

Proposed Recommended Nutrient Densities for Moderately Malnourished Children.

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Abstract

Recommended Nutrient Intakes (RNI) are set for healthy individuals living in clean environments. There are no generally accepted RNI for those with moderate malnutrition, wasting and stunting, who live in poor environments. Two sets of recommendations are made for the dietary intake of 30 essential nutrients in children with moderate malnutrition who require accelerated growth to regain normality. First, for those moderately malnourished children who will receive specially formulated foods and diets; second, for those who are to take mixtures of locally available foods over a longer term to treat or prevent moderate stunting and wasting. Due to the change in definition of severe malnutrition much of the older literature is pertinent to the moderately wasted and stunted child. A factorial approach has been used in deriving the recommendations for both functional, protective nutrients (type I) and growth nutrients (type II).

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Summary

The objective is to derive nutrient requirements for moderately malnourished children that will allow them to have catch-up growth in weight and height, prevent their death from nutritional disease, strengthen their resistance to infection, allow for convalescence from prior illness and promote normal mental, physical and metabolic development.

The malnourished population will have been exposed to nutritional stress and seasonal shortages and will have been living in unhygienic conditions; a proportion will have been severely malnourished. Typically, from 5% to 15% of children aged 6-59 months are moderately wasted and 20% to 50% are stunted in height.

There has been little published on the requirements for the moderately wasted or stunted child *per se*. However, with the change in definition of severe malnutrition from the Wellcome classification based upon weight-for-age to one based upon weight-for-height, re-analysis of the data shows that many of the studies of children <60% weight-for-age included children who were moderately wasted by modern criteria, albeit stunted. The physiological and other data from the older literature therefore is likely to apply to those with moderate as well as severe wasting.

In order to derive the requirements for each nutrient, for moderately malnourished children, the lower and upper boundaries were assumed to lie between the requirement for a normal healthy child living in a clean environment and for treatment of a severely malnourished child living in a contaminated environment. The therapeutic diets used for treatment of the severely malnourished in the developing world have been remarkably successful and are capable of sustaining rates of weight gain of over 10g/kg/d and returning the children to physiological normality.

The requirements for normal Western individuals (RNI) were used as the minimum requirement. They were converted into nutrient: energy densities, using the energy requirement for female children. The most nutrient dense of the various age categories of children was taken as a baseline.

For the growth nutrients (type II nutrients) a factorial method was used to determine the increment that should be added to allow for catch-up at 5g/kg/d. For those with mild non-dehydrating diarrhoea to have their daily losses replaced and to have tissue deficits replaced over a period of about 30 days.

For the type I nutrients (specific function nutrients) modest increments were added to cover the additional oxidative and other stresses that the subjects would be exposed to in unhygienic, polluted conditions; these include smoke pollution in the home, mild enteropathy, mild small intestinal bacterial overgrowth, some ingestion of fungal and other toxins arising from contaminated food, water and recurrent infections such as malaria.

Two sets of requirements are suggested. First, the requirements for rehabilitation when using a variety of appropriately processed locally available foods, this represent the minimum requirement as it is unlikely that the optimal requirement for all nutrients can be consistently reached with unfortified local foods. Second, the optimal requirements are proposed when special complementary, supplementary or rehabilitation foods are being formulated to treat the moderately malnourished children. It is assumed that these foods can be fortified with specific nutrients to achieve an optimal nutrient density for the moderately malnourished child.

Each nutrient is considered in turn where its peculiarities are considered. The nutrient: nutrient ratios

were examined to ensure that the diet would not be unbalanced or that there would be detrimental interactions between the nutrients.

The results are shown in the table. The RNI values for healthy Western populations and the nutrient densities used for rehabilitation of the severely malnourished (F100 formulation) are also shown as these represent the lower and upper boundaries within which it is expected that the values for most nutrients needed by the moderately malnourished will lie.

It should be emphasised that there are many uncertainties involved in deriving these first estimates of the nutrient requirements for the moderately malnourished.

As new data become available it is anticipated that the proposed nutrient requirements will be incrementally refined and expert opinion will converge.

The particular forms of the nutrients (salts and purity), which can affect the taste, availability, dietary interaction, acid-base balance, efficacy and cost, that should be considered in formulating any supplementary foods or fortification are considered. The effects of anti-nutrients that affect absorption and availability or directly damage the intestine as well as a more detailed discussion of the essential fatty acids are considered in the companion paper by Michaelsen *et al.*[1].

A summary of the derived nutrient requirements is given in Table 1.

Introduction

National and international recommendations for nutrient intakes (Recommended Nutrient Intakes – RNIs) are derived from experimental data from normal healthy individuals, living in a clean, secure environment, and developing and growing normally.

In the developing world most individuals do not live in such a clean, secure environment. One could argue that the RNIs do not apply to much of the world's population. In general, the environment is unhygienic; the children have recurrent infections, drink contaminated water, are exposed to smoke pollution from cooking fires, eat food containing fungal and bacterial toxins and subsist on a limited range of crops grown in the immediate vicinity of their homes. Their growth and development is retarded. In such circumstances it is likely that the requirement for nutrients is higher than for those living in safe secure environments. The reality is that their diets are much poorer than those living without such stresses and where food comes from a wide variety of sources. When they get an infection and lose their appetites there is an acute loss of weight; this is so for all children in all societies. However, in impoverished households there is no subsequent catch-up growth during convalescence. The diets are of insufficient quality to replace the nutrients lost during the illness and allow the children to return to normal. From 5% to 15% of the world's children are wasted (low weight-for-height) with the peak prevalence being between 6 and 24 months of age; 20% to 40% are stunted in height by the time that they reach two years of age (low height-for-age).

There are no internationally agreed RNIs for such children; although there have been published recommendations, there has been no justification for the levels chosen [2-4]. FAO/WHO and IOM have addressed this need in their reports' narrative but have not proposed any changes to the RNIs for such circumstances. However, agreed recommendations are needed in order to plan programs, treat moderate malnutrition, prevent deterioration, and to assess diets of those living in stressful environments or at risk of malnutrition. The recommendations for healthy Western populations are based upon relatively extensive experimental data; these RNIs give a necessary bench mark from which to start [5-13]. However, for many essential nutrients there are major gaps in the data upon which the RNIs are based. This is particularly when deficiency in the West is not encountered in the healthy (e.g. potassium, magnesium, phosphorus) or emphasis is on excess intake (e.g. sodium); these nutrients become critically important when there are abnormal losses from the body, for example with diarrhoea or enteropathy, and in the malnourished. Deficiency of these same nutrients is usually reported by those caring for patients with gastroenterological disease or requiring parenteral nutrition. For many other nutrients their bioavailability from the complex matrix of foodstuffs, commonly taken where malnutrition is common, is unknown [14]. Furthermore, for children in the age group 6 to 59 months there are few direct experimental measurements and RNIs have been assessed by extrapolation from either older age groups or from the composition of breast milk [15]. The resulting judgements for normal children differ from committee to committee, sometimes quite dramatically.

Those who need to replenish the tissues that have been lost whilst developing moderate malnutrition or require to have catch-up during convalescence from illness, will have higher nutrient requirements for nutrients laid down in growing tissue than normal children. Children living in a hostile environment will also require a higher intake of "protective" nutrients than those who are not under stress. Normal children gain weight and height at a slow pace relative to other mammals; thus, the increments in nutrient intake required for growth, over that required for maintenance for the normal child are quite modest. However, the malnourished child will need to grow at an accelerated rate to catch-up; in these circumstances the requirement for growth becomes a higher proportion of the total requirement and the

balance of nutrients changes; a richer, more nutrient dense, diet is needed to synthesise functional tissue more rapidly than normal.

The effects of giving modern therapeutic diets to severely wasted children are dramatic. The children regain their appetites and ingest sufficient of the diet to gain weight at up to 20 times the normal rate of weight gain; indeed the Sphere standards require that an average rate of weight gain of over 8g/kg/d is achieved [16]. However, with the older diets, when emphasis was placed upon energy density, the children did not regain physiological or immunological normality; thus, delayed hypersensitivity [17], thymic size [18], Na pump function [19], glucose tolerance [20], renal concentrating ability [21], muscle size [22], etc. remained abnormal after treatment. Even though they gained weight rapidly and reached normal weight-for-height, they had a deficit of functional tissue and an excess of fat tissue: they were relatively obese [23-27] because the balance of nutrients was not correct to allow appropriate amounts of lean tissue to be synthesised. When the limiting “growth nutrient” was added to the diet, the children would regain more functional tissue and their physiology and immunity would improve [28-30] presumably until the next essential nutrient limited further growth. With the modern diets based upon the F100 formula, they regain physiological and biochemical normality [31, 32].

This raises a critical point. Weight gain, of itself, does not indicate a return to physiological, biochemical, immunological or anatomical normality. Indeed, eating “empty calories” that do not contain all the nutrients in the correct balance necessary to regain functional tissue results in the deposition of the excess energy as adipose tissue. In this way an inadequate diet may well convert a thin undernourished individual into an obese *undernourished* individual¹; this was often the experience with the older diets used to treat malnutrition and with attempts to treat stunted children with energy supplements alone [33]. Indeed, many overweight children are stunted in height indicating that they have had a chronic deficiency of nutrients required for growth [34, 35]. We should not rely only on an observed rate of weight gain or final body weight-for-height when we judge the adequacy of diets or supplementary foods. It is likely that accelerated growth in height is a better indicator of nutritional adequacy for a child than weight gain.

Nevertheless, the composition of the modern diets for treating severe malnutrition (F100 [36-39] and the derivative RUTFs [40]), give a probable upper limit to the nutrient intakes that are likely to be required by the moderately malnourished or convalescent child living in a hostile environment.

Thus, for any new recommendations for the moderately malnourished the requirements for most nutrients are likely to lie somewhere between the requirements for a normal child living in a clean, safe environment (the RNI) and a severely malnourished child recovering in a hostile environment (F100 formula).

Variables determining the increments needed for the moderately malnourished.

The derivation of recommendations for the moderately malnourished to have catch-up growth depends upon five variables.

1. the amount of new tissue that needs to be synthesised to become normal;
2. the time available for the child to recover;

¹ Obesity is only “overnutrition” in terms of energy. These individuals can be undernourished in terms of many essential nutrients; the empty calories are laid down as fat because energy *per se* cannot be excreted, but the missing nutrients result in their undernutrition. It is misleading to think of obesity as “overnutrition”; nutrition is much more than simple energy intake.

3. the composition of the new tissue in terms of the ratio of adipose to lean tissue (and skeletal tissue) that should be deposited to achieve functional normality;
4. the extent of any initial nutrient deficit, or excess, in the body tissues brought about by physiological adaptation to the malnourished state;
5. and whether there are likely to be changes in nutrient availability due to the intestinal abnormalities in the moderately malnourished or ongoing pathological losses.

Each of these variables affects the desirable daily intake of the nutrients essential for replenishing and synthesizing new tissue. When considering individual nutrients the effect of each of the variables needs to be examined.

Nevertheless, there are considerable uncertainties when attempting to derive requirements of the moderately malnourished child. Indeed, there are uncertainties in the derivation of the RNIs for normal healthy children; for some nutrients the extant data are not sufficient to set RNIs therefore AIs (Adequate intakes), which are observed intakes from American children that have no apparent detrimental effect on health, are used. The uncertainties also include the degree of wasting and stunting that has to be corrected, the initial deficits of the tissues themselves and the body stores of nutrients that need to be corrected, the composition of the tissue that needs to be deposited, the rate of weight or height gain that is achievable (the length of time over which recovery should take place), the effect of changes in intestinal function in moderate malnutrition on the absorption of nutrients from the diet, as well as the effect of intercurrent infections, diarrhoea, accompanying chronic infections, and environmental pollution on nutrient requirements. Each of these factors is potentially of critical importance in determining the quality of recovery of the malnourished child and should be considered in setting requirements. However, reliable and quantitative data are lacking for many of these considerations. Thus, it is likely that there will be many points upon which expert's opinions diverge. The present paper is deliberately conservative. For example, even if a mean rate of weight gain of 5g/kg/d is not frequently achieved in a group of children under traditional treatment, there will both be individuals within the group who will achieve greater rates of weight gain and the current treatment itself may be limiting the rate of recovery. Thus, it is reasonable to set the requirements at a level that permits such a rate of recovery, and not to set them at a level that restricts the weight gain, or physiological recovery of some of the children with moderate malnutrition. Similarly, for body composition; if the deficit is mainly of adipose tissue, then the nutrient density requirements for its replacement will be relatively modest and giving a diet that is more nutrient dense will have no detrimental effect. On the other hand, if the deficit is mainly functional tissue, to set the requirements at a level that would allow mainly for adipose tissue synthesis, would fail to return some of the children to normality and may promote obesity. The RNIs, in the face of such uncertainty, should be set at a level that will not compromise groups of children and yet are achievable with both mixtures of local foods and also with fortified foods where the fortification is not elevated to a level that would pose a hazard if taken exclusively. As with the RNIs for healthy children, this will necessarily involve value judgements and compromises to be made, but it must be understood that the degree of uncertainty is much higher than with normal healthy children and the consequences of underestimating the requirements more likely to lead to death.

As new data become available it is anticipated that the proposed nutrient requirements will be incrementally refined and expert opinion will converge.

Rates of tissue accretion.

The wasted child should be able to replenish both the lean and fat tissues within a reasonable length of time to reach the normal range of weight-for-height. It is usual for these children to have several episodes of acute illness each year. If most children with moderate malnutrition are to regain normality before the next attack of acute illness it is reasonable for a child to regain their weight deficit in 30 days or less. If this is to be from -2Z (just moderately malnourished) to -1Z (the lower limit of normal/upper limit for mild wasting) then the rate of weight gain required will be less than if a child is to gain weight from -3Z to achieve the median weight-for-height of 0Z. The rates of weight gain to achieve different degrees of catch-up in from 14 to 40 days are shown in table 2.

In general girls need to achieve a slightly higher rate of weight gain than boys. As the definition of moderate malnutrition is from -2 to -3 Z, for a child of -2 to become normal (0 Z) or a child of -3Z to achieve -1Z, over a period of about 30 days, the rate of weight gain will need to be about 5.5g/kg/d². For the purposes of making recommendations for the moderately malnourished child, the diet should be capable of supporting rates of weight gain of at least 5g/kg/d.

Although lower rates of recovery for the moderately malnourished are often found in practice, it is unreasonable to set the recommendations at a level that would restrict the recovery of children because of an inadequate nutrient intake. On the other hand, it is desirable that recovery could take place with a mixture of locally available foods; if the target weight gain is excessive, this could be unachievable. If higher rates of weight gain (to have a shorter recovery period or greater total weight gain) need to be achieved under special circumstances, then the nutrient composition of the diet should approach that of F100.

Energy cost of tissue synthesis

To determine the extra energy and nutrients required for new tissue synthesis at an accelerated rate, we need to know the nutrients and energy that are to be sequestered in the tissue and the energy needed to synthesise the tissue. Theoretically, fat has 9.6 kcal/g and adipose tissue is usually slightly less than 80% anhydrous tissue; so that the energy deposited in adipose tissue is about 8 kcal/g. The energy content of protein is 4 kcal/g³. Lean tissue contains between 18 and 20% solid⁴ and the rest is water. So the energy deposited in lean tissue is about 0.8 kcal/g of tissue. It takes little energy to synthesise one gram of adipose tissue, but to assemble one gram of lean tissue requires about 1.0 kcal/g. So to make adipose tissue takes 8 kcal/g and lean tissue 1.8 kcal/g. If mixed tissue is being made (half lean and half fat) then the theoretical energy required to make that gram of new tissue is 4.9 kcal/g. However, there is usually at least 10% of the diet malabsorbed in the recovering malnourished child without diarrhoea, so the ingested energy required to synthesise one gram of mixed tissue is about 5.5 kcal/g.

² If the same table is constructed using the weight at 0 Z-score as the divisor then the corresponding figure is about 4.9g/kg median z-score/d.

³ The Atwater factors, used to calculate metabolisable energy content of food, use 4kcal/g for protein – this is because the urea that is excreted contains the residual energy from the protein. If the dietary energy intake is calculated using bomb calorimetry factors instead of Atwater factors then the energy content of protein is 5.6 kcal/g.

⁴ The water content of lean tissue varies with the rate of growth/ tissue synthesis. During rapid growth the cytoplasm contains a higher proportion of low molecular weight osmolytes and the tissue is more hydrated. This is the reason that, for example, the muscle of the newborn is much more hydrated than that of an adult. The changes in hydration with growth rate in the malnourished are illustrated by the data of Patrick *et al* [41]. This variable has not been taken into account for any of the calculations in this paper. Over the first few days of rapid growth the energy cost of weight gain can be low because of the water accompanying the accumulation of low molecular weight anabolytes and glycogen.

In children recovering from severe malnutrition this is the figure that has been determined experimentally in a number of studies (table 3) and the mean when a complete diet is given also is about 5 kcal/g of new tissue. In one elegant experiment where the children's muscle mass was measured, Jackson et al [46] were able to predict the proportion of newly synthesised tissue that was lean tissue by measuring the energy cost of weight gained. When the diet has a low density of an essential nutrient the energy cost of tissue synthesis rises as more of the energy is deposited as fat (table 3). In one experiment using a diet deficient in zinc the energy cost rose above that predicted if only fat was being deposited; this was due to the deficiency on intestinal absorption; as it became more severe, energy was lost from the body by malabsorption. It should be noted that many of the studies reported on malnutrition were conducted before we understood the importance of such nutrients as zinc on the quality of the tissue synthesised. For the purposes of calculation of the requirements for tissue synthesis, a figure of 5kcal/g can be used for general mixed tissue synthesis. For individual nutrients it is possible to calculate the requirements for different proportions of lean and fat tissue being synthesised using the energy cost of fat and lean tissue synthesis separately. The energy cost of skeletal growth is unknown, but is assumed to be low as skeletal accretion is relatively slow.

It is important to note that the energy requirement is higher, and the essential nutrient requirement lower, for adipose tissue synthesis than lean tissue synthesis. Conversely, when lean tissue is to be synthesised the energy requirement is relatively low and the nutrient requirement high. In this way the nutrient density is a determining factor in the type of tissue that can be synthesised during catch-up growth: the nutrient density has to be sufficient to allow the child to regain physiological, anatomical, and immunological normality, whilst not depositing excess adipose tissue.

Stunting considerations.

“Stunting” is a dynamic process. In order for a normal child to fulfil the definition of being moderately or severely stunted (<-2 Z-Score and <-3 Z-score height for age respectively) that child will have to have been growing at less than that of a normal child for some time. For example, if a normally-grown one-year-old child starts to gain height at only 70% of normal (i.e. that child is in the process of stunting) she will not fall below the cut-off point to be defined as stunted until 2 years of age [53]. This is why the stunted child is regarded as having “chronic malnutrition”. Undoubtedly, most stunted children have been stunting for a long time. However, in the young child growth in height is sufficiently rapid for a child to fall behind her normal peers quickly; she can also have accelerated height gain within a few weeks or months to catch-up completely. At a population level changes in mean height-for-age can be rapid and responsive to changing conditions. This is clear from the seasonal changes in the prevalence of stunting seen in some countries⁵ [54]. It is misleading to think of “stunting” as a chronic process; it is an active, cumulative, ongoing condition. Although stunting (the process) may be acute, when a child is stunted (the end result), we can say that the process has been present for a long time. Perhaps it would be more appropriate to refer to the stunted child as having “persistent malnutrition” rather than chronic malnutrition.

In terms of examining the requirements for such children, it is useful to differentiate the process of failure to grow in height from the long-term outcome of having failed to grow in height for a

⁵ The seasonality of stunting and of wasting can occur at different times of the year. In this study, it appeared that the children were gaining height and weight at different times of the year, so that with the gain in height there was a fall in weight-for-height and an increase in height-for-age, with the gain in weight there was a gain in weight-for-height and a fall in height-for-age. It is likely that the seasonal change in diet quality was responsible for the differences in height and weight gain. It is possible that the weight gain was mainly adipose tissue without either lean tissue or skeletal tissue growth. Unfortunately body composition was not assessed.

considerable period. The adverse nutrition and environment of these children usually do not change so the process is ongoing; the children are found in the community because persistent stunting is compatible with life. The older and further behind, the longer the child will have to maintain an accelerated rate of growth for full catch-up. Conversely, the younger the child is identified to be stunting the easier and more rapid its reversal. For the older child a stage may be reached where there is simply insufficient time remaining to make a complete and full recovery; however, studies of children whose circumstances have changed show clearly that the potential for catch up remains until at least adolescence [53]. It is wrong to think that after the age of two or three treatment is totally ineffective. However, for increased rates of height gain to be maintained over a prolonged period a permanent change in the quality of the child's diet is required; this is rarely the case so that many observational studies show that the deficit acquired in early life does not usually change [55, 56]. To prevent stunting this improvement must occur over the time the child is actively stunting which is during the first two years of life. It is at this age that children are fed monotonously on "traditional weaning foods", usually cereal paps of very low energy and nutrient density [57] and are less able to compete with siblings for food. Increasing the energy density alone has no effect on stunting but does increase the child's fat mass [33]. Preventive intervention should be strongly focused on the young child, certainly below the age of two and preferably from birth; but treatment should be offered to all stunted children irrespective of their age.

Stunted children: catch up in height.

