvinylchloride bags adsorbs vitamin A and continues to do so over time without saturation of binding sites. Such adsorption appears to be greater with retinyl palmitate (available in the USA but not the UK) than with retinyl acetate (available in the UK). There is much interest in reports of patients on long-term parenteral nutrition who develop frank night blindness despite the inclusion of the recommended amounts of vitamin A (retinyl palmitate) in their parenteral nutrition mixtures.[24]

The bioavailability of various other vitamins may also be reduced. Thiamine availability is reduced by 0–90%[22] depending on the solution used, temperature, pH, and the presence of sulphite, which is an antioxidant of some aminoacid solutions. The sulphite present in one commercial preparation (Synthamin, Travenol) was removed in 1988 as a result of a new process that involved filling bottles under nitrogen. However, another aminoacid preparation (FreAmine, Fresenius) contains sulphite and is marketed in the USA and many European countries. As much as 30–35% of vitamin E may be lost.[22] More than half the riboflavin and pyridoxine may deteriorate in sunlight, but the loss is negligible under fluorescent light. 50% or more of vitamin C may degrade over 24 h in parenteral nutrition mixtures especially in the presence of oxygen and copper, which catalyses the reaction.[23]

The shelf life of "all-in-one" parenteral nutrition mixtures seems to be limited mainly because of the stability and bioavailability of vitamins. By ensuring that the bags are kept away from sunlight, that retinyl acetate is used instead of retinyl palmitate, and by using multilayered bags that are 100 times less permeable to oxygen (and removing air from within bags), it has been possible to assign shelf lives to mixed parenteral nutrition bags for a month or more. This extended shelf-life is especially valuable to patients on home parenteral nutrition who receive parenteral nutrition bags intermittently.

One focus of research has involved the antioxidant properties of some vitamins (C, E, and β-carotene, a precursor of vitamin A) to prevent or treat the damage produced by free radicals, which are generated in a wide range of acute and chronic diseases[25,26] (eg, acute respiratory distress syndrome, acute pancreatitis, reperfusion injury, and burn resuscitation). Although there is much scope for intervention with antioxidants, and many studies provide encouraging results, trials of antioxidants (vitamin or non-vitamin) in various experimental and disease states have produced variable

results. Animal studies with superoxide dismutase in myocardial infarction and reperfusion injury are disappointing, and the use of antioxidants in the respiratory distress syndrome in man is inconclusive. Although oxidant damage undoubtedly occurs in many acute and chronic conditions, there is much less certainty as to whether oxidative damage has a dominant role in disease progression, or simply represents a system for disposing of tissue that has already been damaged by other mechanisms (eg, toxins). Localised high-intensity oxidative damage may be beneficial to a patient (eg, to destroy bacteria), but unchecked oxidative damage in other parts of the body may be detrimental. Unfortunately, methods for measuring reactive oxygen species in vivo are still at an early stage. The multiple factors involved in initiating tissue damage even in the same disease may differ between individuals, and therefore it may be more fruitful to contemplate multiple therapeutic strategies rather than a single one.

Finally, although β-carotene (which is present in the diet but not in parenteral or enteral regimens) and vitamin C have well-established oxidant properties, they also have pro-oxidant properties.[27] For example, at low oxygen tensions vitamin C converts Fe^{3+} to Fe^{4+}, which catalyses the formation of the reactive hydroxyl radical (Fenton reaction). Some vitamin E analogues also show some pro-oxidant properties. Therefore, although some experimental studies support the use of antioxidants, to provide firm recommendations about the routine use of high-dose antioxidant vitamins in patients receiving artificial nutritional support is not possible.

Furthermore, owing to the many conditions now treated with artificial nutrition (some of which involve oxidant stress), it is difficult to provide universal recommendations. Reports suggesting that administration of β-carotene increases mortality primarily because of more deaths from myocardial ischaemia and lung cancer[28] and that megadose supplements of vitamin A may increase the prevalence of childhood diarrhoea and acute respiratory infections[29] remind us of the possible double-edged sword of antioxidant or vitamin administration. Important developments in this area may alter our views, especially as more information becomes available for specific groups of patients. However, at the very least, patients with disease should not be vitamin deficient.

Nutritional pharmacology (panel)

Parenteral nutrition is unphysiological[8] because it bypasses the gut and lacks nutrients such as glutamine, β-carotene, and inositol, which are present in the normal diet. The use of long-term enteral feeds without fibre is also unphysiological. Here, I shall briefly discuss three other types of unphysiological process. My aim is to indicate the breadth of this rapidly growing specialty, rather than provide a detailed critique of individual studies.