The maximum rate of height gain that can be achieved by a stunted child, with optimal provision of nutrients and otherwise without disease, is not known. One way to consider what is biologically possible is to compare the absolute rate of height gain of young infants to those of older children. For example, a child growing from 2 to 3 months of age gains about one mm per day. If a 24 month old child gained height at one mm per day then her height gain would be 3.5 times the normal rate for a child of that age. The "potential" computed in this way is shown in figure 1.

A wasted child, having catch-up weight gain, can lay down tissue faster than a normal child at any age⁶; absolute or relative rates of height gain above those of a young infant do not seem to have been documented in the child over 6 months of age. This may be due to a change in the Karlberg phase of growth [58]. However, it is reasonable to suppose that gain in height of a taller, older child could occur at the same absolute rate of height gain as a shorter younger child. Another way to examine the maximum potential for catch up in height comes from Western children treated for growth retarding diseases [59, 60]. Unfortunately, nearly all examples come from children older than 24 months of age. However, older children with pituitary disorders treated with growth hormone, hypothyroid children treated with thyroxin, and coeliac children treated with a gluten free diet, all catch up, initially, at between 3 and 4 times the normal rate of height gain for their age [60, 61]. As these accelerated height gains were maintained for long periods of time, it is likely that even higher rates of height gain could be achieved over short periods of rehabilitation. Dramatic changes in height are also seen in recovering malnourished children, albeit sustained for relatively short periods of time and not properly documented. Children treated for *Trichuris* dysentery syndrome and not given any particular nutritional supplement gained height at up to three times the normal rate [62]. For children recovering from Shigellosis, Kabir *et al* [63] reported that 33 month old children (86cm) gained 10.2 ± 4.4 mm (sd) over 21 days convalescence. The average is about twice the normal (WHO₂₀₀₅) rate of height gain. If we now take mean plus 2 standard deviations the rate of height gain was 0.9mm/d, compared with a normal rate of height gain of 0.3mm/d for children of 86cm (WHO₂₀₀₅); it is even higher when compared with the normal rate of height gain of children of 33months of age. Thus, in Bangladesh they observed rates up to 3 times the normal rate of height

⁶ Up to 20 times the normal rate of weight gain for a child of the same age or height.

gain; given that these children were probably fed suboptimal diets with respect to the ratios of type II nutrients and that these children were already 33 months old, this is likely to be a conservative estimate of what is possible in the younger malnourished child receiving an optimum diet. The extent to which seasonal changes in the prevalence of stunting are due to spontaneous catch-up in height at rates greater than normal is unknown –but if a child after one year has a normal height, and has only been gaining in height for one third of the year because of seasonal shortages, the height gain during the 4 months of active growth will have been at three times the expected rate.

Thus, for the purposes of this analysis it will be assumed that children over the age of 6 months have the potential to gain height at least three times the normal rate of height gain.

For children to catch-up in height, they will need to have a sustained increase in dietary nutrient quality for sufficiently long to allow them to recover. Figure 2 shows the number of days required to catch up either one, two or three Z-score units height-for-age if the child is gaining at between two and four times the normal rate of height gain for her age. The less than one year old child can gain one Z-score unit in between two and four weeks. The severely stunted (-3Z score Ht-for-age) 6 month old child could fully return to normal (0z score) height-for-age in about 6 weeks. A child of 12 months can catch up one z-score unit in about 3 weeks and fully catch up in height in about two months. Thus, although “stunting”⁷ is often termed “chronic malnutrition” it should not be thought that its reversal in the young child requires prolonged intervention. However, to prevent the process of stunting continuing, will require a sustained change in the child’s usual nutrition.

Thus, young children have the potential to catch-up in height quite rapidly. Height deficits should no longer be thought of as “untreatable” within the time frame children are usually under therapeutic care. Rapid height catch up is frequently seen in practice when modern therapeutic diets are used to treat severe wasting. About 10% of children do not reach the weight-for-height criterion for discharge but remain in the program because their height increases at a sufficient rate for the children to fail to reach the weight-for-height discharge criteria; their weight is “chasing” the increasing height (unpublished). If they remained in the program presumably they would fully reverse their stunting as well as their wasting⁸.

A child who is stunted, but not wasted, who catches up in height at an accelerated rate will need to have an associated increase in rate of weight gain if she is to remain of normal weight-for-height. Thus, when considering the nutritional requirements for height gain the requirements for the associated lean tissue accretion need to be included with any particular nutrient needs for bone and cartilage formation. In effect, the reversal of stunting requires “accelerated normal growth” and not “stretching” of the child so that in gaining height there is a reduction in weight-for-height. If this happened, an increasing height could lead a child who is normal weight-for-height becoming moderately wasted, despite the fact that the child is actually growing at an accelerated rate. This is occasionally seen in practice. It may occur when children are gaining height because their diet

⁷ There is a problem with nomenclature in English – the term “stunting” is a verb denoting an ongoing process, and yet it is applied to the child who is already “stunted” (a noun representing the state of the child). Confusion of the process and the end-result occurs because of this unfortunate nomenclature. “Stunting” is here used in the conventional, rather than the correct way.

⁸ The data of Golden and Walker [64] which suggested that children only gained height after they had reached their target weight-for-height was based on children being treated with the older diets that did not contain the full range of balanced nutrients that the modern diets contain. In this respect the results reported in this study should be disregarded. These children’s weight gain consisted of an excess of adipose tissue and insufficient functional tissue; they failed to gain height until they had recovered to normal weight-for-height and took a mixed diet. This is not seen with modern diets based upon the F100 formula. Measurements of wasted children recovering on F100 show that they start to gain in height at about the same time as they start to regain weight (Bernabeau, Grellety and Golden, unpublished), and that height gain is sustained after discharge for at least several weeks.

becomes richer in growth nutrients but lower in energy so that they “exchange” adipose tissue for lean and skeletal tissue [33]. Seasonal differences in weight and height growth can be explained in this way [54, 65].

In order to examine the nutrient requirements for the reversal of stunting⁹, the height deficit, the time available for accelerated height gain and the rate of weight gain that should accompany the height gain need to be examined.

Figure 3 shows the rate of weight gain that should accompany accelerated height gain. A child who is in the process of reversal of stunting needs also to gain weight at an increased rate. A child of 6 to 9 months, who is gaining height at 3 times the normal rate, will need an average weight gain of 4g/kg/d to maintain weight-for-height. This is close to the weight gain derived for moderately wasted children catching up in weight alone, and higher than that reported from some programs of home treatment of severely wasted children.

Thus, although there are no data to address the question of the different nutrient requirements for stunted and wasted children directly, most malnourished children have both wasting and stunting. It is desirable that both abnormalities are reversed by the nutritional treatments. Should we even consider whether there are “different” nutrient requirements for ponderal and longitudinal growth rather than the requirements for normal growth at an accelerated rate?

Diets that do not produce height-gain in children that are both stunted and wasted probably do not contain the appropriate content of the essential nutrients required for the balanced accretion of tissue needed to regain normality. Although, weight gain is frequently simply a result of a positive energy balance without adequate lean tissue synthesis; height gain is unlikely to occur without the necessary nutrients to make skeletal tissue, synthesise accompanying lean tissue, and allow for an appropriate and healthy hormonal and synthetic metabolic state. A gain in height is a better indicator of the adequacy of a diet than gain in weight.

Are specific nutrients needed for reversal of stunting?

During 1 cm growth in height there should be an accompanying weight gain of about 210g¹⁰. To what extent are the nutrients sequestered in the new skeletal tissue different from those in the new lean tissue, and what are the relative proportions? Is a different balance of nutrients required for skeletal tissue and lean tissue formation? Or, more correctly, will the nutrients needed to synthesise 210g of balanced soft tissue change substantially if there is also 1 cm of skeletal growth. For most nutrients this seems unlikely. The exceptions may be those nutrients that are particularly concentrated in bone and cartilage: calcium, phosphorus, sulphur and probably magnesium. For other nutrients, if the skeletal requirements are the same or lower than those for soft tissue formation then the needs for accelerated longitudinal growth can be ignored¹¹.

The nutrients required specifically for skeletal growth are those that are in high concentration in cartilage and bone. Skeletal growth depends initially upon cartilage synthesis, followed by maturation and ossification of the cartilage and then remodelling of the osteoid of the mineralised cartilage. The

⁹ With regard to various deficits in weight-for-age seen in many populations regression analysis of the weight-for-age against the weight-for-height and height-for-age shows statistically that about 80% of the variance in weight-for-age is accounted for by the degree to which the children are stunted and about 20% of the variance to the degree to which they are wasted. Low weight-for-age is thus dominated by the stunting component of growth.

¹⁰ For a girl between 60cm and 85cm, 1 cm of height gain is accompanied by a weight gain of between 183g and 253g. A stunted child of 6 to 24 months, who has a deficit of 1 cm in height, has a deficit of about 210g (175g to 241g).

¹¹ This presumes that the nutritional requirements for hormone and growth factor formation are being met for normal lean tissue synthesis, in particular vitamin D, iodine and essential fatty acids.

nutrients needed for cartilage synthesis at the growth plates are thus the crucial factor in determining if there is to be nutritional limitation of skeletal growth.

Cartilage is mainly composed of glycoaminoglycans such as chondroitin sulphate. These are highly branched carbohydrate chains attached to a small protein core. The characteristic of the carbohydrates moieties is that they are highly sulphated. The main essential nutrient needed in abundance to make cartilage is sulphur¹². Inorganic sulphate can be used; however, most of the sulphate in the body is derived from catabolism of the amino acids methionine and cystine¹³. Thus, there either needs to be adequate protein, relatively rich in sulphur amino acids, or inorganic sulphate in the diet, to permit height gain. The other nutrient essential for normal cartilage maturation is vitamin D.

Bone is composed predominantly of phosphorus and calcium. The scaffolding is mainly collagen, which contains a low proportion of essential amino acids (less than the lean tissue accretion accompanying skeletal growth), so that the specific amino acid requirements for bone collagen synthesis can be ignored. However, vitamin C and copper are essential co-factors for the maturation of collagen. Vitamin K is required for osteocalcin to “capture” calcium during bone formation and magnesium both for the synthesis and secretion of calcium regulating hormones and as a constituent of bone itself. Thus, the specific nutrients that are potentially needed in higher amounts for skeletal than lean tissue growth include sulphur, phosphorus, calcium, magnesium, vitamin D, vitamin K, vitamin C and copper.

The effect of nutrient deficiency on bone growth is illustrated by the classical experiments of McCance and Widdowson [69]. Figure 4 shows three pigs born from the same litter. The large pig was given a normal diet, the smallest pig a restricted diet and the pig on the left a protein deficient diet. Note the growth of the lower jaw bone of the protein deficient pig. It has grown normally, whereas the rest of the bones are short. The jaw bone is formed directly from the periosteum and does not require prior cartilage formation, whereas the leg bones require cartilage synthesis. It appears that protein deficiency has not caused a restriction of bone formation *per se* as the jaw is normal, but has had a specific effect upon cartilage growth. This is most likely due to sulphur deficiency¹⁴.

In terms of ossified tissue where calcium is the dominant nutrient, figure 5 shows the bones of a feral pig, living wild, on the left and a domestic pig, on the right, from New Zealand (they are genetically similar as there are no wild pigs in New Zealand) [70]. The weight of the bone from the domestic pig is heavier and contains more calcium than that of the feral pig. But the feral pigs' bones are longer. Calcium deficiency does not affect longitudinal growth. Deficient animals grow normally but have thin weak bones. In contrast, with phosphorus deficiency growth ceases.

Even though calcium might not be important in stunting children with moderate or severe malnutrition have thin demineralised bones. Many have costochondral junction swelling, a sign of defective bone

¹² In animal studies “bone” growth is measured by the incorporation of radioactive sulphur into skeletal tissue [66, 67]. These assays, when used for factors in blood that stimulate bone growth, show low levels in malnourished children [68].

¹³ If these amino acids are in limited supply they are likely to be consumed first for protein synthesis, then by the liver for synthesis of taurine a component of bile salts and for excretion of those toxins and metabolites that are eliminated as sulphates, and lastly, by the skeletal tissue to make cartilage. It is partly for this reason that gain in height pre-supposes sufficient sulphur amino acids present in the diet to fully satisfy these other essential nutrient requirements; height gain is also a better measure of nutritional adequacy than weight gain from this standpoint.

¹⁴ The protein deficient pig is also almost hairless. Hair proteins contain a high proportion of sulphur amino acids. There is disproportional growth failure in the different bones of stunted children. The long bones are most affected, the spine less affected and the facial bones least affected of children who are stunted in height. Tooth formation is usually normal. This change in body shape is different from that seen in other causes of short stature such as deficient secretion of growth hormone. The relatively short legs of the stunted may lead to underdiagnosis of wasting based upon weight-for-height measurements and sitting height/leg length should be taken.

mineralisation. This is likely to be due to either calcium or phosphorus deficiency.

Classification of the essential nutrients

There are about 40 nutrients essential for health; each of them has to be in the diet that is supplied to children. If any one is not present in adequate amounts then the child will not be healthy, will not grow normally, will not resist disease and will not convalesce satisfactorily from illness. If they are all important for the health and well being of a normal Western child then each one is likely to be critical for children living under conditions of environmental and infective stress and who has persistent or acute malnutrition. They are classified according to the response to a deficiency [57, 71]. Type I nutrients are those that are needed for particular biochemical functions in the body; without them the child will develop specific symptoms and signs of deficiency, if severe, and will be less healthy and susceptible to stress and infection if the level is sub-optimal. However, deficiency of these nutrients does not generally lead to growth failure, at least until the deficiency results in overt clinical illness. Thus, children that are classified as normal or even overweight, on the basis of weight-for-height, height-for-age, weight-for-age, or MUAC, may have quite severe deficiencies of any of the type I nutrients. Although this under-nutrition can lead to death, the children are not classified as “malnourished” because they have no anthropometric abnormality. Similarly, provision of adequate amounts of these nutrients will not lead to reversal of anthropometric malnutrition, but will improve health and immune function. There are convenient clinical features and tests for several of these nutrients; because of this they have received most attention (iron, iodine, vitamin A). For others there are no pathognomonic clinical features and biochemical tests are inconvenient or expensive, so that their deficiency is frequently unrecognised until the deficiency is severe and life threatening or causes an unfavourable outcome from intercurrent illness.

The type II nutrients are the growth nutrients. They are the building blocks of tissue and are necessary for nearly all biochemical pathways. With deficient intakes of any one of these nutrients the child will not grow. With a mild deficiency this leads to stunting, with a more profound deficiency, or more commonly a pathological loss of the nutrient, there is also wasting. As all tissues need these nutrients for cellular division and growth, those whose cells turn over rapidly are most vulnerable. The enterocyte of the intestine has a life span of about 3 days and some of the immune and inflammatory cells have life spans of only a few days, therefore a type II deficiency may aggravate or cause malabsorption and immune dysfunction. As the moderately malnourished child (anthropometrically) has not grown, by definition there is a deficit¹⁵ of *all* the type II nutrients. This holds irrespective of whether the catabolic episode was due to an infection, a pathological loss, a specific type II nutrient deficiency, another cause of loss of appetite or starvation. As there are no body stores of these nutrients, apart from the functional tissues¹⁶, during tissue catabolism all the nutrients released from the tissue are lost from the body [73]. During treatment they *all* have to be replaced in balance if they are to be used efficiently for new functional tissue synthesis. This is the basis for the modern diets used to treat severe malnutrition; the same principles apply to moderate malnutrition, convalescence from illness or any other condition that requires growth at an accelerated rate.

However, as children with moderate malnutrition (stunting or wasting) have normally been taking a diet deficient in many nutrients, both type I and type II, multiple deficiencies are common. It would be inappropriate to only give the type II nutrients in an attempt to reverse wasting or stunting and ignore

¹⁵ It is useful to differentiate a “deficit” from a “deficiency”. A deficit is used to denote not having enough of the nutrient in the body whereas a deficiency is a correctable cause of a deficit. For example, an energy deficit can be caused by anorexia due to zinc deficiency [72]; similarly, a potassium, magnesium or phosphorus deficit can be caused by protein deficiency [73].

¹⁶ For most of the nutrients there are small “labile pools” that may function physiologically to buffer the effects of intermittent fasting and feeding over a few hours.

the high prevalence of many of the type I nutrient deficiencies.

There has been an unfortunate tendency for medical researchers to give nutrients one at a time to observe whether they have an effect; the current fashion is for zinc pills in the hope of finding the simple magic bullet. The history of parenteral nutrition is salutary. One nutrient after another was “discovered” to be important for human health as they were added one-by-one and successive patients presented with deficiency of the “next” limiting nutrient. No animal or farm study would be carried out in this way. If one wanted to see the effects of a particular nutrient deficiency, every known essential nutrient would be given in what is thought to be adequate amounts, so that the diet was optimal and then the nutrient of interest reduced or omitted to observe the specific effect. The same principles have to be applied to treatment of the malnourished; all essential nutrients have to be in the diet in adequate amounts to support health, if we are uncertain about the necessity for a particular nutrient then the correct procedure is to ensure that the amount that is currently thought to be optimal is in the diet. To examine the requirement for type II nutrients for the malnourished, the amount could be reduced incrementally until the accelerated growth rate slows. Simply giving energy, protein, iron, iodine, vitamin A, or more recently zinc, will not return malnourished children to full health. It was once thought that there would be sufficient adventitious zinc in most diets; that was false. Many people still consider nutrients such as pantothenic acid, biotin, essential fatty acids or choline to be of little relevance; the devastating outbreak of irreversible neurological damage in refugees in Afghanistan from pantothenic acid deficiency should not have happened [74].

In deriving the requirements for moderately malnourished children all nutrients known to be essential have to be considered and the diets should contain sufficient quantities to restore full health. This was the principle behind development of F100 and derivative foods used to treat severe malnutrition so successfully, and more recently to treat and prevent malnutrition in vulnerable populations [75]. If this can be achieved with a mix of local foods that would be preferable, if not then there will need to be some fortification or supplementation to ensure adequate nutrition for the moderately wasted and stunted.

Most populations have seasonal shortages and changes in their diets so that the prevalence of malnutrition fluctuates quite markedly with the time of year. The children usually have depleted stores of type I nutrients (such as iron, vitamin A, riboflavin etc.) and will have lost weight from a diminished appetite with low intakes of energy and type II nutrients. They are likely to have, or recently have had, diarrhoea. The moderately malnourished, therefore, do not start at the same baseline as those who are anthropometrically normal within the same population.

Anthropometric malnutrition has been used to calculate that about half of all deaths are due to malnutrition [76]. This is related to acute or persistent deficits of the type II nutrients. However, there are also widespread deficiencies of type I nutrients, such as vitamin A, iodine, iron, riboflavin, folate, vitamin B12 and selenium, that are not causally associated with anthropometric changes but do cause death. Thus, another implication of the classification of nutrients into type I and type II, is that the deaths from type I deficiencies (where there is not associated type II deficiency) need to be *added* to the deaths attributable to type II nutrient deficiency to derive the total mortality due to underlying nutrient deficiency.

Data on children with moderate malnutrition

There are few papers specifically addressing the functional¹⁷ and nutritional deficits of the

¹⁷ An exception is the mental and behavioural development of malnourished children where the retardation is related to the degree of stunting rather than wasting.

moderately malnourished or stunted child. However, the criterion used for diagnosis of severe malnutrition at the time when many studies were reported was either the Gomez or Wellcome classification. The diagnosis of severe malnutrition at that time was less than 60% weight-for-age¹⁸. Many of the subjects of these studies were stunted. With the sequential revision of the way we define moderate wasting to less than 70% weight-for-height and then to $-3Z$ score weight-for-height, much of the data published on “severe malnutrition” included a large proportion of children who would now be classified as having moderate wasting rather than severe malnutrition. For example, reanalysis of the weights and heights of “marasmic” children studied in TMRU, Jamaica (1980-1990) and reported as “severely malnourished”, shows that 61% had moderate wasting (<-2 to $>-3 Z_{\text{scoreNCHS}}$ weight-for-height) and only 39% severe wasting; when the same children are reassessed using the WHO₂₀₀₅ standards, 29% would still be classified as moderately wasted. These children were severely stunted (60% $<-3Z$, 32% $<-4Z$, 16% $<-5Z$). The same confusion about definition of “severe” and “moderate” malnutrition occurs even in recent publications (for example El Diop et al, 2003[77], where half the severely malnourished children would be classified as moderate on the basis of weight-for-height). Thus, there is a considerable amount of information about the moderately wasted (and also stunted) child, which has not been separately reported from the data on the severely wasted child. For this reason, it would be safe to assume that the moderately wasted child has many of the physiological, immunological and other features reported in the literature as “severe malnutrition” when weight-for-age has been used to classify the children. Examination of some of the physiological data, for example renal excretion of acid after an acid load [78] or cardiac output [79], shows that the moderately wasted children lie between the recovered child and the severely wasted. However, there is considerable overlap between the degree of functional abnormality of moderately and severely wasted children.

Thus, it is proposed that the effects of physiological changes reported for children diagnosed as having severe malnutrition on weight-for-age criteria should be taken into account when assessing the nutrient needs of the moderately malnourished. From this point of view the diets should be closer to those formulated specifically for, and used successfully in, the severely malnourished child, than the requirements derived for normal children in a clean environment. As most of these children are “uncomplicated” metabolically they will have similar metabolic adaptations [80] to those reported. There is likely to have been an ascertainment bias towards children with complicated malnutrition on admission in the series reported from hospitals. Most experimental studies do not include the acutely ill children for ethical reasons; the children are studied after they have recovered from acute infections and other major complications. Thus, it is proposed that the increments added because of the initial tissue deficits should be included in the assessment of the requirements of the moderately wasted child. This proposal is speculative and is not based upon either direct measurements or reanalysis of archival data.

ENERGY REQUIREMENTS

The absolute amount of wholesome food that a normal individual eats is determined primarily by his/her energy needs: when there is an energy deficit they feel hungry¹⁹ and when sufficient energy is taken they feel satiety. It is remarkable how precisely energy balance is maintained even in the obese

¹⁸ Usually using the Harvard standards published in earlier editions of Nelson's Textbook of Paediatrics.

¹⁹ Provided there is no major metabolic disturbance such as liver disease, acute infection, or type II nutrient imbalance, all of which lead to anorexia. A low food intake because of such anorexia is often taken to represent an energy deficiency, rather than a deficit caused by some other factor. A low energy intake can be due to deficiency in many other nutrients that give rise to anorexia. There does not need to be major anorexia to lead to malnutrition. If mild anorexia leads to an energy intake of 90kcal/kg/d and the requirement is 100kcal/kg/d the child will lose about 2g/kg/d (5kcal/g). In 10days 2% of body weight is lost and in 3 months the child has lost 20% of body weight and is now classified as moderately malnourished (assuming no physiological adaptation). A tiny increment in anorexia over this time period will lead to severe malnutrition and a high risk of death.

gaining weight (if an adult gains 5 kg in one year, energy intake and expenditure is balanced to within 2%). The variation in individual energy intake over time is much less than the uncertainties in the other constituents of the diet. The foods that are chosen to satisfy energy needs depend upon learned tastes from the mother during pregnancy and the family in infancy, modulated by taste appreciation, habituation, organoleptic properties, tradition, culture and learnt feelings of well-being associated with different foods and aversions with co-incident illness.

If the quantity of food a person eats is closely related to energy requirement (at any particular level of adaptation), then that total quantity of food has to contain all the nutrients for health. If “empty calories” form a large proportion of the diet, then it is likely that the foods that make up the remainder of the diet will not be sufficiently nutrient-rich to maintain health. This phenomenon of “eating to satisfy energy needs” is one of the principle reasons why we should use nutrient density as the main way of judging diets and specifying nutrient requirements. Simply adding oil to make a diet energy dense may have the effect of diluting all the essential nutrients: it does not prevent stunting [33]. A good diet is characterised by the consumption of a wide variety of different foods; each food providing a different blend of nutrients. A highly varied diet is most likely to provide all the essential nutrients. A poor diet is characterised by large quantities of nutrient-poor staple food, restriction of diversity and incredible monotony. This is particularly so for infants after weaning who are then given nothing but dilute traditional cereal porridge repeatedly at each meal. As a diet becomes more and more monotonous then the probability of there being a deficiency of any one essential nutritional component rises exponentially. There is no single natural food that is complete in all the nutrients needed to maintain health in the long term²⁰. As a diet becomes more restricted then the balance of nutrients that is contained within the remaining few items must more nearly approach the ideal balance; such “ideal” foods are not commonly available.

Suppose a diet is composed of two foods each forming half the diet, one of which is devoid in nutrient X, say a local staple, sugar or oil, and the other is perfectly balanced, say a blended complementary or relief food, then the diet *as a whole* will only contain half the amount of nutrient X and the person will become deficient in that nutrient. This problem can limit the impact of food programs using “perfect foods” and accounts for the deficiencies in some infants who take traditional weaning foods as well as breast-milk. Even adding oil (relatively “empty calories”) can cause nutrient deficiency. If one substantial item is insufficiently dense in a nutrient it must be compensated by a dietary item that is correspondingly more nutrient dense than required. In order to have a complete diet, it would be necessary to increase the nutrient content of some items in the diet to compensate for the impoverished state of the remainder of the diet. There is an example of this problem. Adolescents were given 100, 200 or 300 kcal/d as biscuits that were nutritionally deficient in several type II nutrients. The supplement was detrimental for the adolescents, with a negative “dose” response: those taking 300kcal being the worst. Presumably, the home diet was marginal in these nutrients, adding a biscuit that displaced a proportion of the normal diet led to a reduction in the overall intake of the nutrients missing from the biscuit and thus had a detrimental effect on the health and wellbeing of the pupils [82].

There is an important corollary of this concept. Say that only two foods are taken and they each have the appropriate nutrient density to fully satisfy the nutrient requirements if taken exclusively, then the nutritional requirements of the child will be fully met with *any* admixture of the two foods. For

²⁰ Even human breast milk has low levels of iron and copper. This is not at all harmful as physiologically the foetus accumulates stores of these nutrients to maintain supplies until weaning (premature infants may need supplements because the physiological mechanisms have been interrupted by the premature delivery), possibly to prevent intestinal infection [81]. Many moderately malnourished children have had either prematurity or inter-uterine growth retardation; the additional requirements for those nutrients that have foetal stores and low breast milk concentrations for this particular group of moderately malnourished infants are not considered in this report. The concentration of other type I nutrients in breast milk varies with the mother's status. The nutritional requirements of the lactating mother to enable her to provide milk with optimal amounts of nutrients in her breast milk are not considered in this report.

example, if only breast milk²¹ and a fully fortified complementary food of appropriate nutrient density and bioavailability are taken, then it does not matter what proportions of each food comprise the diet, it will be adequate. If this is the case, and the complementary food does not interfere with the availability of nutrients from the breast milk, there could be a smooth change in the proportions of breast milk and complementary food taken by the infant, which will vary from infant to infant, without there being any nutritional deficit.

USE OF ENERGY AS THE REFERENCE POINT FOR DETERMINING NUTRIENT REQUIREMENTS.

Using energy as the reference point has sometimes been suggested by those making dietary recommendations [83, 84]. However, none of the committees have published recommendations based upon nutrient densities for their major RNI reports, although the WHO report does convert some of the nutrient requirements into densities in an annex [83]. Usually energy is quoted for males and female children separately, but nutrient recommendations combine the sexes; there are often differences in the age ranges used for the RNIs and energy requirements and between different authorities.

Energy requirements are set at the mean intake necessary for a certain age or physiological category to maintain energy balance and for normal growth in children; there is an assumed Gaussian variation of individual requirements around this mean requirement. The RNIs are quoted in absolute amounts that will satisfy the physiological requirements of at least 97.5% of the population within a particular age/sex group. However, the actual requirements of both energy and each nutrient (say nutrient X) for each individual vary within the population. If the requirement for energy and nutrient X vary completely independently then to cover 97% of the population's requirements, when expressed as a nutrient:energy density (X per kcal), it would be necessary to increase the observed variation of the nutrient requirement to account for the additional variation due to the spread of energy requirements. Unfortunately, in the experiments that have been done to determine the requirements of nutrient X, simultaneous measurements of energy balance have not been reported. For this reason it is unknown whether a person in the lower tail of the distribution for energy requirements is also in the lower tail of the distribution for all the essential nutrients.

In order to justify the use of nutrient densities (nutrient: energy ratio) in the design of diets for the moderately malnourished the following were considered.

- a) The absolute nutrient requirements are given for an age class. Within this age class there will be physically smaller and larger individuals. A physically smaller individual is likely to have a lower requirement for both energy and nutrient X than the larger individual within that age class. When recommendations are made for a specific *age* group, this source of variation is taken into consideration and contributes to the variance used to make the recommendation. The moderately malnourished are smaller and lighter than the standards, to a variable degree, rendering recommendations based upon age inappropriate.
- b) For individuals of the same weight, most of the variation in requirement is due to differences in body composition. Thus, the difference between male and female requirements is largely due to females having a higher percentage of their body weight as fat. Fat has a lower requirement for maintenance for energy and all other nutrients than lean tissue; thus, with a higher proportion of the body as fat all the nutritional requirements, when expressed per kilo body weight, are lower. Bone,

²¹ Note that, as stated before, this argument does not apply to iron or copper because of the low levels in breast milk.

muscle and skin, in turn, have lower maintenance requirements than the viscera. The variation in body composition is the major reason why different individuals have different nutrient requirements. Because infants have a much higher proportion of their body weight as highly active tissues (brain and viscera) than adults they also have much higher energy and nutrient requirements per kilo body weight. There is substantial variation in body composition within any one weight class. Such variation is likely to affect both energy and nutrient needs in the same direction and perhaps by similar proportions so that expressing nutrient needs in relation to energy requirements will automatically compensate for these differences. The moderately malnourished child (both wasted and stunted) has a lower proportion of body weight as fat and muscle and a higher proportion as viscera and brain. Thus, the malnourished child would require more energy and nutrients per kilo body weight, if there were no metabolic adaptation. This is sometimes found in practice in stunted children [85] despite presumed metabolic adaptation [80].

- c) The basal metabolic rate is the major determinant of energy requirement. It varies from one individual to another depending upon their body composition and physiological state. As physiological state changes the needs for both energy and each nutrient are likely to change in parallel. With an increased rate of tissue turnover, replacement or repair, consumption of both nutrients and the energy increase; with adaptation to a chronically low intake tissue turnover decreases [86]. To set requirements per unit energy automatically compensates for such changes in metabolic state, so that as the malnourished child goes from an adapted hypometabolic state with relatively low requirements, to a hypermetabolic state with active anabolism during recovery. Both energy and nutrient intake will increase as the appetite increases. This is more appropriate than setting RNIs in absolute amounts for these children based upon either age or weight criteria as it takes the metabolic status of the child into consideration.
- d) The energy requirements are clearly related to changes in physical activity. It is argued that the variance in basal metabolic rate itself co-varies with the requirements for other nutrients. Does physical activity affect the irreversible disposal of nutrients as well as energy? As physical activity increases there are increases in the losses, and therefore in requirements, of many nutrients, most frequently demonstrated by urinary nitrogen increases with exercise. There are insufficient data on the exact nature of the changes in energy and most other nutrient needs with changed physical activity, and what data there is comes from adult athletes and not children or the malnourished. It may be that the incremental need for energy is somewhat higher than for other nutrients. Nevertheless, most energy is consumed for basal and resting metabolism and the variation of physical activity level between people is relatively small. A discrepancy would not have a major effect upon the nutrient requirements when expressed as a nutrient: energy density. The malnourished are unlikely to engage in extreme physical activity.
- e) In children, and the convalescent, there are also the energy and nutrient requirements for growth. The increment in nutrients required for new tissue formation is likely to be higher than the increment in energy to achieve that growth. In normal children growing at a normal rate, the proportion of energy that is consumed for growth is a relatively small proportion of the total energy intake after 6 months of age. However, the relative needs of energy and nutrients needed for growth are likely to be quite different from those needed for tissue maintenance. This becomes the critical issue for children that need to gain weight and height at accelerated rates. Furthermore, the relative energy and nutrient intake required to support accelerated growth depends upon the type of new tissue that should be synthesised to return the child to normal; if the child is to make predominantly adipose tissue the energy requirement will be high and the nutrient requirement lower, alternatively if the child is to make lean tissue the energy requirement will be relatively low and the nutrient requirement higher.

Much of the remainder of this paper deals with the calculation of the increments needed in energy and nutrients to maintain increased growth whilst making balanced tissue

NUTRIENT: ENERGY DENSITY REQUIREMENTS FOR NORMAL PEOPLE.

In order to compute the nutrient: energy density requirements the following data were used:

- 1) The FAO/WHO energy requirements 2004 [7]
- 2) The IOM series of publications [8-13]. The age ranges used for the IOM reports are not the same as FAO.
- 3) The UK-DRVs [87]. Typical weights are given for the population groups.

For several of the trace-elements the estimates from the previous WHO/FAO/IAEA publication are presented [5].

For all calculations the FAO/WHO energy requirements [88] have been used, making appropriate adjustments for the age ranges the different documents use. The energy requirements for children are given separately for males and females, whereas the RNIs for the nutrients are given as a combined figure. For the purposes of calculation the energy requirements of females have been used. As these are slightly lower than the male-child's energy requirements the derived nutrient: energy ratio is marginally higher when calculated using the female energy requirement.

For previous estimates of nutrient densities needed for stressed populations either the old factorial data [2] or the values of the IDECG [89] were used [3, 4]. Although the IDECG figures are lower than those derived before the doubly labelled water technique were used exclusively, they are still higher than the present estimates of energy requirements; this change in the denominator has resulted in an *increase* in the nutrient density required in a diet to satisfy the nutrient requirements.

For each of the nutrients, for young children the nutrient: energy density was computed and expressed as the amount of nutrient required per 1000 kcal of diet. The resulting values are presented in the appendix and given in the tables associated with each individual nutrient²²

Where there are major discrepancies between the different bodies that have made recommendations, those of the FAO/WHO have been preferred. Where other bodies have set higher values the reasons for the choice have been examined in the original documents: if the reasoning of the committee is both cogent and applicable to a deprived population then these values are considered. In general the FAO/WHO 2001 and the IOM recommendations are in agreement and are based upon more extensive and up-to-date experimental data; they also take into consideration the prevention of more subtle forms of deficiency, such as effects upon the immune system, the need for adequate anti-oxidant defence and maintaining biomarkers within the physiological range.

²² When expressed as nutrient:energy densities requirements are similar across the age groups from children to adults [3]. Thus, for nearly all age groups including pregnancy and lactation the increments in nutrient and energy requirements are about the same proportionately. The conclusion is that the same food can be eaten and fully satisfy the nutrient needs of the whole family

ARE THE NUTRIENT: ENERGY DENSITY REQUIREMENTS DERIVED FOR NORMAL WESTERN PEOPLE APPLICABLE TO THE MALNOURISHED?

The conclusion is that the variation in requirements within a normal population is largely due to differences in body weight, body composition and physiological state so that there is a direct relationship between the requirements for energy and most nutrients. These RNIs when expressed as densities can then be applied directly to the malnourished. The RNIs for maintenance and normal rates of growth for a child of the same height should relate directly to the stunted child if that child is to gain height and weight at the rate of a normal child, but only when expressed as a nutrient density, not in absolute amounts in relation to either height or age. If the child is to have accelerated weight and height gain increments will need to be added to the nutrient density to allow for the increased rates of tissue synthesis.

An important advantage of expressing the nutrient needs per unit energy, instead of in absolute amounts, is that when the foods comprising the diet are taken to appetite, and the energy requirements of each individual are satisfied, then all the nutrient requirements will automatically be met for that individual, no matter what the body composition or physiological state, and the same requirements will apply to males and females. However, if an individual is moderately malnourished and needs to have catch-up growth then the increment in energy required for catch-up growth will be less than the increment in nutrients if the tissue is to be mainly functional, lean tissue. There are data from the recovering severely and moderately wasted child. As the child with severe malnutrition gains weight, he quite quickly passes to the stage of being moderately wasted and then normal. The nutrient densities found to be so successful for the severely malnourished child are clearly adequate for the recovery of moderately wasted children. In terms of new tissue accretion, the critical factors are the rate and type of new tissue that needs to be synthesised and not the degree of malnutrition (severe, moderate, mild or convalescent) the child has initially; the same principles and calculations apply to each condition. The difference between the groups is the length of time that the increased rate of weight and height gain has to be sustained. Thus, if one wanted a moderately malnourished, or convalescent, child to recover very rapidly then the same diet used for the severely malnourished child would be appropriate, and we could use the nutrient balance represented by the F100 formula; if the appropriate rate of tissue accretion is less rapid, then a diet that is less nutrient dense could be used. In other words the nutritional composition of F100 is also appropriate for moderately malnourished or convalescent children, particularly if it is expected that a further infection or other circumstance will curtail the length of time available for recovery.

GOING FROM RECOMMENDATIONS FOR A HEALTHY POPULATION TO A POPULATION WITH A BASELINE OF NUTRITIONAL DEFICIENCY AND MODERATE MALNUTRITION.

In deriving the requirements, no attempt will be made to provide therapeutic amounts of nutrients to rapidly reverse overt nutrient deficiency. The recommendations are not designed for treatment of clinical deficiency.

Nevertheless, it is desirable for the recommended nutrient densities to be enriched over and above that required to maintain a healthy western population living in a conducive and relatively hazard free environment. The RNIs, as nutrient densities, need to be adjusted to make allowance for the following factors that are usual in most populations of children with moderate malnutrition.

- 1) There is a reduction in the intestinal absorptive function of most that live in poverty in a chronically contaminated environment. This is partly due to overgrowth of bacteria in the small

intestine [90-98] which appears to be ubiquitous in the malnourished and present in all populations of such children that have been investigated. Most malnourished children spend a substantial proportion of their lives with, at least, mild diarrhoea. This may, in part, be due to the prolonged high intake of lectins, saponins and other anti-nutrients in the unrefined diet [99]. The levels of anti-nutrients allowable in foodstuffs have not been established by the Codex Alimentarius. This question is addressed by Michaelsen et al [1]. The recommendations for nutrient intakes for the malnourished need to take into consideration reduced bioavailability from the typical matrices of a poor traditional diet. This is likely to be exacerbated by the reduced capacity of the moderately malnourished to absorb nutrients, the reduced levels of digestive enzymes [100, 101] and gastric acid [102], the bacterial overgrowth and the increased vulnerability of such an intestine to anti-nutrients and naturally occurring toxic factors in foods. Bioavailability studies have not normally been conducted in subjects with such fragile intestinal function.

- 2) These children are repeatedly exposed to infectious agents. In such conditions it is important to ensure adequate intake of all the nutrients critical for the maintenance of the immune system. The children are also ubiquitously exposed to pollutants, particularly smoke from cooking fires [103-105]. There is a particular increase in the need for many of the anti-oxidant nutrients under conditions of both infection and of exposure to pollution. For example, the IOM specifically increases the requirement of vitamin C for cigarette smokers, a cause of oxidative stress; such stress may also underlie the anaemia associated with use of biomass as fuel [106].
- 3) The diets of most poor people are predominantly vegetarian. Because of the fibre and phytate within these items there will be a low bioavailability of several divalent cations (Ca, Mg, Zn, Fe); of equal importance phosphorus will be deficient (phytate is the storage form of phosphorus for the plant – inositol hexaphosphate - and if it is lost in the faeces then the available phosphorus will be lower than needed). Seeds have the correct ratio of nitrogen: potassium: magnesium: phosphorus to make cytoplasm for the growing plant. If the phosphorus is malabsorbed because it is in the form of phytate then the balance of absorbed type II nutrients needed to make cytoplasm will be incorrect and the other nutrients will be used inefficiently. If the culinary methods for food preparation do not release the phosphate from the phytic acid (fermentation, germination, and use of plant ash) then the requirement for nutrients such as phosphate should be expressed in terms of *non-phytate* phosphorus. Nearly all food composition tables only give total phosphorus for plant foods. However, up to 80% of this phosphorus is in the form of phytic acid and is potentially unavailable. To use total phosphorus in food composition tables is not adequate in terms of assessing foods to be included in the diet. Also phytate is a strong chelating agent for divalent ions – their requirement will need to be greatly increased from diets containing excessive phytate. Thus, there needs to be special consideration paid to mineral elements that have low bioavailability.

Given these constraints, the diet has to provide the additional nutritional requirements, in a readily available form, to effect rapid growth and recovery of malnourished, infected and diseased patients in a polluted environment. Several million children have been successfully treated with the F100 milk based formula, which sustains rates of weight gain of up to 2% of body weight each day. Such high rates of weight gain are attained after the existing tissue deficits are restored. These requirements are only in excess of those required by the moderately malnourished if they are to recuperate at a slower rate. The F100 formula gives an upper-limit to the nutrient density that has been tried and tested in the same environment in which the moderately malnourished live. There is clearly no necessity to have the intake of any of the nutrients higher than that provided for with F100 for weight gain provided that the availability from the matrix is the same; there may be additional requirements for height gain.

Comparison of nutrient: energy densities.

Table 4 shows the nutrient densities for FAO/WHO RNIs, other RNIs, F100 and the differences between the RNIs for healthy children and F100.

All the values in the table are expressed per 1000 kcal energy requirement (FAO) of a female child of the same age range given for the recommended absolute intake. The table shows the highest FAO/WHO value for any of the age ranges considered and the highest non-FAO/WHO value from the other sets of recommendations. The data from which this summary table is derived are given in appendix 1. The increments of nutrient density in F100 over the highest RNI for healthy children range from negative to more than 300%, but in general are about 80% above the FAO/WHO RNIs and about 60% above the RNIs set by other committees. Given the need for accelerated growth and the environmental stresses that these children are under these increments appear reasonable.

Approach to estimating changes in nutrient density due to growth

In order to examine the extent to which growth affects the desirable concentrations of nutrients per unit energy, it is necessary first to examine the energy requirements for catch-up growth. The levels of the different nutrients are then similarly calculated and the ratio of the total requirement (maintenance plus the additional nutrient needs for rapid growth) to total energy needs are computed. These calculations are performed both without provision for a prior deficit in nutrient and then again for the sort of deficit that has been found by analysis of biopsies of tissues of children with malnutrition (or in some cases whole body analysis). As the data do not differentiate moderately wasted from severely wasted children the figures for malnourished children using weight-for-age criteria have been used. Until specific data for the moderately wasted become available, this approach should ensure that the recommendations for them are not insufficient.