Type I: administration of precursors

Certain nutrients are deficient or missing from parenteral nutrition solutions[21] because of their poor solubility (eg, cystine, tyrosine) or instability. For instance, heat sterilisation destroys glutamine. However, in certain situations various aminoacids may become essential. For example, in some patients with liver disease, the hepatic conversion of phenylalanine to tyrosine, and methionine to cystine, is inadequate, and unless sufficient cystine/tyrosine is administered,[30] repletion of lean tissue (net protein synthesis) will be substantially limited and body function will be impaired. Glutamine, which is also absent from commercial parenteral nutrition solutions, may also have beneficial effects on nitrogen balance and tissue function (see below).[31,32] All these aminoacids can be delivered in large quantities as synthetic dipeptides (eg, glycyltyrosine, alanylcystine, alanylglutamine, glycylglutamine), which are water soluble and stable during storage.[31] The dipeptides are rapidly hydrolysed within the body, either intracellularly or at the cell membrane, where their constituent aminoacids are released.

Another example of type I nutritional pharmacology is the intravenous administration of phosphate as organic phosphate (glucose phosphate, fructose phosphate, fructose bisphosphate, glycerol phosphate). One of the potential compounding problems for intravenous nutrition is calcium phosphate precipitation, which occurs above certain concentrations of calcium and phosphate. These critical concentrations depend on pH, temperature, and other constituents of parenteral nutrition mixtures, but the precipitate may not become noticeable until 12 h or more after preparation of the mixture, and it may not be apparent at all in opalescent mixtures that include lipid. A 1994 safety alert[33] issued by the US Food and Drug Administration warned that respiratory distress caused by calcium phosphate precipitation could lead to death. Multiple pulmonary microvascular emboli containing calcium phosphate have been found at necropsy. This safety alert has produced rapid reaction about quality assurance in parenteral nutrition.

The most important clinical problems occur in infants and young children who have high calcium and phosphate requirements, especially those whose clinical condition requires fluid restriction (eg, patients in intensive-care units with renal failure, head injury, or fluid overload from any cause). A solution to this problem is to provide phosphate in organic form such as glycerol phosphate,[34] which is hydrolysed within the body to yield free phosphate. Commercial preparations of various organic

Panel: **Some examples of nutritional pharmacology**

Type I (prenutrients)	Dipeptides Acetylated aminoacids* Organic phosphates
Type II (pharmacological doses)	**Carbohydrates** Fructose Xylitol Sorbitol Glycerol **Fat** Medium-chain triglycerides Short-chain triglycerides n-3 fatty acids **Vitamins** **Bacteria†** Lactobacilli Bifidobacteria Oligofructose
Type III (bioactive substances in nutritional support)	**Growth factors** Growth hormone Insulin-like growth factor Epidermal growth factor* **Other** Erythropoietin Lactoferrin Lysozyme

*Poorly used in man. †Or their substrates.

phosphates have been available for several years in some European countries, such as Germany and France, but not in others because of delays in legislative procedures. In the UK, approval is expected shortly.

Type II: administration of nutrients in pharmacological doses

This type of nutritional pharmacology has involved every class of macronutrients (proteins/aminoacids, carbohydrates, fats). For example, although glucose remains the carbohydrate of choice for intravenous nutrition, large quantities of specific sugars (fructose) or sugar alcohols (eg, sorbitol) have been used with the purpose of reducing the hyperglycaemia and insulin requirements associated with stress. Large doses of medium-chain triglycerides, which account for 50% of all the fat, have also been used[35] to decrease infusional hyperlipidaemia because they are rapidly cleared, thereby reducing hepatic steatosis, and reducing or avoiding suppression of the reticuloendothelial system. Triglycerides rich in n-3 fatty acids (found in fish oils) administered enterally or parenterally alter membrane fluidity and insulin sensitivity and modify prostaglandin, leukotriene, and cytotoxin production.[35]

Early observations suggest that administration of triglycerides rich in n-3 fatty acids may have a potential role in the treatment of various diseases—atopic dermatitis, psoriasis, rheumatoid arthritis, Crohn's disease, ulcerative colitis, diabetes mellitus, and other acute inflammatory or infective diseases. Administration of a new class of triglycerides (structured lipids) in which specific fatty acids are esterified on specific locations on the glycerol backbone alters the metabolic response to injury and reduces infection rates and mortality in animal models of injury. However, clinical experience remains limited.