Figure 6 shows the total energy consumed for catch up growth at different rates (grams of body weight gained per kilo initial body weight per day) when different types of tissue are being replaced in the body. At the left hand of the graph 30% of the new tissue is lean tissue and 70% is adipose tissue whereas at the right hand of the graph 80% of the new tissue is lean tissue and 20% adipose tissue. When there has been weight loss leading to malnutrition, there is a loss of both fat and lean tissue; this is clear from pictures of malnourished individuals who have very little subcutaneous fat and the muscle and skin²³ are wasted. During recovery to normal both types of tissues have to be replaced. Measurements have shown that it is desirable to have weight gain of between 50% and 70% of lean tissue with the balance as fat.

It is reasonable to aim for moderately malnourished patients to gain weight at about 5g/kg/d and for them to replace their initial tissue deficits over about 30 days.

The graph (figure 6) has been drawn using the data obtained from experimental studies on children recovering from malnutrition: the requirement for energy is 82 kcal/kg/d and the absorption of energy is 90% of that ingested so that the child needs to ingest 91 kcal/kg/d²⁴[45, 107, 108]. If each gram of new tissue consumes 2.8 kcal for lean tissue and 8 kcal for adipose tissue then the equation for energy requirement is:

²³ The skin is the largest organ of the body: is atrophies in malnutrition

²⁴ The normal calculation for energy requirement for maintenance uses 100kcal/kg/d of offered diet. This includes an increment to account for malabsorption (10%) and also for spillage (5% to 10%). No account of spillage is taken in any of the calculations because the same proportion of energy and nutrients will be spilt. To obtain the amount of the final diet that should be offered to malnourished children it is important to re-instate an increment for spillage.

Energy = $[82 + (2.8 \cdot \text{lean} + 8 \cdot (1 - \text{lean})) \cdot \text{RWG}] / 0.9$ kcal/kg/d (see legend to table 5 for detailed explanation of the equation).

For example, if the rate of weight gain is to be 5g/kg/d and the tissue is 70% lean tissue, then the equation becomes: $[82 + (2.8 \cdot 0.7 + 8 \cdot 0.3) \cdot 5] / 0.9 = 115$ kcal/kg/d.

For each of the growth nutrients similar equations were derived from the amounts needed to maintain body weight, and then the increments added from the concentrations of the nutrient in lean and fat tissue. Additional increments were added to account for an initial tissue deficit that has to be replaced. These were then divided by the energy equation, using the same proportions of lean and fat tissue and rate of weight gain.

The factors and equations used to calculate the requirements for the type II nutrients are given in table 5.

TYPE II NUTRIENTS

Protein

The protein energy content of breast milk is about 15g/1000kcal (6% energy): this protein is perfectly balanced to meet requirements; however, a proportion is immunoglobulin A that is not absorbed so that the available protein is less than 6% of dietary energy. Using cow's milk protein F100 contains 28g/1000kcal (11.2% of energy). This is sufficient for rapid catch up growth at over 20g/kg/d during recuperation. As this is sufficient for intense anabolism, it is unlikely that a higher protein requirement is needed for skeletal growth provided that the other nutrients are all present at a sufficient density.

The RNIs are shown in table 6. The definition of the age groups used by different authorities in this and subsequent tables are given in appendix 1.

The highest figure is 22.3g/1000kcal (FAO 1989) which should cover 97.5% of normal children's requirements. More recently, WHO/FAO/UNU (2007) have revised these figures drastically to conform to the IOM calculations. These requirements are between 20% and 33% lower than the 1985 figures. This appears to be based upon the lower maintenance requirements assumed in the 2007 report.

The *average* protein requirement for malnourished children needed for maintenance without growth, is 0.6g/kg/d [109]. This does not allow for any individual variation. Furthermore, with this intake severely malnourished children cannot resynthesise liver proteins [110] indicating that this figure, derived from nitrogen balance data, is an underestimate or the true maintenance requirement. The minimum requirement for normal children is about 1.2g/kg; this is the amount of protein supplied by F75, the diet used for severely malnourished children on admission. The content of lean tissue is about 20% protein [111] and of fat tissue 2% protein (wet weight). During rapid weight gain the additional protein is used to make new tissue with about 60% efficiency [112]. It is assumed that the 90% of the protein is absorbed. To attain a rate of weight gain of 5g/kg/d with 70% of the new tissue as lean tissue would require 23.3g/1000kcal (9.2% of energy as protein). The parameters for the equation are given in table 5, and the results of these calculations are shown in table 7.

These calculations assume that the amino-acid ratio of the protein source is sufficiently high and the protein contains the essential amino-acids in the appropriate balance to make new lean tissue.

If protein sources of lower quality are used, a higher density of protein should be used.

In the past, increasing the protein content of diets and relief foods used in treatment of malnutrition has

not resulted in an increase in the rate of rehabilitation. This is thought to be because other type II nutrients have been limiting in these diets [113, 114]. Where the diet is imbalanced the excess protein will be broken down to energy and the nitrogen excreted.

It has been found that high protein diets can be detrimental in severe malnutrition. This is thought to be for two reasons: first, wherever there is any compromise in hepatic function additional protein that cannot be utilised for tissue synthesis requires to be broken down by the liver and excreted – this process requires energy, which may be compromised in malnutrition [115], and generates an acid load [116, 117]. In experimental animals a high protein load given in the face of a dysfunctional liver can precipitate acute hepatic failure. Where the protein cannot be adequately metabolised by the liver a situation similar to an inborn error of amino-acid metabolism occurs (malnourished children have acquired errors of amino acid metabolism [118-122]). Mild liver dysfunction is common in undernourished populations, particularly those that have been consuming aflatoxin contaminated food, living on certain wild foods or receiving herbal medicines. The second reason why it is unwise to have a high protein intake is the renal solute load excess protein generates. Each gram of protein results in 5.7 mmol of urea. In countries where the climate is hot and dry, the water turnover can be up to one third of body water per day [123]. A high protein diet is a reason for a high water requirement and can even lead to hyperosmolar dehydration.

As both these factors are exacerbated by diets that contain low-quality protein, it is necessary for the amino-acid score of the diet to be at least 70% of the reference protein.

The FAO/WHO and IOM recommendations for normal children are 21g/1000kcal and 22 g/1000kcal; F100 contains 28.4g/1000kcal but is designed to sustain a higher rate of weight gain than under consideration for the moderately malnourished. The present calculations suggest that an intake of 23.3g/1000 kcal of high quality protein would be adequate for the moderately wasted or stunted child.

It is therefore proposed that the requirements should contain 24g protein with a quality of at least 70% of reference protein per 1000kcal. A protein source with a lower amino-acid score should not be used for the treatment of the moderately malnourished.

If supplementary foods are being formulated it is reasonable to increase the total dietary intake to 26g/1000kcal to account for the uncertainties of the calculations and any additional needs there are for stunted children. It is recommended that protein sources rich in the sulphur amino acids should be used preferentially in stunted populations.

The appendix (table 45) gives the amino acid requirements per 1000 kcal for normal children. There are insufficient data to make recommendations for individual amino acids for the moderately malnourished child. Nevertheless, the diet of these children should not fall below these figures for any of the essential amino acids.

Sulphur

There are important uses for amino acids beyond the synthesis of protein. In particular, the metabolite, sulphate is used to synthesise 3'-phosphoadenosine 5'-phosphosulfate (PAPS). This is the high-energy sulphate compound used to make glycosaminoglycans for basement membranes and cartilage. The sulphate is mainly derived from the amino-acids cystine and methionine. There is experimental evidence that addition of inorganic sulphate can alleviate some of the requirement for these amino acids, in both animals and humans [11] and sulphate added to a protein deficient diet can result in a growth response. On the other hand, excess sulphate in the diet is not absorbed and can, if excessive, give rise to an osmotic diarrhoea (magnesium sulphate is used as a laxative). The

average intake of sulphur from all sources of children up to 5 years in the USA is between 0.5 and 1.5 grams per day [11] which is high in comparison with the IOM requirement for sulphur amino acids of 575mg/1000kcal; this equates to about 170 mg sulphur/1000kcal.

There may be a particular requirement for additional sulphate in stunted children as they will require accelerated cartilage synthesis. If this is not taken in the form of protein then there should be adequate inorganic sulphate in the diet.

There is a further reason why sulphur generating amino acids are important in a hostile environment. Many relatively hydrophobic toxins and drugs are eliminated by conjugation in the liver with sulphate for elimination in the bile. Other xenobiotics and products of free radical damage are co-valently bound with the sulphhydryl moiety of glutathione and eliminated in the urine as mercapturic acids; their excretion is elevated in the malnourished child [124]. If there is a high exposure to such toxins (smoke, food toxins and bacterial products) then additional sulphur containing amino acids, over and above those needed for protein and glycosaminoglycan synthesis need to be supplied.

Low levels of sulphate are excreted by children on a typical African diet [125] and those with malnutrition [126, 127] and they have under-sulphation of glycosaminoglycans [128-130]. This may be particularly important to prevent viral infection [131, 132]

Because of the additional needs for cartilage synthesis in the stunted child and toxin elimination in those living under stressful conditions, it is suggested that additional sulphate should be in the diet of these children. The amount is uncertain, but is clearly an important research topic. It is suggested that about 200mg of sulphur /1000kcal, as sulphate, be incorporated in the diet, *in addition* to the sulphur that is present in the form of amino acids. This is likely to be particularly important in stunted populations.

Potassium

There is considerable uncertainty about the requirements for potassium for normal people. For this reason most committees have omitted setting RNIs or AIs for potassium even though it is a critical essential nutrient. This is partly because normal dietary intake in the West is thought to greatly exceed the minimum requirement and because the homeostatic mechanisms for conserving potassium are very efficient in a healthy population, so that deficiency is nearly always associated with pathological losses or physiological adaptation. The healthy do not get potassium deficiency: the diseased do²⁵. In particular, there is a major depletion of potassium in all malnourished patients [133-142]. The early studies based upon weight-for-age definition of marasmus, show that this applies to both moderate and severe malnutrition. Potassium is critical in the management of patients with malnutrition; it has even been suggested that heroic amounts lower mortality²⁶ [143]. Some committees have suggested minimum intakes or adequate intakes (AI) for Western populations. The uncertainty is reflected in the marked difference in the published figures (see table 8). The US 10th edition [144] gives minimum values between 800 to 1000 mg/ 1000kcal. The UK

²⁵ Especially diarrhoea, diuretic induced renal losses, anorexia and any abnormalities of the sodium pump or cell membrane such as those present in moderate and severe wasting.

²⁶ There is one report that severely malnourished children have a better outcome with higher amounts [143], but the baseline mortality was high with all diets that were being used in this study; if this was due to excess sodium administration it would account for both the high mortality and the unexpected beneficial effects of exceptionally large amounts of potassium. There is the potential for hyperkalaemia and cardiac effects when very large amounts of potassium are given. This appears to have been the situation when the wrong measure was used to add mineral mix to children recovering from malnutrition in Kivu, DR Congo resulting in an increased potassium intake.

safe allowance is 1100mg/1000kcal. The recent IOM recommendations are considerably higher than this, going up to nearly 3g/1000kcal for a 1-3 year old child. The IOM figure is very high and in disagreement with all other estimates of requirement in normal children. The report states that the AI is based upon little scientific evidence and is mainly set to “mitigate the effects of a high sodium intake”. It is above the level of potassium used in F100. This number will therefore be ignored in setting the recommendations for the moderately malnourished, and the UK figure of 1099mg/1000 kcal used.

The amount of potassium in F100, 2400mg (61mmol)/ 1000kcal, is adequate to replete body potassium in the severely malnourished in about two weeks [145] and support rapid weight gain. Thus, this could be considered as the upper boundary for the moderately malnourished. No upper tolerable limit has been determined for potassium in any of the publications, but a proportion of children have impaired renal function in malnutrition [21, 78, 146-150]; high levels of potassium are dangerous in many forms of renal disease and it would be unwise to give excess potassium to these children.

Because potassium is critical for the maintenance of cellular physiology and is required in substantial amounts for convalescent growth and for those with mild diarrhoea or other illness, it clearly has to be incorporated in adequate amounts in the diets of the moderately malnourished, even though the requirements for the normal healthy western person are so uncertain.

In assessing the amount of potassium that is required for the requirements the following factors need to be taken into account.

Normal potassium losses.

On a diet of 780mg (20 mmol) potassium per day adults lost 10,000mg (250 mmol) from their body and some of the subjects had subnormal plasma potassium concentrations. Therefore, this intake was inadequate to meet obligatory losses, even though after the subjects had lost this amount of potassium they adapted to regain potassium balance [151] (despite considerable sodium retention and alkalosis [152]). The minimum daily faecal losses were about 400mg (10mmol) and renal losses 200-400mg (5-10mmol). Such experimental deficiency studies have never been performed in children.

In malnourished children *without* diarrhoea, but with an adequate potassium intake, the stool output was 23 ± 10 mg/kg/d (0.6 sd 0.25 mmol/kg/d) [153], these children all had low total body potassium content and could be said to be “adapted” in a similar way to Squires & Huth’s adults [151]. This would then perhaps give a minimum stool output with an upper 97.5% limit of 43mg (1.1 mmol) per kilo body weight per day.

The minimum urinary losses are unknown. Normally about 3% of filtered potassium is excreted, which corresponds to about 1000mg (26 mmol) per day in a normal adult and correspondingly less in a child in relation to the body surface area. The losses in the urine of normal Western children range from 27 to 90 mg/kg/d (0.7 to 2.3 mmol/kg/d) which is consistent with the figure in adults when converted to body surface area. It is reasonable to assume that the lower bound of this range corresponds with the minimum amount of potassium that it is desirable to have available to excrete in the urine to allow for flexibility of homeostatic adjustment for health. Sweat and other losses are trivial compared to faecal and urinary losses.

It is therefore desirable to have sufficient potassium, at a minimum, to maintain a renal excretion of 27mg (0.7mmol)/kg/d and a faecal excretion of 39mg (1.0 mmol)/kg/d. Giving a *minimum* requirement without diarrhoea of 66mg (1.7 mmol) /kg/d for children.

Pathological losses

The diet is for malnourished children where there is a high prevalence of diarrhoea and tropical enteropathy. It is reasonable to take this into account when formulating the requirements.

Potassium is the major cation in normal faeces; it is exchanged for sodium mainly in the colon. In diarrhoea this exchange is less than perfect so that with increasing volume of diarrhoea the sodium concentration increases and the potassium concentration decreases [154, 155]. Although the concentration of potassium may decrease, this is more than offset by the increased volume so that there is a substantial increase in the amount of potassium lost in all forms of diarrhoea. Indeed, it is not until the volume of stool approaches that typical of cholera that the electrolyte concentrations approach those seen in the extracellular fluid. In modest diarrhoea there is equimolar potassium and sodium and in normal stool potassium reaches 90 mMolar concentration. Thus, although the mean stool potassium output of a malnourished child without diarrhoea was quite modest, with one or two loose stools (that is usual in malnourished children) this increased to 62 ± 23 mg (1.6 ± 0.6 mmol) /kg/d [153]. In acute diarrhoea it can be considerably higher. Ruz and Solomons [156] published an equation for children with diarrhoea, which indicates that the output is related to faecal volume by the relationship: Potassium (mg/kg/h) = $3.11 + 0.96 * \text{faecal volume (ml/kg/h)}$.

The average weight of each diarrhoeal stool from a malnourished child of 6 kg is about 30g; if a child has 2 such stools per day (not sufficient to be diagnosed as acute diarrhoea) there will be a loss of 10g/kg/d of stool and the faecal output of potassium will increase to 90mg/kg/d for replacement. It should be noted that the large increment in this equation goes from normal stool to a watery stool; the increment per stool is more modest. Dehydrating degrees of diarrhoea should be treated with rehydration therapy; the dietary recommendations do not cover such needs. Nevertheless, two "loose stools" that do not dehydrate or cause the parents to seek help will result in an additional potassium loss that must be made good from the diet. This is common in the moderately malnourished.

Thus, the potential requirements to cover the needs of the malnourished child (without any pre-existing potassium deficit) with mild diarrhoea, not severe enough to require special treatment, are shown in table 9.

The effect of growth

It is usually assumed that there are major additional requirements for potassium during convalescence requiring weight gain. The muscle potassium content is about 3590 mg/kg (92mmol/kg) and the fat tissue about 350mg/kg (9 mmol/kg). So that the total body potassium is about 2340mg/kg (60 mmol/kg).

The increment in energy over the basal requirement is greater than the increment in the basal requirement of potassium so that with synthesis of new tissue the nutrient density falls marginally. Therefore, the effect of growth on the requirement for potassium relative to energy in the diet can be ignored in setting recommendations for the moderately malnourished.

The type of tissue does make a difference. When lean tissue is being synthesised, much more potassium is needed than when adipose tissue is laid down. At rates of weight gain up to 5g/kg/d the increment is much less than the uncertainties in the values used for tissue deficit, stool losses and maintenance requirements. With much higher rates of weight gain the tissue that is being deposited becomes steadily more dominant.

THE EFFECT OF MALNUTRITION.

Measurements of tissue biopsies and whole-body potassium show that there is a substantial deficit

in potassium in the tissues of most malnourished children [135, 140, 142, 157]; this is brought about by slowing down of the sodium pump which normally maintains a high potassium concentration inside the cell [158, 159]. It is thought that this change is an adaptation to conserve energy as the sodium pump normally uses about one third of the basal energy consumed. This adaptation probably requires about 6-7 weeks of under nutrition to fully develop. It is likely that the moderately malnourished will have been underfed for at least this length of time.

The deficit is 23% based on measurements of total body potassium basis; it is about 11% based upon fat free dried muscle biopsies. The tissue deficit in potassium is thus greater than that of protein.

If we assume that there is a 23% deficit in the tissue, and that has to be made up in 30 days then there is a requirement of an additional 18mg (0.46 mmol) per kilo per day (calculated as $60 \times 0.23/30$ mmol/kg/d, where there are 60mmol/kg and repletion is to occur over 30 days) to allow for total body repletion. These values are then related to the child's energy requirements. The resulting requirements are shown in table 10

The main reason for the higher value in F100 and F75 (2400mg/1000kcal), is that the tissue deficit has to be corrected more rapidly in severely malnourished children, particularly in those with kwashiorkor (7 to 14 days) and the evidence that mortality rate is lower with high intakes of potassium.

We should assume that the moderately malnourished child will have up to three loose (not watery) stools and that we need to repair the tissue deficit in about 30 days.

In this case the potassium intake should be 1600mg per 1000kcal. If a diet is to be formulated from local foods alone and we assume that there will be only one loose stool per day, then the requirement could be reduced to 1400mg/1000kcal. On a local diet the child will then need additional potassium if there are loose stools (even without clinical diarrhoea).

Magnesium

In general the needs for magnesium in the food for moderately malnourished children have been largely ignored. There is a large tissue magnesium deficit in malnutrition including those with moderate malnutrition. Children remain in strongly positive magnesium balance throughout recovery and even at the time of their full recovery, having regained weight to reach normal weight-for-height, the magnitude of the positive balance for magnesium (avid retention in the body) is impressive and worrying [160-166]. Even current best-practice therapeutic care seems unable to fully replenish the magnesium deficit of severely or moderately malnourished patients within the time to regain normal weight.

It is unclear whether this strongly positive balance is due to magnesium being sequestered into bone with increased bone turnover during convalescence [167], but this is likely to be substantial. Magnesium may be particularly important for the stunted child who needs to grow in height. Secretion of the hormones involved in bone and calcium metabolism (parathormone and calcitonin) are markedly decreased by magnesium depletion [168, 169]. Magnesium depletion, in particular, is thought to exacerbate the osteoporosis and osteomalacia of coeliac and Crohn's disease and may be partly responsible for the osteoporosis of malnutrition. Frequently, patients who have been treated for hypocalcaemia with calcium and vitamin D are completely unresponsive because of magnesium deficiency. If magnesium is given later, the prior doses of vitamin D, to which the child was unresponsive, can now become toxic and cause potentially fatal hypercalcaemia [170]; the correction of magnesium deficiency *must* accompany or precede treatment of rickets.

A second reason for paying particular attention to magnesium is that potassium retention is

absolutely dependent upon having a normal magnesium status. There is no repletion of potassium in the face of a continuing magnesium deficit; it is likely that the delay in return of intracellular potassium concentrations to normal is related to the difficulty in replenishing magnesium. This not only applies in malnutrition; adults taking diuretics for hypertension are frequently given potassium supplements which does not replenish their potassium deficit. If magnesium supplements are given alone (without additional potassium) their potassium status returns to normal [171]. This is probably because magnesium is an important co-factor controlling the sodium pump [172].

There is also evidence that thiamine deficiency cannot be corrected in the face of a magnesium deficiency [173]. Whether this occurs with other nutritional deficiencies is unknown.

Given the role of magnesium in potassium homeostasis and the sodium pump it is clear that adequate magnesium must be supplied in the diet of the wasted child. Magnesium's role in parathyroid hormone metabolism, the content of magnesium in bone and the failure of calcium retention in the face of a magnesium deficiency, also makes adequate magnesium, in an available form, a critical nutrient for the stunted child.

The starting point for the requirements is only 79mg/1000kcal for normal individuals according to the FAO. The IOM have set their requirements at 112mg/1000kcal, whilst the UK DRV for younger children is 121mg/1000kcal (see table 11). This large discrepancy between the committees reflects the difficulties and paucity of experimental data for magnesium requirements in normal children.

The level in F100 is 175mg/1000kcal. This is probably the limiting factor in the F100 diet, particularly as bone sequestration and the needs for stunting were not taken into account during the design of F100.

Losses in normal people

There appears to be considerable variation in magnesium availability from the diet. This is the major factor in the determining magnesium balance. Its absorption is adversely affected by fibre, phytate and oxalic acid [8] (present in many foods, particularly wild foods). In addition, there may be an inhibitory effect of a high fat diet as the magnesium salts of fatty acids, released during digestion, are all insoluble; this effect has not been adequately investigated [174]. It is probable that the magnesium present in breast milk is particularly available (60 to 70%). The average availability from a mixed western diet in adults taking sufficient magnesium to maintain balance is about 50%. This falls to 35% with a high fibre diet [8]. It is assumed that the amount of fibre in the diet will be less in therapeutic diets than the usual diets taken in the developing world; if this is not the case then the magnesium density should be increased by a factor of about 30%. There is an urgent need for studies of magnesium availability from typical developing country diets.

In malnutrition the faecal magnesium output is between 7 and 12 mg/kg/d [175, 176] with an absorption of dietary magnesium of about 30%. The normal kidney can conserve magnesium efficiently, nevertheless in balance studies, in malnourished grossly deficient subjects, the lowest observed urinary magnesium was 1 mg/kg/d with most of the subjects excreting above 2.5 mg/kg/d without supplementation. The absorption of magnesium is under physiological control and related to the intake. With normal intestinal function and a low fibre diet, normal adults absorb less than 25% with high intakes that increase to 75% when the intake is low.

Growth

When the effects of weight gain on magnesium: energy density requirements were examined, the shape of the resulting graphs was similar to those for potassium. They again show that the highest magnesium: energy density requirement occurs when there is no weight gain, and that the increment

in energy for weight gain is higher than the increment in magnesium that needs to be incorporated into that tissue. The type of tissue being synthesised does have an effect, but at rates of weight gain below 5g/kg/d these effects are not as great as the uncertainties about the absorbed fraction or the other variables in the equations. These calculations do not take into account any magnesium sequestered into bone. The effect of growth and the type of soft tissue that is required to be synthesised are thus not relevant to this analysis and will not be presented.

Malnutrition

The deficit that occurs in malnutrition that needs to be made good before the individual can be expected to function normally is substantial. Biopsies of muscle show that there is often a fall from a normal of 220-240 mg/kg wet weight lean tissue to less than half this value 100 mg/kg [163, 164]. During conventional recovery on a milk based diet this value only increased marginally without additional magnesium (to 135mg/kg). On a dry weight basis there is about a 30% depletion of magnesium with respect to the protein content. The normal magnesium: potassium ratio in muscle is 0.11 mol/mol (0.07mg/mg), the malnourished child on admission has a ratio of 0.09 on admission, this falls to 0.08 by discharge. Thus, on the regimens used during these studies, the children's muscle did not return to normal after recovery. It would appear that there was insufficient magnesium in the diet to make up the deficit or synthesis new tissue with an appropriate composition. It is not known what the repletion is when F100 is used (or the effect of F100 on bone health).

If there is a deficit of 100mg (4.1mmol) /kg of lean tissue, and lean tissue comprises 70% of the body, that should be made up in 30 days there has to be an additional 2.3mg/kg/d to allow for soft tissue repletion. However, as the depletion of skeletal tissue is unknown, there is a continuing strongly positive balance at recovery and the muscle does not return to normal, it is assumed that the skeletal deficit is equivalent to the soft tissue deficit giving a total deficit that should be made good of 4.6mg/kg/d.

Diarrhoea

There are substantial increases in magnesium losses with diarrhoea. So much so that western gastroenterologists cite magnesium deficiency as being the most frequent and troublesome deficiency in such diseases as Crohn's disease [177-179]. If we take the minimum faecal output as 7.3mg (0.3 mmol)/kg/d in malnutrition and normal people; and we also assume that malnourished patients without magnesium supplementation, at the upper end of the range of outputs, had mild diarrhoea then the faecal output during the sort of diarrhoea that is likely to be found in moderately malnourished children will be at least twice that found in non-diarrhoea states, 14.6mg (0.6mmol)/kg/d.

Magnesium Requirements.

The following parameters were used in assessing the magnesium requirements (table 12)

Using the parameters shown in table 12 the requirements for magnesium under various conditions can be computed using the form of the equation already described and substituting the values for magnesium. Faecal losses are assumed to be mainly unabsorbed magnesium and so no adjustment has been made for the availability of magnesium lost in the stool, if there are endogenous losses then the effect of diarrhoea would be increased. The resulting requirements are shown in table 13.

With mixed diets it is recommended that the figure of 50% availability with some increased faecal loss is used to derive the recommendation. The requirements for increased skeletal growth also have

to be considered. Thus, although there are insufficient data to make firm recommendations for the moderately malnourished **an adequate intake should be set at 300 mg/1000kcal for fortified diets. Despite the lack of specific data on magnesium metabolism with F100, in view of the positive results obtained when giving F100 to malnourished children, for food based diets it would be reasonable to reduce this to a minimum of 200mg/1000kcal for planning purposes, however, if the diet has a high fibre or phytate or if diarrhoea is anticipated this should be increased.**

Discussion

The values recommended are higher than those derived for F100 (175mg/1000kcal). In designing that diet it was assumed that the magnesium would have 70% availability from a milk based diet without fibre or phytate, and the tissue deficit was underestimated with regard to the data of Montgomery [164], but was in accord with the results published from Thailand by Cadell [160]. In terms of assessing the F100 formula, biochemical parameters, weight gain and lean tissue growth were assessed; magnesium retention, bone health or magnesium metabolism, specifically, were not examined. In view of the persistent strongly positive balance for magnesium and the fall in the magnesium to potassium ratio in muscle during recovery, it would appear that magnesium may now be the limiting type II nutrient in F100. There are no data to address this problem. It would be prudent to examine magnesium metabolism in children recovering from moderate malnutrition to establish a firmer experimental basis for making recommendations on the dietary magnesium requirements for this group of children.

The effect of availability, diarrhoea and the initial deficit are clear in defining the requirements for the moderately malnourished rather than the normal healthy child. About 60% of body magnesium is normally in the bones, and in malnutrition there is a very marked loss of bone [180-182]. Bone turnover increases dramatically during therapeutic feeding [167] to increase magnesium requirements over and above those needed for soft tissue repletion. Thus, for both wasted and stunted children a level higher than that recommended for F100 would be prudent.

OTHER FACTORS

There are several other factors, with respect to magnesium, that need to be considered in the design of the requirements.

Many magnesium salts give an unpleasant taste to foods when they are present in high concentrations. In order to improve acceptability of any fortified foods, the salt will have to be chosen with care. "Food grade" magnesium citrate has a neutral taste, is used in F100 and this avoids the deliquescent properties of magnesium chloride and the cathartic effects of magnesium sulphate. Other salts of magnesium salts have been used; magnesium diglycinate appears to be better tolerated and absorbed in patients with limited intestinal function [183], but there is limited experience with its use.

Children with malnutrition often have low or absent gastric acid [102, 184-187]. This means that inorganic salts of minerals that are insoluble or require an acid gastric environment for absorption should not be used to supplement the foods given to the moderately malnourished. Such salts include magnesium and calcium oxides and phosphates. Magnesium hydroxide was used in the studies reported from the MRC unit in Uganda [188]. Organic salts of magnesium are more available than inorganic salts [189-191]

Magnesium is a weak cation with a poor absorption. When it is given as the salt of a strong anion which is absorbed, the salt will cause a metabolic acidosis. This was shown in severely malnourished children treated with magnesium chloride, some of whom died [192]. The magnesium should always be given as the salt of a weak anion such as the citrate or diglycinate.

Although magnesium is relatively non-toxic and large amounts can be administered either intravenously or by injection (it is used to treat eclampsia in large doses), this is not the case when large amounts are given orally. Epsom salts (magnesium sulphate) have been used to induce diarrhoea and for the treatment of constipation. There should not be sufficient magnesium in the diet to exacerbate any diarrhoea. Although this is largely a theoretical argument, because the doses used as a cathartic are high [193], the malnourished intestine may be less able to cope. This could be one reason why there has been reluctance to add sufficient magnesium to the diets of malnourished children.

Phosphorus

The main phosphorus compound in vegetable diets is phytic acid (inositol hexa-phosphate). This is used by plants to store phosphorus for use after germination. During plant growth the phytate is mobilised to give the appropriate balance of type II nutrients (e.g. nitrogen: phosphorus ratio) for the formation of protoplasm. In terms of the fundamental biochemical processes there is not a marked difference between plants', animals' and man's protoplasm. If the phytic acid is not absorbed then the available nitrogen: phosphorus ratio derived from the foodstuff is unbalanced due to a limited phosphorus supply. The other type II nutrients, particularly protein, are potentially wasted from a high phytate vegetarian diet. Such diets are generally thought to be less nutritious because the phytic acid chelates zinc, iron, calcium and magnesium; this is indeed a problem. However, the problem that phytic acid poses for phosphorus status is not normally a focus of attention. In the West, phosphorus intake generally exceeds requirement through consumption of dairy produce; some cultures get phosphorus and other minerals from chewing bones.

The situation is different with the moderately malnourished child. Nearly every malnourished child has physical signs of bony changes (swelling of the costochondral junction) [36] and X-rays show demineralisation of the bones. This is not adequately explained by vitamin D deficiency, the classical cause of rickets. These common clinical findings in the developing world are now being described in western children who get phosphorus deficient rickets secondary to chronic ingestion of some antacids (aluminium, magnesium and calcium salts) which make phosphorus unavailable [194, 195]. Clinical phosphate deficiency is extremely common in malnutrition [196, 197], even in malnourished adults in Western hospitals [198], is closely related to prognosis [199]. Its correction is likely to partly account for the success of cow's milk in the treatment of malnutrition; it is a particularly rich source of available phosphorus. There is no extraneous phosphorus added to F100 because of the abundant, soluble and available phosphorus in cow's milk. If other foods or ingredients low in phosphorus or high in phytate are substituted for milk, special attention needs to be paid to the phosphorus content and availability. Calcium phosphate is often used ($\text{Ca}_3(\text{PO}_4)_2$); it is very insoluble and should not be the phosphate (or calcium) salt chosen for diets for children with malnutrition. If diets are being assessed for adequacy of the moderately malnourished child, phytate phosphorus should be discounted from the diet. Strategies to reduce the phytate content of plants themselves and thus increase the availability of divalent cations such as iron will have to have an alternative source of available phosphorus.

It is often thought that phosphate is mainly used for bone formation along with calcium; this relationship with calcium is important in infants and renal patients where an unbalanced calcium: phosphorus ratio in the diet can lead to clinical problems of calcium homeostasis and tetany. However, unlike calcium, phosphorus has a high concentration in soft tissues. It is the major intracellular anion with a concentration on a molar basis of 70 to 100% that of potassium. On a total body basis there is much more phosphorus than potassium because of the phosphorus sequestered in bone: the infant has about 5.6g/kg and the adult 12g/kg [200]. The additional

phosphate in adults is in bone and brain. Table 14 shows the phosphorus content of tissues [201].

Phosphate is vital for all metabolic pathways and nearly all active metabolites need to be phosphorylated before they can be used: phosphate compounds are the energy “transducers” of the body. A deficiency of tissue phosphate causes severe disruption to metabolism [202]; indeed, it may be that a high dietary intake of protein or carbohydrates, that require phosphate for their initial metabolism, can cause severe metabolic damage or even death in the face of a phosphate deficiency by acute consumption of hepatic ATP [203-206].

In view of the relative unavailability of the phosphorus from phytic acid (where the food has not been either fermented or germinated), and the high prevalence of phosphate deficiency in malnourished people, it is unsafe to assume that the phosphorus content quoted in food composition tables (analytic values of total phosphorus), will be sufficiently available to satisfy the nutritional needs of malnourished children. The same problem has not been faced by western committees setting recommendations as much of the phosphate comes from a mixed diet containing dairy produce. The availability in western adults is 55 to 70% and in infants is 65 to 90% [8]. There have been few studies of phosphate availability or status in those living in developing countries consuming their habitual, restricted, vegetarian diets to guide the formulation of the requirements.

There appears to be considerable variation between the committees setting the RNI (FAO/WHO has not considered the requirements of phosphorus) (table 15). This is partly because the phosphorus requirements have conventionally been set with respect to maintaining a 1:1 ratio with calcium, so that when calcium requirements are judged the phosphate requirements are derived without independent experimental data. This is not a satisfactory approach when assessing the needs of a moderately malnourished child for whom this is one of the critical elements whose deficiency appears to be quite common. The IOM set the highest requirements for teenagers and the UK for infants.

Parameters

In malnourished children the average minimum amount of phosphorus needed for phosphorus balance is 28mg (0.9mmol) per kilo per day [207]. However, the IOM rejected phosphorus balance as a way of assessing phosphorus requirement because when the subjects are just “in balance” they have a lower than normal plasma phosphate concentration. They suggest that the requirement should be set at a level that maintains a normal plasma phosphorus concentration. Phosphorus, like potassium, magnesium, zinc and protein, is mainly intracellular (or locked in bone) and the plasma concentration not only fails to reflect intracellular or bone concentrations with fidelity but the level is subject to metabolic, hormonal and renal modulation.

For the purposes of setting the requirements for the moderately malnourished the minimum *average* requirement for maintenance has been augmented by 20% as an assumed standard deviation to cover most malnourished children and take account of the IOM criticism; thus 34mg/kg/d is set as the maintenance requirement. The tissue content is 1860mg (60mmol) per kg of lean tissue with about one tenth of this in fat tissue. However, some important lipid rich tissues, such as the brain and adrenal cortex have high concentrations of phosphate because of their content of phospholipids.

There have been few measurements of tissue phosphate levels in malnutrition. The levels in the few samples that have been measured show a reduction of about 18% on a dry weight basis [208] (assumed to be relative to protein). On the other hand the levels of organic phosphorus ATP, ADP and AMP are reduced by about 50% in white blood cell samples, and creatine phosphate in muscle is also low in malnourished adults [209]. Thus, it will be assumed that the soft tissue deficit of phosphorus in moderate malnutrition is 435mg (14mmol) per kg (21%) which is of a similar magnitude to the deficit of potassium and magnesium. If this is to be made up in 30 days, there will

need to be an additional retention of 14.5mg (0.47 mmol) per kg /day.

The availability of phosphorus is very variable in healthy children. It is low from divalent metal salts and phytic acid. Organic phosphates appear to be readily available; phospholipids are available in normal children but may be reduced in the malnourished child because of defects in bile salt metabolism [210].

For the moderately malnourished an availability of 60% is assumed on the basis that it is similar to that of a healthy western child. There are few data to address the values to use for these parameters; the derived values have wide confidence limits (table 16).

Diarrhoea

In ill health phosphate plays another critical role. It is the major acid-base buffer of the body and is critical for renal excretion of acid generated in the body. Any tendency to acidosis will be ameliorated when there is a sufficiently high phosphate intake to have to excrete dihydrogen-phosphate in the urine. When there is a relative phosphate deficiency acidosis cannot be corrected²⁷. Thus, conditions like diarrhoea, pneumonia or malaria that are associated with acidosis are more likely to be fatal in the presence of a limited intake of phosphate. A corollary of this is that conditions that lead to acidosis will further deplete the body of phosphorus used to excrete the titratable acidity.

There is not only a necessary increase in the urinary excretion of phosphate in diarrhoea because of the acidosis, there is also an increase in faecal phosphate loss in diarrhoea; but there have been few studies on this aspect of the change in phosphate requirements that occur in ill health. To meet these additional needs, it is assumed that appropriate balance in mild diarrhoea will be achieved when the daily phosphate losses are doubled. No data to address the increment in phosphate losses with diarrhoea in the moderately malnourished were found. The assumption of a doubling of faecal and urinary losses might be a gross underestimate. However, table 17 shows a balance study on malnourished children on admission and at intervals during recovery. The faecal output is about twice in the malnourished than the recovered state.

This is an area that requires considerable research as the data are totally insufficient and with the trend to use cheap ingredients, rich in phytate, to treat the moderately malnourished the availability of phosphorus from the diet becomes a critical issue.

Growth

The specific requirements for growth are similar to potassium and magnesium, in that there is little change in the requirement per unit energy as the child's rate of weight gain increases.

Phosphorus recommended intakes

Table 18 gives the computed requirements for phosphorus for moderately malnourished children with and without a tissue deficit and diarrhoea

Discussion

As with magnesium, the calculations that have been made are for soft tissue phosphorus requirements only. No account has been taken of the needs for reossification of bone in the moderately malnourished, for continuing skeletal growth or for accelerated height gain in the

²⁷ The magnesium chloride induced acidosis only occurred when the children were on a maintenance diet similar to F75, when the growth diet was given (with the same phosphorus density F100), rich in phosphorus the acidosis disappeared coincident with a high urinary titratable acidity and excretion of dihydrogen phosphate[192]

stunted child. Because of the added requirement for bone formation it is suggested that the phosphorus requirement for the moderately malnourished child should equal or even exceed that of the severely malnourished child. This is because the diet will be taken for longer periods of time for the reversal of stunting, during which time the child may be exposed to repeated episodes of acidosis and diarrhoea.

It is suggested that foods used for calculation of the diets for the moderately malnourished should have the phytate fraction measured. This should be tabulated in food composition tables and completely *discounted* from any assessment of the adequacy of the phosphorus in the diet.

Therefore it is suggested that the diet contain 900mg (29mmol) per 1000kcal of *non-phytate* phosphorus for the child when the diet is fortified, and a minimum of at least 600 mg/1000kcal for an approach based only locally available foods.

Many inorganic phosphorus compounds are marginally soluble and likely to be unavailable if used to fortify diets or foods for the child with defective gastric acid secretion. Excess phosphate may reduce the availability of some divalent metals. The advantage of milk is that the phosphorus is soluble and readily available. The problems of preventing calcium phosphate from precipitating in artificially formulated diets containing the full calcium and phosphorus requirement, without using milk, present a difficult technical problem [211] when the diet should be readily soluble.

Zinc

Zinc has been shown to be the limiting type II nutrient in many diets. Although the zinc: protein ratio is relatively constant in most foodstuffs from vegetables to meat – the availability of the zinc is always less than that of protein, so it is difficult to become protein deficient without being first zinc deficient [212]. Because of this it has been suggested that, with normal diets, it is not possible to have “pure” protein deficiency. Supplementation with zinc has been shown to shorten the secretory phase of diarrhoea and to have a major effect upon the recuperation of such patients. Zinc is also critical for the immune response. The congenital condition acrodermatitis enteropathica, which is due to a congenital defect in zinc absorption, is characterised by immune dysfunction and diarrhoea as well as skin lesions and failure to grow. These same conditions characterise the problems of the malnourished child. On the other hand high doses of zinc can interfere with copper metabolism and have other effects that are detrimental. Early studies in the USA showed that zinc was the limiting nutrient in the diets of children enrolled in the head-start program and this resulted in progressive stunting [213]. Even early types of infant formulae contained insufficient zinc for growth, and those brands based upon soya protein led to clinical deficiency when given to recovering malnourished children: this resulted in abnormalities of immune function, body composition, thymic re-growth and the sodium pump. [18, 28, 214, 215]. It is imperative that the diets of moderately malnourished children contain adequate amounts of available zinc.

Phytic acid is a strong chelator for zinc, this chelation is greatly exacerbated by the presence of excess calcium and the diet should not contain excess calcium if phytate is present [216, 217]. Adding excess calcium in an effort to support bone growth can induce zinc deficiency by this mechanism and zinc deficiency can be partly alleviated by giving a low calcium diet [218], presumably by releasing zinc locked in bone.

Because of the strong association between the dietary matrix and zinc status, FAO/WHO [6] and WHO [5], in publishing their recommendations, give three values corresponding to the different types of diet that are habitually consumed. These have an availability of 56%, 35% and 15% of the zinc in the diet. There is little urinary excretion of zinc so that it can be quantitatively ignored.

Table 19 shows the zinc requirements of the various expert committees. The western committees

have proposed a zinc intake of about 5mg/1000kcal or less for children. The RNI has been considerably reduced by the IOM from the previous USA recommendations [144] possibly because of domestic concerns of induced copper deficiency with high zinc intakes. Nevertheless, the cause for this large variation is mainly due to differences in assumed availability. The dietary zinc requirements published by FAO, for infants taking cereal diets typical of developing countries is over 12mg/1000kcal, and the prior WHO/FAO/IAEA committee's recommendations were over 16mg/1000kcal. These recommendations are for normal children taking different types of diet. It is clear that the matrix has a dominant effect upon the zinc availability and thus dietary requirement.

Zinc losses

The faecal zinc, in zinc deficiency, can fall to low values, and the absorbed amount needed for "maintenance" is only 0.033mg/kg/d [5]; this seems a trivial quantity, in view of the high prevalence of zinc deficiency and the quite large amounts of zinc released into the intestine with pancreatic enzymes, many of which contain zinc.

Growth.

Normal muscle zinc is about 81mg/kg [24]. This content of zinc in soft tissue is high compared to the maintenance requirements and thus the rate of weight gain has a dramatic effect upon the amount of zinc that needs to be present in the diet to support different rates of growth without any compromise of immune or gut function.