Various aminoacids have been administered in pharmacological doses. For example, up to 40 g/day (0·57 g/kg) of glutamine has been given to patients on intravenous nutrition compared with an estimated normal dietary intake of only 3–5 g/day.[31] The large intravenous doses of glutamine improve nitrogen balance and significantly reduce both infection rate and hospital stay[32] (see ref 31 for review and rationale). Large quantities of arginine combined with other immunomodulatory substances (n-3 fatty acids and nucleic acids) have been incorporated into commercial enteral feeds (Impact, Sandoz); this aims to provide "immunonutrition". In one study,[36] this type of diet significantly reduced infection and wound complications after major surgery (11 *vs* 37%) and reduced hospital stay (16 *vs* 20 days). Encouraging results have also been reported in intensive-care patients. Unfortunately, the control patients in these studies received less nitrogen and more medium-chain triglycerides. The rationale for the use of a mixture containing a high ratio of branched-chain aminoacids (BCAA) to aromatic aminoacids (up to 3 times normal intake of BCAA) in patients with liver disease is that BCAAs compete with aromatic aminoacids for entry to the brain; in this way aromatic aminoacids cannot be used to form unusually large quantities of the neurotransmitters that may promote the development of hepatic encephalopathy. Results of this type of treatment have been variable, but improved mental recovery has often been reported.[37] Plauth and colleagues' carefully controlled, double-blind, crossover trial[38] suggests that BCAAs improve psychomotor function and capacity to drive a car.

In children receiving home intravenous nutrition, large doses of ornithine a-ketoglutarate have produced improvement in growth.[39] The administration of megadoses of antioxidant vitamins is also a form of type II pharmacology. Finally, the rectal administration of short-chain fatty acids to treat inflammatory disorders of the colon can also be regarded as type II nutritional pharmacology because short-chain fatty acids, such as butyrate, are preferentially used by the colon. Clinical benefits of such treatment have been reported in patients with colitis, pouchitis, and diversion colitis.[40]

A change in intestinal microflora to inhibit or reduce the growth of potentially pathogenic gut organisms[41] is also a possibility—eg, the administration of live lactobacilli or bifidobacteria, or fermentable bifidogenic substrates such as oligofructose or inulin, which are present in some enteral feeds. However, the clinical benefits of this form of nutritional pharmacology remain to be proven.

Type III: bioactive substances in nutritional support

Growth hormone administration[10] has been reported to improve nitrogen balance and muscle function after elective abdominal surgery, and to improve respiratory muscle function in patients with chronic obstructive airways disease. Some patients with intestinal failure who require long-term parenteral nutrition have been weaned on to an enteral diet as a result of improvement in intestinal function after administration of a combination of growth hormone, glutamine, and fibre.[42] In a double-blind study of seriously burned children, Herndon and colleagues[43] reported improved healing of burns with growth hormone; there was a significant reduction in hospital stay (from 46 to 32 days). The reduced cost of hospital stay can probably counteract the cost of the growth hormone. Similar data are being collected for insulin-like growth factors.

One of the triumphs of recombinant technology in clinical medicine is the use of recombinant human erythropoeitin (normally produced by the kidney) in treating the anaemia of end-stage renal failure, which develops as a result of the inability of the body to use iron adequately for haemoglobin synthesis[10,44] Erythropoietin administration not only results in a reduction in the requirement for blood transfusion (an estimated 0·5 million units per year in the USA for this condition) but also reduces hospital stay, risk of iron overload, and bloodborne infections, including HIV.[44] It also increases subjective feelings of energy and wellbeing (Nottingham Health Profile Score and Karnofsky Score). The Canadian Perioperative Erythropoeitin Study investigators also reported that the administration of erythropoeitin for 1 week before and 4 days after surgery in patients undergoing hip replacement reduced the frequency of perioperative anaemia (haemoglobin <8·0 g/dL) (46 *vs* 23%) and the proportion of patients requiring transfusion (26 *vs* 3%).[45]

Implications

The new specialty of nutritional pharmacology has raised legislative and ethical controversies. One worry was the use of cows or sheep to produce recombinant human bioactive substances (eg, human lactoferrin) in their milk for incorporation into enteral feeds or milk formulas. In

some countries, such as the Netherlands, debates about such nutritional products have already occurred at government level, whereas in most other countries, there has not been any governmental debate.

It has also been argued that some forms of nutritional pharmacology have little place in nutritional support because of their unphysiological nature. However, much of medicine is unphysiological, and the ultimate goals of physicians, health planners, and administrators are efficacious and cost-effective treatments. Some of the benefits of nutritional pharmacology are clear, but others remain controversial and very expensive. Until there is enough evidence to show clinical and economic efficacy, many forms of nutritional pharmacology are unlikely to gain widespread clinical acceptance. In the mean time, new products, which have been called "nutriceuticals" to denote both their nutritional and their pharmaceutical nature, offer exciting new ways to investigate nutritional physiology and to provide new forms of therapy in a wide range of medical specialties.

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