Conversely, during weight loss, with the catabolism of muscle there are relatively large amounts of zinc liberated from the tissues [219]. Anorexia is a primary and cardinal feature of those taking a low zinc diet [220]. In dietary surveys the resulting low energy intake is often interpreted as an "energy deficiency" when the prime cause is the poor appetite due to an inadequate supply of available zinc [72]. With an intake less than maintenance, the zinc that is released from the catabolised tissue, alleviates the deficiency and relieves the anorexia somewhat, at the expense of continued gradual weight loss [221]. It is critical that there is sufficient available zinc in the requirements to prevent this anorexia from occurring and to support at least normal rates of growth.

Malnutrition

In severe or moderate malnutrition the muscle zinc falls from about 81 to 64 mg/kg [24]. This deficit is of the same order of magnitude of the other intracellular minerals (21%), and is a metabolic adaptation. The zinc content of fat tissue is much less than that of muscle; the tissue deficit is thus of the order of 17mg/kg, and that this has to be made good in about 30days. This will require an additional retention of 0.57 mg/kg/d. This is a large proportion of the dietary zinc intake of normal children. There are relatively few data on the deficit in malnourished children, particularly moderately wasted or stunted children. The type of tissue being synthesised has relatively little effect upon the zinc: energy requirement within the range of 50 to 70% lean tissue synthesised, although if the proportions of lean to fat tissue change there is a significant effect. The calculations presented are for 70% lean tissue and 30% fat tissue.

Diarrhoea

Zinc deficiency is not only a cause of diarrhoea but also substantial zinc is lost in diarrhoeal stool. The zinc output in the faeces increased threefold from 0.050 to 0.160mg/kg/d with diarrhoea [222]. However, the dominant features in deciding upon zinc requirements are the magnitude of the deficit and the rate of weight gain. Uncertainties in these assumptions far outweigh the variation due to diarrhoea. For that reason no allowance will be made for diarrhoea in calculation of zinc: energy

ratio required. The resulting calculations are shown in table 20.

Discussion

Table 19 shows the effect of the three different availabilities, at different rates of weight gain without an initial deficit or with a deficit of either 8g/kg or of 17mg/kg that is to be made good in 30 days. Shown are the necessary zinc: energy densities per 1000kcal and the absolute zinc intake required in mg/kg/d.

Breast milk has about 1.7mg zinc per 1000 kcal – this corresponds in the table to a rate of weight gain of 1g/kg/d with a highly available source of zinc. The effect of both availability and depletion are more dramatic with zinc than with any other nutrient. The effects are of such magnitude that *it is unrealistic to attempt to replete a moderately malnourished child over short periods of time with a low-availability diet without adding large amounts of zinc*. The question arises about the utility of having sufficient amounts of the other type II nutrients in the diet to allow for rapid growth if it becomes impossible for sufficient zinc to be absorbed [73]. The RNIs for normal children living on a western diet are completely inadequate for a wasted or stunted child taking a cereal/pulse based diet. Even children taking a strict vegetarian diet in Holland grow similarly to children in the developing world [223], indicating that the infective burden or care practices are not the dominant causes of malnutrition in those taking traditional weaning diets.

RUTF and F100 which are special milk-based diets for the severely malnourished have more than ten times the concentration of zinc found in breast milk; with the high availability from such a diet, this amount allows repletion of the deficit and rates of weight gain at well over 10g/kg/d. This is what is routinely found in practice, however, the rate of recovery declines markedly when phytate containing porridges are added to the feeding regime (unpublished). The fact that even *adding* cereal based porridges to an exclusively milk based diet *decreases* the rate of weight gain shows not only that the zinc contained in these diets is of low availability, but also that the diets themselves interfere with the availability of nutrients such as zinc in the formula diet. If children are taking RUTF at home with considerable amounts of high phytate “other foods” then zinc may become the limiting nutrient in recovery unless the foods are taken at different times of the day. The instructions for taking such foods should include advice that they are taken separately.

The amount of zinc that would need to be added to a diet to allow for catch up at a reasonable rate and at the same time replenish the existing tissues, with a diet in which the zinc is only 15% available is so large that a marked increase in the availability could potentially lead to the absorption of excessive amounts of zinc; and, most certainly, to local concentrations in the intestine that would seriously interfere with copper absorption. Such sudden increases in availability could occur, for example, if the diet was fermented to reduce the phytate.

In general the copper to zinc ratio should be approximately 1:10 on a molar basis; but if a large amount of zinc is added to achieve rapid growth in the face of antinutrients, then the appropriate absorbed ratio of copper: zinc might be achieved with lower dietary ratios if the antinutrients specifically affect zinc absorption²⁸. It is important to collect data to address this interaction in the malnourished child. Thus, it is not feasible to have meaningful catch-up growth in an already

²⁸ The adverse effect of large amounts of zinc on copper absorption is mediated by induction of metallothionein in the enterocyte. If the zinc is bound to phytate or other chelating agent and does not enter the enterocyte, then this interaction may not occur.

depleted state on a diet with low zinc availability.

A minimum of 13mg/1000 kcal should be given where the diet is of moderate availability and the children are to be rehabilitated with local foods alone. If the diet is to be formulated, again in a matrix that will give moderate availability, then this should be increased to 20mg/1000kcal.

When very high levels of zinc are given (>6mg/kg/d) there is a danger of toxicity, with increased mortality [224]; although in the study quoted, no copper supplements were given²⁹. The prescription of zinc as a separate supplement that is given irrespective of the appetite or physiological state of the child is different from the addition of the zinc in a fixed ratio to energy (and copper) in the food; this obviates the problem somewhat as those with poor appetites and not gaining weight will take less of the diet. When they are gaining weight rapidly and are sequestering nutrients into tissue, their intake will increase, not only of zinc but of copper and the other nutrients as well. With F100, taken at 100kcal/kg/d, the intake is 2.3mg/kg/d; when the child is gaining weight rapidly on the same diet and takes 200kcal/kg/d the intake will be 4.6mg/kg/d. Children very rarely take more than this amount of diet. This fundamental difference between giving a nutrient as a pharmaceutical on a body weight or age basis³⁰ and incorporating an appropriate amount in a diet is critical when treating children with all forms of malnutrition. This is the main conceptual change in treatment using diets such as F100 and the practice before this when individual supplements were given on a body weight basis.

Phytase

The availability of zinc, calcium, iron, phosphorus, magnesium and even protein[225] can be considerably enhanced by adding commercially available microbial phytase to diets [1]; this has been confirmed in humans with respect to iron [226]. This has been successful in the nutrition of mono-gastric farm animals, but has not yet been used for human feeding. The addition of phytase to the diet would obviate the need to reject bulk ingredients which lead to low-availability of these components from the requirements. The levels of microbial phytase that have been found to lead to a linear increase in growth and nutrient utilisation are up to about 2000 units³¹ per kilo of feedstuff (about 500units per 1000kcal). It is therefore recommended that trials of the effect of enzymatic breakdown of phytic acid on the nutritional status of moderately malnourished children be conducted. This can be either through externally added microbial phytase in the case of formulated foods or fermentation/germination in the case of local food use. Even quite simple soaking can halve the phytic acid content [227]. It would be useful to study traditional methods of food preparation among populations living where different foodstuffs originated [57, 228].

²⁹ It is also unclear whether potassium, magnesium and the other essential trace elements were given: the children did receive a vitamin supplement.

³⁰ When zinc tablets are given, for example, there is always the danger of an overdose particularly if the tablets are made to taste pleasant. With a pharmaceutical approach there is also the problem of changing the Zinc: copper ratio so that acute copper deficiency can be induced. There is also the danger of giving the tablets in an acute catabolic state when large amounts of zinc are being released from the tissues [219] and sequestered in the liver or lost from the body. Physiologically the body reduces plasma zinc during infections as high concentrations can blunt the immune response (see references in [224]). These dangers are not present when the zinc is incorporated into the diet. There is no necessity to give higher amounts of zinc than those found in F100 (supplying 2 to 5mg/kg/d depending upon the intake), unless the matrix of the diet decreases availability substantially or to give additional zinc to those in an acute catabolic state (when the appetite is suppressed).

³¹ one unit is defined as the amount of enzyme that releases 1 umol inorganic phosphate per min from 5.1 mmolar sodium phytate. PH 5.5, 37oC

Sodium

Sodium is the main electrolyte in the extra-cellular fluid. Normally there is an extraordinary capacity to conserve sodium. Adults without pathological losses can maintain balance on between 70 and 460 mg/d, and there are healthy populations that have a mean adult intake of about 920 mg/d. It is almost impossible to induce sodium deficiency without a pathological loss [229]; this was achieved by McCance by induction of excess sweating in volunteers. Normal intake far exceeds minimum requirements for healthy people in nearly every country (table 21). The minimum maintenance amount for the malnourished child is unknown, but as there is excess sodium in the body which has to be lost during recovery, there is probably little requirement in the absence of ongoing pathological losses. For the normal healthy child there were no experimental data on minimum requirements during salt restriction found. The minimum requirement has been set at 10mg/kg/d by extrapolation from the adult balance figures.

Taste

There is a benefit to having sodium in the diet as it adds “taste” and improves the acceptability of the diet: condiments such as mono-sodium glutamate are on sale in most developing country markets. Although the actual “requirement” may be low it is not desirable to have a very low sodium content from the point of view of acceptability. Rice diets which were formulated to treat renal failure before dialysis were very low in sodium, tasteless and very difficult to eat [230, 231].

Diarrhoea

Although in health the capacity to conserve sodium is remarkable, considerable losses can occur in pathological states. The most common is infective diarrhoea³² [232, 233].

It is assumed that acute episodes of watery diarrhoea will be treated with ORS. Nevertheless there will commonly be lesser degrees of “loose stools” in the moderately malnourished.

The stool concentration of sodium in diarrhoeal stool from malnourished children is less than in stool from a normal child producing the same volume of diarrhoea. In malnourished children the stool output was 0.9mg/g stool without any diarrhoea which rose to 10.1 ± 8.7 mg/g stool with non-dehydrating diarrhoea that did not require special administration of electrolytes [153]. The output would then be up to 27mg/kg/d (97% CI). This is thus the *minimum* requirement for sodium to cover mild diarrhoea in the moderately malnourished.

The stool sodium output in normal children with infective diarrhoea is higher than that of malnourished children with diarrhoea. It amounts to about $1.43 + 1.45 * \text{stool volume (ml/kg/h)}$, mg/kg/h [156].

Malnutrition

Sodium is unlike other nutrients in malnutrition as the total body sodium *increases* considerably instead of decreasing. This is probably secondary to a slowing of the sodium pump or potassium depletion with a consequent rise in intracellular sodium [159, 234, 235]; during treatment this sodium has to come out of the cells and be excreted; if this occurs rapidly the patients can die from acute heart failure [236]. For this reason sodium should be *restricted* in the diets of the moderately

³² Far less sodium is lost in osmotic diarrhoea where the main osmolytes in the stool are the substances that are malabsorbed.

malnourished. Where the malnourished children have a concomitant pathological loss of sodium, a difficult balance has to be struck between replacing the losses and anticipating the influx of sodium from the cells to the extracellular compartment as the child starts to recover or enters an anabolic state.

In muscle, on a dry weight basis the increase is of the order of 50 to 60%, but as the tissue is more hydrous the increase amounts to between 20% and 34% on a wet weight basis (table 22).

The tissue sodium is about 1380mg/kg. Thus, during the first 30 days when the moderately malnourished subjects are convalescent there is a need to *lose* this additional sodium at a rate of about *minus* 17.5mg/kg/d. The severely malnourished child is particularly sensitive to increased sodium intake and treatment of the malnourished child with diarrhoea presents a major problem [21]. However, because of their “sodium retaining state” the diarrhoea of the malnourished child contains less sodium than the stools of the normal child so that the stool losses in malnutrition are less than in the normal child. However, the diets based on the RNIs will be taken by the normal as well as malnourished children and also children after they have reversed their physiological abnormalities. An association between stunting and abnormal sodium homeostasis is unexplored. Nevertheless, if the normally nourished have less or no diarrhoea and also have normal physiology, then their sodium needs will be adequately satisfied by a diet that is suitable for the malnourished. It is also likely that sodium will be added to the diet extraneously as condiment.

Discussion

Table 23 shows the various needs computed for normal children, those with malnutrition and those with stool losses of 27 or 62mg/kg/d.

If only normally nourished children were to take the diet then the level could be set at a level that would improve the organoleptic properties and give some protection against diarrhoea. But the requirements for the moderately malnourished should be far less than that for the normal child. In areas where there kwashiorkor occurs in some children, the nutritional deficiencies and physiological changes that lead to the oedema in that geographical area appear in many of the wasted children, albeit to a lesser extent. The moderately malnourished in these areas should not be given high sodium diets.

The computed amount for a malnourished child with mild loose stools gaining weight at 5g/kg/d is almost the same as the nutrient density found in breast milk. This should be considered as an adequate sodium intake for diets for the moderately malnourished.

Nevertheless, a maximum level of about 550mg/1000kcal would also satisfy the normal child with mild diarrhoea who is not gaining weight, as well as the malnourished child with additional losses: it is twice the concentration found in breast milk. Higher concentrations should not be given in kwashiorkor areas or in children who are severely malnourished. It would be inappropriate to design a diet for moderate malnutrition that would be dangerous if taken by the severely wasted child.

An important further disadvantage to increasing the sodium is that it increases the renal solute load that will need to be excreted and thus increase the water requirement; this can be of major

importance in desert areas.

Water requirements

Renal solute load.

Water is an essential nutrient. It is required ubiquitously and there has to be sufficient both to excrete heat from the body and to carry excretory products in the urine. With insufficient water there is either heat exhaustion (fever) in a humid environment or hyperosmolar dehydration in a dry environment, or a mixture of both syndromes.

One of the main reasons why breast milk is low in protein and electrolytes is to maintain as low a renal solute load as possible. The renal osmotic load from breast-milk is 145 mOsm /1000kcal [241].

The fixed osmolytes that need to be excreted are mainly sodium, potassium (matched by their anions) and urea, with smaller contributions from magnesium, calcium and phosphate. In the non-growing individual none of these elements are stored in the body.

If 26g/1000kcal of protein is taken, of which 90% is absorbed, 135 mOsm/1000kcal urea will be generated; Similarly, potassium will give 82 mOsm/1000kcal, sodium 48 mOsm/1000kcal, and 12 mOsm/1000kcal from magnesium, including their associated anions. The magnesium will be given as an organic salt. There will be an additional load from phosphate and calcium, but this is relatively small³³ [242-245].

The total renal solute load that will be generated will thus be about 280 mOsm per 1000kcal (urea+cations+anions). Additional protein or electrolytes should not be added to the diet without ensuring that there is a sufficient water intake. The suggested diet provides about twice the renal solute load provided by human breast milk. Insensible water balance is dependent upon the temperature and the metabolic heat produced that needs to be dissipated – in general, at thermoneutrality, it is about 25g/kg/d, but rises exponentially as environmental temperature approaches or exceeds body temperature.

The renal concentrating ability is severely compromised in malnutrition, including moderate malnutrition and those that recovered on the older diets, so that the maximum that can be achieved by many children is about 400mOsm/litre [78]. If a young child is taking 100kcal/kg/d contributing 28mOsm that need to be excreted and losing 25g/kg/d water through insensible loss, then the minimum water that needs to be taken, if the urine concentration is not to go above 400 mOsm/l, is 100ml/kg/d. If only the diet is being taken the energy density cannot be higher than 1 kcal/ml without the danger of hypernatraemic/hyperosmolar dehydration and the protein and electrolyte concentration of the diet needs to be limited to levels that do not pose a threat of hypernatraemic dehydration/ water deficiency [244, 246-249]. Of course if additional water is taken with or after meals, the foods of the diet can be more energy dense. In other words, with this protein and electrolyte content, if the whole diet is in the form of porridge for feeding the children either the energy density must not rise above 1000kcal/litre of the wet porridge or additional water must be given. Even the addition of oil to the diet will not alleviate this need, as then less of the diet will be

³³ During rapid weight gain it is sometimes assumed that there is a substantial saving of solute load due to the osmols laid down in newly formed tissues. The “saving” is relatively small (0.9mOsm per g lean tissue); this is offset to some extent by failure to generate “metabolic” water from oxidation of ingested fat and carbohydrate (1.07ml/g and 0.55ml/g respectively) when it is deposited in tissue instead of being burnt. The reason why these children do not so readily develop hyperosmolar syndrome is that the increased dietary intake needed to sustain weight gain provides an increment of water over and above the “fixed” requirement for heat dissipation.

taken to satisfy energy needs and there will be less ingested water to excrete the osmolytes present in the diet.

If the temperature is above thermoneutrality (28°C to 32°C), the humidity is low, the subject has a fever, or the children are malnourished patients (in whom the ability to concentrate may not rise above 300mOsm/Litre) then either the energy density of the porridge needs to be reduced or additional water must be taken. These conditions of heat, low humidity and fever are very common in most places where moderately malnourished children occur. It is dangerous to attempt to make a diet excessively energy dense for feeding young children. In Tchad in May (daytime temperature 45°C, relative humidity <15%) the water turnover of the malnourished children was one third of total body water per day [123]. This is particularly the case in the infant of 6 to 12 months, where they cannot adequately indicate to the mother that they are thirsty rather than hungry.

The osmolarity of the diet itself is quite a different consideration from the renal solute load as both organic (e.g. sugar) and inorganic osmolytes contribute to dietary osmolarity. There also needs to be sufficient water mixed with the diet to reduce its osmolarity to a level that can be easily absorbed by the intestine of the malnourished child and will not provoke osmotic diarrhoea. One of the benefits of fat, as an energy source, is that there is no associated increase in the diet's osmolarity when fat is incorporated.

TYPE I NUTRIENTS

The considerations with type I nutrients are not the same as for type II nutrients. Here, the maintenance or replenishment of body stores and the specific functions the nutrients play need to be considered. The requirement for these nutrients is likely to be affected particularly by the environment and stresses to which the moderately malnourished child is exposed. These are likely to be quite different from those of a healthy Western child living in a clean, hygienic and safe environment.

Calcium

Although not a micronutrient calcium is nevertheless a type I nutrient and its metabolism and retention is not dependent upon the balance of the type II nutrients (see balance studies of Rudman et al [73]). Unlike phosphorus, if we only consider soft tissue regeneration, the requirement for calcium is extremely low. The vast majority of calcium is required for bone formation and the maintenance of bone health has not so far been considered in formulating diets for the malnourished wasted children. Nevertheless, all malnourished subjects have substantial osteoporosis [180, 181, 250]. Thus, although there is a considerable bony deficit that has to be made good, there is no substantial soft tissue requirement for calcium and this requirement has been ignored, partly because it is assumed that the requirements will be met from milk. The intracellular content is effectively zero and the extracellular level is normal in the malnourished. Even though this has not been considered when the requirements for phosphorus or magnesium were set, it is desirable that there is adequate calcium to maintain positive balance, and the phosphate: calcium ratio should be such that there is no danger of induction of hypocalcaemic tetany.

The total body calcium of even normal children living in the developing world is low and their diet is normally low in calcium [251]. Even though calcium may not be directly involved in promotion of longitudinal growth, it is vital to give adequate density to the bone and prevent deformity or calcium deficient rickets [252, 253] particularly when the diet or supplementary food is maize based [254]. It is clear that most moderately malnourished children have been subsisting on a diet with inadequate available calcium for a long time. The diet of these children needs to contain sufficient available calcium to replenish and allow normal bone density to be restored and maintained.

The amounts recommended by the authorities are shown in table 24. The IOM levels are considerably below those of either the FAO/WHO or the UK for younger children and higher for older children, with a different gradation from younger to older; the reason for this is unclear.

A phosphorus requirement of 900mg (29mmol)/1000kcal has been set (600mg if a food only based approach is used). If a low calcium intake were to be recommended then the calcium: phosphate ratio would be inappropriate.

It is appropriate that the calcium: phosphorus ratio is maintained within the range 0.7 to 1.3 for all over 6 months of age. Therefore 840mg (21mmol) /1000kcal of calcium should be included in the diet if the diet is to be fortified. This level will be impossible to reach with a food based approach that does not include animal milk or milk products. The recommendation for the intake that should be achieved if only local foods are used is 600mg/1000kcal.

The recommendation when a fortified diet is used is higher than the FAO/WHO recommendations for normal children. Such a level would give a molar ratio of calcium to phosphorus of 0.7 mol/mol, which is adequate. It is unknown if the food based recommendation will supply sufficient calcium to replenish bone mineral [255].

Food constituents such as oxalate which inhibit inorganic calcium absorption do not affect the calcium from milk [256]. Although in normal adults calcium from inorganic sources is as available as from milk [257], this is unlikely in children with limited gastric acid.

Nevertheless, excess inorganic calcium should not be added to the diet in an effort to overcome the inhibitory effects of phytate. Calcium phytate is a more efficient chelator of transition metals than phytic acid alone. The concentration of calcium in F100 is about 1000mg Ca/1000kcal; the severely malnourished children on this diet have an increased bone turnover [167] and non-oedematous children start to grow in length within a few days of starting the diet even though they still have a substantial weight deficit.

Iron

Of all the nutrients that are added to malnourished child rations, iron has received the most attention, and its nutrition has been extensively researched. The RNIs are based upon firm and extensive research data [10]. Most iron deficiency in the developing world is longstanding chronic deficiency. The diets of moderately malnourished children should not be used as a vehicle for delivery of *therapeutic* doses of iron to all moderately malnourished children to treat the severely anaemic. There are numerous programs of iron supplementation. They have not had the success of other deficiency elimination programs. Indeed, the management of iron status is tackled more satisfactorily by giving a balanced diet with all the other nutrients necessary for efficient iron utilisation and haemoglobin synthesis than simply by increasing the dose of iron. The results of one study on the Saharawi stunted children is particularly illuminating – anaemia responded, and severe anaemia was eliminated, by a more balanced diet [258]. The effect of adding riboflavin to the diet had a greater effect upon ferritin levels than increasing the level of iron to the therapeutic range [259-261]; it would appear that anaemia in the moderately malnourished is usually a multi-micronutrient disorder and not simple iron deficiency. There is evidence in the malnourished child of deficiencies of many haematinics: folate, cobalamin, riboflavin, pyridoxine, vitamin C, vitamin E, and copper; there are often high blood lead levels possibly due to the low phosphate levels in the

diet leading to increased absorption; there are frequently chronic infections, malaria and intestinal parasites; a proportion of children have haemoglobinopathies, or G-6-PD deficiency. Indeed, there are multiple causes of anaemia in the malnourished child. There are also metabolic effects that lead to unresponsiveness of the bone marrow [262] despite high levels of erythropoietin [263].

It is well known that iron deficiency is particularly common in the developing world. However, it is rarely appreciated that this mainly affects the normally grown children! In most malnourished children, including severe and moderate wasting and kwashiorkor the storage levels of iron in the children are *increased*, not decreased, even in the face of quite severe anaemia [264-273] and this appears to increase mortality [268, 274, 275], particularly if therapeutic iron is given [276]. There are therefore cogent reasons not to have a high iron nutrient density in the diets designed for the malnourished child, and particularly not in areas where kwashiorkor is common. It is a mistake to assume that the anaemia usually present in the malnourished child is due to simple iron deficiency alone. Treating non-iron deficient anaemia with iron or even anaemia due to multiple deficiencies with iron alone, in these circumstances may increase the mortality rate. It is for this reason that there is no iron added to F100, and efforts are made to keep the ingredients as low in iron as possible. This is because F100 is sometimes used in phase one of treatment when the children are acutely ill with low levels of iron binding proteins. For diets such as RUTF that are used exclusively during phase 2 of treatment *a modest* amount of iron is added to the formulation.

Nevertheless, iron deficiency is widespread in the normally nourished and mildly malnourished children. This is partly due to the poor obstetric practice of early cord clamping, thus denying the neonate a placental transfusion during the third stage of labour [277, 278]. Iron deficiency is also common in infants who are malnourished because they have been born prematurely or had intrauterine-growth-retardation and have not laid down adequate iron and copper stores during gestation. Further, the older ambulant child who has intestinal parasitic infection may be iron deficient. Thus, a fine balance has to be struck so that there is sufficient iron to ensure that mild deficiency is reversed and stores are replenished without causing toxic effects in those with replete or excess storage iron.

There are a number of other reasons for keeping iron densities in the diet modest.

First, inclusion of iron, being a redox active metal, dramatically reduces the shelf life of foods and causes rancidity and generation of free radical products in the food.

Second, high levels of iron not only cause the food to become rancid more quickly, they also destroy redox sensitive micronutrients in the food. Thus, a high iron level during cooking or prolonged storage will destroy a portion of the vitamin C [279], riboflavin and folic acid that are critical to the health of the malnourished child population.

Third, a high intake of iron in malarious areas is associated with an increased mortality [280]. Although this study did not examine “food iron” it would be prudent not to add high levels of iron to a diet designed for use in a malaria endemic area.

Fourth, apart from malaria, there is some evidence that excess iron, as well as iron deficiency is associated with increased infection [281], albeit most of the studies were conducted in malarious areas. Of the two conditions iron deficiency is probably the more damaging and certainly affects a higher proportion of the anthropometrically normal population. Thus, in recommending the level of iron a compromise has to be reached between the aim of treating those with some pre-existing iron deficiency and not either causing or exacerbating dietary vitamin deficiency (particularly scurvy) or giving excess to the malnourished or the iron replete within the population.

Fifth, iron overload also occurs in populations that ferment food in iron cooking pots [282]. It can

also occur in patients with haemoglobinopathies; these are common in malarious areas.

Sixth, iron readily forms complexes with selenium that are totally insoluble, particularly in anaerobic environments such as the intestine or some soils, and so high iron intakes may also precipitate selenium deficiency when its intake is marginal [283]. This nutrition-nutrient interaction does not seem to have been considered, in the list of detrimental effects of using foods designed for the moderately malnourished as a therapeutic vehicle.

Thus, balance has to be struck when setting the requirements for the moderately malnourished child.

Table 25 gives the iron requirements for normal children taking diets with various availabilities of iron (5% to 15%). As with zinc, if the diet is such that the iron is simply not sufficiently available, there is little point in adding high levels of iron to the diet in an effort to force some into the child; the correct strategy would be to increase the availability (or use a different strategy to give additional iron to those that need it). Availability has a dramatic effect upon iron requirements. It is not possible to set a single requirement. If it is assumed that the iron is 10% available then 8.9mg/1000 kcal would be required.

In view of the uncertainty of whether the iron content of the diet should be increased to treat anaemia, or decreased to avoid the deleterious effects, it is suggested that the RNIs for iron set by FAO/WHO for normal children should be applied to the moderately malnourished.

If the diet is to be fortified and the iron is of low availability then 18mg/1000kcal should be present, however, diets with low iron availability should not be formulated for treatment of the moderately malnourished wherever possible. For a food based approach, and for most formulated diets, it is important that the basic ingredients are such that the iron is more available, in which case a level of 9mg/1000kcal should be used.

For special groups such as pregnant women it is difficult, from a poor diet, to achieve a high enough iron concentration to satisfy their RNIs. The diet will then be potentially toxic for the malnourished child particularly in a malarious area, and particularly if therapeutic doses of iron are given from another source so that the cumulative intake from all sources becomes excessive. The levels of iron in the diet should not be such that children who are enrolled in programs for the treatment or prevention of iron deficiency get a “double dose”. It would be better if an alternative strategy was used for groups with particularly high requirements such as using micronutrient powders or spreads that should contain high levels of all haematinics. Special groups and using food as a therapeutic vehicle should not be a consideration in formulating dietary recommendations for general use by moderately wasted or stunted children with respect to iron any more than the other nutrients whose deficiency is common.

Thus, with respect to iron no special provision need be made for the malnourished, those with diarrhoea, an infection or for convalescence from illness.

The form that the iron is present in the food is important. Iron destroys many vitamins that are vulnerable to oxidation including as vitamin C, and it greatly decreases the shelf life of the product. For these reasons it is strongly recommended that the iron should be physically encapsulated (using encapsulation material that is removed in the intestine of the moderately malnourished) or be in the form of amino-acid complexes or iron-EDTA, which is now commercially available and has undergone successful trials. Iron EDTA is less prone to matrix effects of the diet and, as important, is less prone to redox cycling. The additional cost of the iron in these forms, or encapsulated, is offset by the lesser amount of iron that needs to be added, the longer shelf life of the product and the fact that lower amounts of the vitamins need to be added to compensate for storage losses.

The only other important redox metal is copper. The same considerations apply to copper that is added to the diet in terms of using a stable but available chelate and exploring microencapsulation

technology³⁴. Zinc, although a divalent transition metal, is not redox active and does not pose this problem.

Copper

Copper deficiency affects about 25% of malnourished children [284]. Clinical copper deficiency occurs particularly in the Andes [285]. Copper deficiency causes anaemia, neutropenia and osteoporosis and is critical for collagen maturation. Deficiency is particularly associated with persistent diarrhoea. Malnourished children who receive adequate copper are less likely to get an infection during recovery [286].

On the other hand, copper toxicity used to occur in some parts of India and Bangladesh where milk is fermented in brass vessels which can release sufficiently high levels of this element to produce cirrhosis of the liver [287, 288]. This no longer is a common problem as most cooking vessels now used are aluminium and should not be a consideration in formulating the diets. Animal milks, including human milk, are particularly low in copper (if given exclusively to experimental animals they get clinical copper deficiency). Physiologically, infants are born with a large store of copper in their liver³⁵; its function is to provide sufficient copper to last from birth to weaning. Breast-milk content of copper is not an appropriate guide to copper requirements. Iron and copper may be particularly low in human milk in order to control the colonisation of the intestine of the child [81]; if this is so then high copper (and iron) levels may have an adverse effect by promoting small bowel bacterial overgrowth, a problem with all malnourished children and those with chronic diarrhoea.

In contrast to iron, copper availability is adversely affected by vitamin C (it is the cupric species that is absorbed and reduction to cuprous copper makes it unavailable). Copper absorption is also inhibited by intakes of zinc sufficiently large to induce a mucosal block in the intestine due to the induction of metallothioneine³⁶ and large doses of zinc have led to clinical copper deficiency. In general the molar ratio of copper to zinc in the diet should be about 1:10 to prevent zinc induced copper deficiency³⁷ and should not fall below 1:20³⁸.

Copper is also a redox active metal and large amounts will adversely affect the shelf life of products and potentially destroy redox sensitive vitamins. Although the molar activity of copper in this respect is higher than that of iron, because it is present in relatively small amounts the effect is less important than the redox action of iron.

The RNIs are shown in table 26. There is no FAO/WHO recommendation. The level set by the IOM and the UK is between 300 and 500 micrograms. However, with a recommended zinc intake of 20mg/1000kcal then if a ratio of 1:10 is to be achieved the intake of copper would need to be increased considerably above the recommended RNIs. This is excessive, and certainly should not be used in areas where there is abundant adventitial copper in the diet or water.

In view of the common occurrence of persistent diarrhoea in moderately malnourished children, the

³⁴ Indeed, chemically copper is a more potent redox agent than iron, but is normally present in lower concentrations so that its overall pro-oxidant effect is less.

³⁵ In a special foetal protein called mitochondriocuprin

³⁶ Metallothioneine is exceptionally rich in sulphur amino-acids; their relatively low levels in malnutrition may limit its synthesis and ameliorate the interaction in these circumstances.

³⁷ Whether the reverse interaction occurs, also due to metallothioneine induction is unknown.

³⁸ This will normally occur temporarily when zinc supplements are given to children after diarrhoea, when additional copper is not part of the recommendations; such treatment should not be prolonged and may be ill-advised in areas where copper deficiency is common.

relatively high prevalence of copper deficiency in the malnourished and the lack of any programs where additional copper is likely to be added to the diet, it is proposed that the **copper density be set at 890 micrograms/1000kcal for a fortified diet, and at 680 micrograms/1000kcal for a food based approach.**

This will result in a zinc: copper ratio of about 1:19 which should avoid zinc induced copper deficiency, and provide sufficient to allow for repletion of stores and correction of copper status in malnourished children. It is important to note that the upper limit for zinc set by the IOM has been established to prevent zinc induced copper deficiency. It is critical that adequate copper is present in the diet to avoid this interaction.

Molybdenum in the diet, particularly in the presence of sulphur containing amino acids or other sulphur compounds renders copper totally unavailable by precipitation as copper thiomolybdate in the lumen of the intestine [289, 290]. Indeed, soluble thiomolybdates are now used as a drug to treat copper toxicity in animals and remove copper from the liver in humans with Wilson's disease. A high molybdenum intake has been associated with clinical copper deficiency in farm animals and in humans. One of the main determinants of copper status will be the dietary molybdenum intake. In turn, molybdenum availability from the soil is dependent not only upon the levels in the parent rocks and but also on the water level in the soil. In India, when a new hydroelectric scheme altered the water table and made molybdenum more available, there was widespread copper deficiency induced in the human and animal population (personal communication, Colin Mills). Care must be taken when formulating the requirements that excess molybdenum is not present to precipitate copper deficiency in those who already have a marginal copper status particularly as it is recommended that a diet rich in sulphur amino acids should be used. On the other hand molybdenum is an essential element and sufficient has to be present in the diet (see section on molybdenum).

Selenium

Selenium has been largely ignored in setting malnourished child rations; there have been fears about its relative toxicity at high levels.

That its inclusion has been overlooked is unfortunate as selenium deficiency has been found to be very common wherever it has been sought. The selenium content of foods is dependent upon the soil in which the plant was grown and many areas have low levels of selenium in the soil³⁹, so that all plant foods which are grown in that neighbourhood will be low in selenium. Although in the same class of the periodic table as sulphur, the chemistry of selenium is quite distinct. The soil chemistry of selenium is critical in this process. As the soil Eh (reduction-oxidation potential) goes from an oxidising to a reducing state selenate is progressively reduced from selenate to selenite, to inorganic selenium and then to selenide. Selenide and inorganic selenium are completely insoluble and not available. Thus, wet soils where there is a high water table or a lot of organic matter (both of which reduce the Eh) are almost all selenium deficient – this applies to much of the wet tropics.

Second, there is an interaction between iron oxides in soil and selenium to bind and precipitate any selenium into insoluble complexes. "Red" soils are particularly likely to be selenium deficient – again this applies to much of Africa (see ref [283] for a full description of selenium soil chemistry with references).

³⁹ Particularly Keshan Province of China where the deficiency causes Keshan disease. Low soil levels have affected farm animals and humans in many countries including New Zealand, Finland, parts of the UK and USA. Most of the developing world has not been surveyed. In Jamaica free range hen's eggs were used as a proxy for environmental selenium deficiency, this was found to be widespread [291].

Third, like iodine, soluble selenium in the soil is readily leached to levels beyond the roots of crops and any place that has iodine deficiency is also likely to have selenium deficiency unless the parent rock is seleniferous (e.g. parts of Venezuela). Selenium deficiency has been found in Central America, the Caribbean, Southeast Asia, West and Central Africa, and China [292-295]. It is likely that selenium deficiency is widespread in the developing world. Particularly low levels probably occur in the Congo Basin where even maternal milk is sufficiently low in selenium to have cause selenium deficiency in fully breast-fed infants; the milk samples have no antioxidant power at all [296].

Selenium is important for several reasons.

First, it is central to the ability to withstand oxidative stress –the main enzymes necessary for this (glutathione peroxidases) are selenium dependent. In kwashiorkor there is evidence of an acute selenium deficiency prior to development of the disease, and the selenium status is closely related to prognosis [275, 297]. It is speculated that ensuring an adequate selenium status of the malnourished child could prevent kwashiorkor, although one study failed to prevent kwashiorkor in Malawi [298]. The malnourished children are all exposed to increased oxidative stress coming from infections and smoke pollution, quantitative evidence for this increased stress comes from the high level of mercapturic acids (the detoxification products of radical damage) in the urine of the malnourished [124]. Therefore an adequate selenium intake is critical for children's protection.

Second, selenium, through a compound know as thioredoxin, is responsible for the maintenance of the redox state of cells [299]. Without adequate functioning of this compound most of the control processes in the body are compromised [300]. This includes the leakage of sodium into cells and potassium out of cells as well as cardiac and renal function. Indeed, it is postulated that many of the differences between the reaction of a malnourished child to an infection and that of a well fed westerner (for example measles mortality) may be related the selenium status of the individuals [297]. Of particular interest is the finding that selenium added in vitro increases the thioredoxin and this can reduce HIV virus replication rate up to ten fold [301].

Third, selenium is responsible for the conversion of thyroid hormone (T4) to its active metabolite (T3). Where there is combined iodine/selenium deficiency massive goitres occur whereas with iodine deficiency alone the goitres are smaller [302]. Such large goitres are predictably characteristic of much of Africa. Large doses of iodine can overcome lack of the T3 hormone even in the face of a selenium deficiency, but where the intake of iodine is marginal then selenium status becomes critical in determining the extent of the physiological damage. Iodine deficiency is widespread; the extent to which this is due to, or exacerbated by, co-existing selenium deficiency has not been adequately investigated.

Fourth, perhaps the most important reason for paying particular attention to selenium status is its role in viral infections. It has been shown in animals and confirmed in humans, that if a selenium deficient individual acquires a viral infection (coxsackie virus was the first to be studied as it's increased pathogenicity is the cause of Keshan disease) the virus is likely to undergo a mutation, in the host, to produce a more virulent strain of the virus [303, 304]. This will then be passed to the next individual who contracts a more serious form of the disease. Indeed, this is another possible reason why the measles that is found in the developing world is more likely to kill than that found in the Occident. This is an active area of current research. The results of these experiments provide a rationale for why flu pandemics of new virulent strains arise almost exclusively from the swine and ducks fed together in the selenium deficient areas of China. It might be one reason why the HIV virus has mutated in Africa to give virulent strains that are of global concern. It could be such mutations that give animal virus the ability to cross the species barrier. Also selenium deficiency may be a reason why resistance to antibiotics and anti-malarials arise quickly in some areas and

why “new” epidemics of “exotic” diseases seem to arise spontaneously and particularly in Central and Western Africa and Southern China. The veracity of these speculations is being confirmed by current research [305-316]. Selenium deficiency not only causes mutation in viruses but also in bacteria such as *Mycobacterium tuberculosis*. Resistant strains and the progression of HIV infection are now thought to be intimately related to selenium status. However, in the past few years these new findings are sufficiently well documented to make translation into a public health policy a priority, particularly as selenium deficiency is widespread and has many other major detrimental effects. A malnourished population, living crowded together in unhygienic environments and eating a selenium deficient diet is precisely the situation where such virulent strains of infective disease could arise. Even in normal British Adults, selenium supplementation with 100µg/d augmented their immune function, led to more rapid removal of polio virus (vaccine strain) from the blood and lower mutation rates of the polio virus [317].

Fifth, in some areas of the world, such as Bangladesh, the digging of tube wells has led to an epidemic of arsenic poisoning. Selenium is the natural antagonist of arsenic; when present they are both excreted in the bile as an insoluble complex [318-324]. High doses of selenium can be used to treat arsenic poisoning and vice versa. It is possible that the high prevalence of arsenic poisoning in Bangladesh and India, when the arsenic content of the water is not enormously high, is related to coincidental selenium deficiency. Perhaps we could use the observation of arsenic poisoning as an indication that selenium deficiency is also widespread in the Indian subcontinent. Furthermore, any arsenic in the water or food will greatly exacerbate an existing selenium deficiency. In areas where this is a potential hazard it is important to have a high selenium intake in the diet. Such considerations may underlie the lethality in some locations of arsenic containing drugs used to treat trypanosomiasis (sleeping sickness) [325].

The grains from some parts of the USA, particularly maize, are largely selenium deficient [283]. It is perhaps important that none of the foods designed to treat moderately malnourished children have had selenium added to them. Selenium is normally omitted from the specifications and is not normally measured or assayed. It is now clear that this is a critical omission.

Table 27 gives the RNIs for selenium. The level for young children from the IOM is twice that given by FAO. The reason for this discrepancy appears to be the difficulty in assessing selenium status of a normal population or individual. The level that is present in F100/RUTF is 55µg/1000kcal. This is because selenium deficiency is so common in malnourished children and the fact that they have active infections, nutritional immuno-incompetence and are living in highly stressful environments; such nutrients are likely to have a higher requirement for those in the developing world than those studied in safe clean environments. It is not at all clear why such low levels were set by the FAO committee and why that committee reduced the levels previously recommended by the WHO/FAO consultation [6]. Human milk levels vary considerably, depending upon the mother’s selenium status. As such human milk concentrations cannot be used as a guide unless we are sure that the mothers’ selenium status was adequate at the time of sampling. The average is about 29 µg/1000kcal.

The selenium content of many of the foods and ingredients currently used to treat moderately malnourished children is low. Furthermore, there are major gaps in food composition tables with selenium concentrations rarely quoted; this is partly because of the high variability of plant selenium content, which is dependent to a large extent upon the availability and concentration of selenium in the soil in which they were grown.

Excess selenium is excreted in the urine. The availability of selenium is quite variable depending upon whether it is given as inorganic or organic selenium. Selenomethionine, found in selenized

yeast is often used to supplement diets because of its low toxicity. However, its metabolism is completely different from both inorganic selenium and methionine in the malnourished child [326]. Selenomethionine may fail to treat acute selenium deficiency in animal studies. Furthermore, the same chemistry that occurs in soil can occur in the intestine; selenium can be precipitated in an anaerobic intestine with bacterial overgrowth (highly reducing conditions); this accounts for the very high dietary selenium requirements of ruminants in comparison with monogastric animals. A high iron intake may also cause the precipitation of inorganic selenium in the intestine and induce selenium deficiency, with the attendant metabolic complications.

In view of the recent research, the special vulnerability of the malnourished child and the lack of any other public health initiatives to combat selenium deficiency, it is **recommended that the diet contains 55 micrograms/1000kcal of selenium for a fortified food approach (the same level that is contained in RUFT and F100), when a food based approach is used the IOM level of 30 micrograms/1000kcal can be used.**

Selenium nutrition and status should be the most active area of research in moderately malnourished child health so that these figures can be amended in the light of any new findings. The level of 55 µg/1000kcal present in F100 is safe and does not lead to high plasma levels of selenium.

There may be concern, if these recommendations are to be used in areas where the bed rock and plants are high in selenium (e.g. some parts of Venezuela). When we consider the nutrient content of foods in terms of nutrient: energy density, it is clear that this problem is not of major concern. Thus, the selenium: energy ration of the habitual foods of the population living in seleniferous areas will far exceed the densities proposed. So, when a fortified food, containing the recommended densities of selenium is taken in place of a local food, the total intake of selenium will fall⁴⁰.

It is clear that for children living in a polluted, contaminated environment the selenium status is more critical than for healthy children living in a clean unpolluted country.

Iodine

Iodine deficiency is recognised to be widespread throughout those areas where malnourished children are commonly found. There are a number of highly successful public health measures that address this problem, particularly iodisation of salt.

There is a large store of iodine in the body so that those who are deficient have normally subsisted on a locally grown iodine deficient diet for a long time. There should be no attempt to have sufficient iodine in the requirements to provide therapeutic levels for the chronically deficient. Sudden intake of large doses of iodine in the face of longstanding deficiency can precipitate thyrotoxicosis. On the other hand, it is dangerous to rely on one source of iodine and have all the other foods in the diet devoid of iodine as some within the population may not take or receive iodised salt. In principle, we should aim at diversification of the dietary sources of essential nutrients with no single item having such a high level that, if taken exclusively, would lead to toxicity or “double dosing”. The whole idea of expressing the nutrient requirements as a density is so we can design a diet which is balanced, with, if possible, several food items contributing significant amounts of each essential nutrient. Thus, iodine should be present in the diets and foods taken by the moderately malnourished at a level that will give a normal iodine intake when the foods are ingested to meet energy requirements. Any iodine that comes from the salt will then be in

⁴⁰ The same argument applies to copper content of fortified foods given in Bangladesh or India.

addition to this “normal dietary” level and will help to alleviate overt iodine deficiency without the danger of excess supply. In other words, the fact that salt is being fortified with iodine is *not* a reason for omitting iodine supplementation from formulated diets for the moderately malnourished.

The recommended intake of iodine is particularly high for the infant. The FAO/WHO and IOM committees have recommended that this particular group should have a density of iodine that is more than twice that of the other groups (table 28). This may be partly in view of the recognised widespread deficiency and partly to compensate for the low levels in the breast milk of iodine deficient mothers.

However, in view of the widespread occurrence of iodine deficiency, the need to satisfy the infant from 6 months and the fact that the 6 to 12 month old infant is not likely to be fed a family meal to which distributed fortified salt has been added, it is **proposed that the RNI for the moderately malnourished should be set at 200 micrograms/1000kcal Iodine.**

For a food based approach to treating the moderately malnourished the iodine level in salt should be taken into account. However, for a fortified complementary food approach, iodine should also be incorporated into the diet at the recommended nutrient density, irrespective of whether iodised salt is available in the area. The level recommended will not lead to thyrotoxicosis even if modest amounts of iodised salt are taken along with the fortified food. F100 contains 190 µg/1000kcal and human milk from an iodine sufficient population about 170µg/1000kcal.

Thiamine

Thiamine requirements are traditionally closely linked to energy and calculated as a nutrient density before converting to absolute units. This is because thiamine is the major cofactor in both pyruvate metabolism and for the hexose monophosphate shunt.

Its deficiency gives rise to wet, dry or Shoshin beri-beri and Korsakoff/Wernikes syndrome in adults; the corresponding syndromes in children are meningo-encephalitis, aphonic beri-beri and cardiac failure. Deficiency is particularly found in poor populations that have been eating polished rice. Its concentration in breast milk rises and falls with the status of the mother, so that fully breast fed infants can die from thiamine deficiency when the mother is symptomless. Many of these deaths are misdiagnosed [327].

Deficiency is not related to anthropometric status and fat people become thiamine deficient as readily as thin people. An anthropometric survey of the population will not warn of potential problems with thiamine status and the anthropometric status of the breast-feeding mother does not relate to the risk to her child. Deficiency is particularly likely in adults with a high alcohol intake which may affect breast milk being taken by malnourished children.

Thiamine in food is unstable at neutral and alkaline pH and it is readily destroyed by oxidation (iron) and heat [9]. Cooking typically leads to losses of up to 60%. It is particularly susceptible to destruction by sulphite and chlorine. Sodium hypochlorite (or metabisulphite) is commonly added to water and food used to prepare meals for malnourished children as disinfectant; if this water is used to prepare the food, without prior exposure to air, the likelihood of thiamine deficiency is increased. A high intake of sulphate, which can be reduced to sulphite by bacteria in mouth and the intestine, can also compromise thiamine status. Sulphites are added as a preservative to foods and beverages; they will destroy the thiamine. The same process occurs in contaminated food, and

fermentation of rice can lead to removal of the tiny amount of thiamine present. Raw fish and some bacteria contain enzymes that destroy thiamine. Betel nut also contains a thiamine antinutrient so that betel nut chewing as well as eating raw fish will magnify the chances of thiamine deficiency [328].

The biological half life of thiamine is 9 to 18 days. Malnourished children that start with a poor thiamine status are likely to become overtly deficient within two weeks.

Thiamine is not toxic even in very high doses.

The recommendations are generally for between 400 and 500 μ g/1000kcal. There is little spread between the authorities, this is probably because they all relate thiamine requirement to energy intake in the same way (table 29). The FAO/WHO recommendation for normal 1 to 3 year old children is 523 μ g/1000 kcal. F100 contains 700 μ g/1000kcal.

Many of the moderately malnourished children treated using these recommendations are likely to be in rice eating populations, who will be already depleted. It would be prudent to ensure that the malnourished children have more than the levels recommended for normal children.

If allowance is made for a 60% loss during preparation of meals for malnourished children, it would also be prudent to raise the levels of thiamine substantially. Thus, when a complementary or fortified food program is to be used it is **recommended that the requirements should contain 1000 micrograms/ 1000kcal. When a food based approach is used the levels should be above those for a healthy child; it is proposed that the diet contain 600 μ g/1000kcal.**

Riboflavin

Meat, milk and green leafy vegetables are the main dietary sources. These foods are not taken commonly or sufficiently by malnourished children or many poor people. Biochemical evidence of riboflavin deficiency is common; in Jamaica 80% of "control" children failed to meet the international standards for riboflavin sufficiency [329] and similar results have been found in most developing countries [261]. In India, Indonesia, and elsewhere, riboflavin deficiency is a major cause of mild anaemia and haemoglobin levels do not return to normal with iron alone in these populations without the administration of riboflavin, needed for iron utilisation. Riboflavin deficiency is also a cause of poor intestinal absorption [330, 331].

Unfortunately the clinical signs of severe riboflavin deficiency are not pathognomonic. Riboflavin is essential to the metabolism of carbohydrates, amino acids and lipids. It is also the critical co-factor in glutathione reductase, an enzyme that is essential for the protection against oxidative stress. Any population that is exposed to excess oxidative stress needs additional riboflavin. Epidemic severe riboflavin deficiency has occurred in Bhutanese malnourished children in Nepal, where large numbers of subjects developed classical overt riboflavin deficiency.

Riboflavin is heat stable and little is lost during cooking. However, it is very susceptible to destruction by exposure to light or any other free radical process. Thus, not only is it important in those exposed to oxidative stress, but oxidation either in food or in the body will greatly increase the loss of riboflavin. As with vitamin C, this may have been partly related to destruction during cooking from the high iron in the diets.

There is remarkable consistency across age groups, physiological states and different committees in

the recommendations for riboflavin (table 30), with levels around 600 µg/1000kcal for normal people living in uncontaminated environments.

Normal subjects who were fed 550µg/d (approximately 250µg/1000kcal) for four months developed overt clinical signs of deficiency [332, 333]. This early work on human deficiency shows that the margin between adequacy and clinical deficiency is quite narrow and approaches the IOM value for 4-8 year old children when allowance is made for a 10% standard deviation. It is possible that with more stringent ways of assessing the needs to remain healthy that these figures will be increased. Most committees are reluctant to raise the RNIs to higher levels because so few “apparently healthy” individuals would then meet the requirements; however, wherever investigations have been carried out there is a high prevalence of biochemical deficiency in apparently healthy people. Furthermore, the role of riboflavin as part of the antioxidant repertoire has not been adequately assessed and as more sensitive ways of assessing status are developed it is anticipated that the RNIs will be increased.

Most of the present products used to treat the moderately malnourished have well in excess of the committee’s requirements (800 to 3000µg/1000kcal). Because of riboflavin’s critical role in oxidative stress RUTF/F100 has 2000µg/1000kcal. Other nutrients that are important for oxidative protection and whose half life has been measured show a dramatic increase in turnover with even mild oxidative stress, the most compelling example being the effect of smoking on vitamin C turnover (see vitamin C section).

The moderately malnourished are exposed to considerable environmental and infective oxidative stress compared even to smokers in the USA, and many will be recuperating from illness. Furthermore, the margin of safety between the levels that cause overt deficiency and the estimated average requirement is narrower for riboflavin than for most other micronutrients.

It is recommended that the level of riboflavin be set at 1800µg/1000kcal for the moderately malnourished when a fortified food approach is used (riboflavin is non-toxic even in very high doses and is relatively inexpensive). When a food based approach is used for the moderately malnourished the RNI for healthy children is inadequate and a level of 800µg/1000kcal could be used.

Niacin

Deficiency of Niacin is particularly associated with a maize based diet. Recurrent epidemics of pellagra have occurred in Mozambique, Angola and elsewhere in the recent past [334-339]. Niacin nutrition is likely to be, at best, marginal over much of Africa where maize is the staple food and the population do not use the alkalising culinary techniques of Central America. It should be emphasised that pellagra is not simply due to a lack of niacin in the diet. Rather, it is a multi-nutrient deficiency syndrome where insufficient conversion of tryptophan (protein) to niacin occurs and there is not sufficient preformed niacin in the diet to compensate for this inadequacy. The conversion is sensitive to tryptophan, pyridoxine, riboflavin, iron and zinc status, so that a person with pellagra is likely to be marginal or deficient in several nutrients. Indeed, there is still uncertainty about the exact dietary deficiencies that lead to some outbreaks of pellagra [340]. Although about 60mg of tryptophan will give rise to 1 mg of niacin, there is a large inter-individual variation in the efficiency of this conversion, the hormonal/genetic/biochemical basis of which is incompletely understood. Although pellagra can be treated with therapeutic doses of niacin, this conversion is vital to maintain niacin status with the normal dietary intakes; few individuals could survive on the levels of preformed niacin found in foods. Thus, individuals with a perfectly

adequate niacin intake, but a deficiency of tryptophan, develop pellagra⁴¹. For this reason there is uncertainty about the total amount of niacin required for normal metabolism, the commonly used conversion factor of 60mg tryptophan generating one mg of niacin and the extent of inter-individual variation (particularly in females and in pregnancy); they do not have a sufficiently firm experimental basis to set population requirements confidently. How these parameters are affected by malnutrition appears to be unexplored. Milk, which is low in preformed niacin, quickly relieves the symptoms of pellagra, presumably because of its tryptophan content.

The typical skin lesions are caused by lack of antioxidant protection against UV-light energy (a free-radical initiator); this is thought to be because of inability to regenerate sufficient of the niacin derived compound, NADPH. Apart from the other nutrients involved in the conversion of tryptophan to niacin, riboflavin and thiamine are also critical in the regeneration of NADPH; furthermore, most of these patients have insufficient compensatory skin protection from the other antioxidants, so that the appearance of the skin lesions in pellagra is more complex than simply niacin and tryptophan metabolic defects. The importance of this is that there can be actual niacin deficiency, affecting many other bodily functions, without the typical skin lesions if the skin antioxidant defences are otherwise adequate or sunlight exposure is minimal. Typically, the skin which is not directly traumatised by the sun looks and feels entirely normal.

The nutrients implicated in pellagra are type I nutrients, with the exception of zinc and tryptophan, so that an anthropometric survey will not inform us of the pre-existing status of the children in the area of the malnourished. Indeed, when switched to a “pellagrigenic” diet, it has been observed that fat people tend to show symptoms before thin people. In a family, adults, particularly females⁴², tend to get the skin lesions. The other family members, who eat the same diet and have similar niacin: energy requirements are not so diagnosed, indeed the lesions which constitute the “case definition” are said not to occur in younger children. Thus, children and others may be susceptible to the other features of niacin deficiency (namely diarrhoea and a cerebral dysfunction similar to dementia) without showing the classical skin lesions that are central to the case definition and clinical recognition. A further complication is that the skin lesions are similar to those of kwashiorkor (indeed kwashiorkor was at one time termed “infantile pellagra” e.g. [344]).

It is unknown how frequently diarrhoea in children, in areas and families prone to pellagra, is due to niacin deficiency rather than infection, but the possibility that the symptoms of deficiency are quite different in children and that at least some of the cases of diarrhoea are misdiagnosed need to be entertained. If this were so, then the prevalence of niacin deficiency and the public health measures that should be instituted would be more important than currently assumed.

Niacin is stable during storage and to normal methods of food preparation (moist heat). It is present in many foods covalently bound to small peptides and carbohydrates and not released by digestion so that the availability is normally only about 30%. Alkaline heat hydrolysis of the covalently bound niacin improves availability.

The RNIs are consistent across the age and physiological states with between 6 and 7mg/1000kcal being required by normal healthy children (table 31).

Higher amounts are added to foods used for rehabilitating the moderately malnourished. Because of the frequency with which maize is the staple food of malnourished children and that maize itself

⁴¹ This occurs in Hartnup disease (renal loss of amino acids) and with carcinoid tumours (consumption of tryptophan to synthesise serotonin, the product of his tumour) both of which result in increased tryptophan loss from the body but have no influence on preformed niacin metabolism.

⁴² Female sex hormones reduce the conversion of tryptophan to niacin [341-343]. It is likely that the conversion factor of 60mg tryptophan: 1mg niacin, is less efficient for post-pubertal females and is particularly compromised in pregnancy.

is often a basic ingredient in many diets used for the moderately malnourished (CSB, UNIMIX), the levels for these children should be substantially above the requirements for normal children. F100 has 10mg/1000kcal, but also contains high quality milk as its base with adequate levels of tryptophan.

The tryptophan levels are important in consideration of the levels of niacin to have in the diet. The requirements for normal children were set by the IOM and FAO/WHO on the basis that normal healthy children would receive high quality protein and milk in their diets; this is often not the case with the diets taken by moderately malnourished children.

It is therefore recommend that there should be a threefold increase in niacin for the moderately malnourished child, to 18mg/1000 kcal if a fortified food approach is used. For a food based approach the FAO/WHO level for 4-6 year old children should be increased by about 30% to 8.5mg/1000kcal. This level is approximately the level set by the UK DRV committee and should allow for the replenishment of niacin stores.

Pyridoxine

Pyridoxine is mainly used for the metabolism of amino acids. There have not been reports of clinical deficiency in malnourished children. This may be because the clinical symptoms of pyridoxine deficiency can all be ascribed to other causes (seborrhoeic dermatitis, anaemia, fatty liver, mouth lesions, neuropathy, seizures and mental changes) and there are no pathognomonic features. On the other hand each of these clinical features is commonly encountered in paediatric practice in Africa and elsewhere in the developing world. Thus, the most likely reason for a lack of clinical recognition is that deficiency has not been sought. Of great interest, one study of the breast milk pyridoxine in Nepalese women showed it to be about 10% of American women [345, 346]. Thus, there may be widespread unrecognised compromised pyridoxine status.

Animal sources of pyridoxine are highly available, but, in plants, a variable proportion is in the form of glycosides (rice 20%, wheat 28%, beans 15-57%). These forms are not as biologically available (there is controversy about the precise availability in humans, but it may be low). However, the presence of these glycosides in food or in the intestine even reduces the availability of free pyridoxine from other sources, possibly by blocking transport processes. For example, the pyridoxine of wheat bran is largely unavailable in the form of glycosides; adding wheat bran to food reduces the absorption of all the pyridoxine in the diet. These are the probable reasons for the low levels found in Nepal and elsewhere where whole grain is used as the basis of the diet. It is possible that all populations subsisting on whole cereals and beans have a poor pyridoxine status. The biological half life of the pyridoxine pool is about 25days. There are no convenient field tests of pyridoxine status, so that, with the lack of clinical signs its deficiency is normally not recognised.

Of importance, pyridoxine status may affect the behaviour or both the mother and the infant, a low status is related to poor mother-infant interaction [347]. Abnormal behaviour is frequently seen in both malnourished infants and their mothers, if this is partly due to deficiency of a simple vitamin, its supplementation would make a substantial difference to the success of programs aimed at improving the care of infants and children.

Pyridoxine in food is stable under acid conditions, but breaks down when in a neutral or alkaline matrix (the conditions that make niacin available). The losses in cooking vary from 0% to about 40%. However, pyridoxine hydrochloride, the normal food additive is remarkably stable and little loss occurs.

The requirements are fairly uniform across the committees and age ranges compared to other nutrients, the highest for normal people being that of FAO/WHO (table 32).

The levels that have been put into malnourished children's foods are much higher than these values. This is appropriate because 1), there is likely to be a pre-existing deficiency in those whose intakes have been largely from whole grain cereals (nearly all the developing world) and pulses ; 2) the breast milk pyridoxine is low in the beneficiary populations wherever it has been measured; 3) from most diets the availability will be lower than that assumed by the committees making recommendations for developed countries; 4) any cases that do occur will not be correctly diagnosed so that deficiency will be unrecognised; and 5) the body stores of pyridoxine are depleted in the moderately malnourished child and they should be made good. If the child will subsequently be eating a diet based upon maize, beans and oil the pyridoxine status may become precarious; and 6) the matrix of foods used to supplement the diets of the malnourished frequently adversely affects pyridoxine bioavailability. These are not considerations pertinent to the committees that set the RNIs for healthy Western children.

Thus, similarly to the other water soluble vitamins, it would be prudent to substantially increase the pyridoxine intake of the moderately malnourished child.

It is recommended that the requirement be set at 1800 micrograms (1.8mg) of pyridoxine per 1000kcal for a fortified food approach. Where mixed diets are being designed from local foods a level of 800 µg/1000kcal should be adequate unless the children are receiving milled whole cereals in which case the level should be increased to 1000 µg/1000kcal.

Cobalamin (Vitamin B 12)

Vitamin B12 does not occur in plants. The populations where moderate malnutrition is common are almost entirely vegetarian by necessity. Surprisingly, the circulating levels of B12 in severely malnourished children are not low [294, 348-353]. This may be because concomitant liver injury releases cobalamin into the circulation [353, 354]. The levels have not been examined with modern methods, and liver stores have not been measured. Ruminants get their vitamin B12 from bacterial and protozoal synthesis in the rumen. Synthesis of vitamin B12 may be one beneficial effect of small bowel bacterial overgrowth when the dietary intake is very low [355, 356], but intestinal bacteria also convert dietary B12 into nutritionally inert metabolites [357, 358] so that the net effect of small bowel bacterial overgrowth is normally detrimental.

There are normally large stores of vitamin B12 in the liver so that clinical deficiency can take many years of depletion to develop in adults. However, of concern, is the finding that the breast milk levels in Guatemala were low [359]. As with pyridoxine, there seems to be behavioural changes in the mother-child relationship with B12 deficiency [360]. Young children of deficient mothers often have depleted liver stores and are more anaemic than those of normal mothers. The diets that are usually given to malnourished children are almost devoid in vitamin B12. Because of its long half life many consider that vitamin B12 status will remain stable over the course of treatment of moderate malnutrition. This is to ignore the likelihood of a pre-existing marginal vitamin B12 status with a vegetarian mother and an exclusively cereal based diet for the child. It would be prudent during treatment of moderate malnutrition to ensure that there are adequate liver stores established to maintain the child until family food containing animal products is taken.

Vitamin B12 has a complex absorption that requires a complexing protein secreted by the stomach; the complex is absorbed in the terminal ileum. Any atrophy of the stomach or disease of the ileum

compromises vitamin B12 absorption, so that patients with malabsorption frequently present with vitamin B12 deficiency [361]. Malabsorption causes vitamin B12 deficiency much more quickly than dietary deficiency because the entero-hepatic circulation of vitamin B12 is disrupted. For these reasons it is necessary to have adequate vitamin B12 in the recommendations for moderately malnourished children, despite the long half-life of vitamin B12 and the large hepatic store in a healthy Western child.

Those that are marginal in vitamin B12 and are given large folic acid supplements will first present with severe and irreversible neurological disease rather than the normal presentation of anaemia [362-364] although the evidence comes mainly from the older literature; the levels of folate intake recommended have not been shown to cause this problem [365] although it remains a theoretical possibility [366]. In the face of vitamin B12 deficiency, folate is not recycled in the body as it becomes “trapped” in its methyl form so that the person becomes dependent upon the daily intake of “fresh” folate. Folic acid is frequently given to children (and pregnant women along with iron) without attention to the vitamin B12 status of these largely vegetarian subjects or populations. These people could develop irreversible spinal cord damage, or dementia. In the circumstances of the typical developing country diet, all programs that supplement with folic acid should also include vitamin B12.

The RNIs for vitamin B12 are given in table 33.

Vitamin B12 is not toxic even at high levels and is stable in foods.

It would be wise to take the opportunity of giving the moderately malnourished child under treatment sufficient vitamin B12 to replete their hepatic store. Vitamin B12 is the only essential nutrient that is known to be completely absent from the normal malnourished child’s exclusively plant-based diet.

As most moderately malnourished children will be under treatment for a relatively short time, it is recommended that 2.6 microgram/1000 kcal be set as the recommended intake when a fortified/complementary food program is designed. For a food based approach a level of 1.0 microgram/1000 kcal as recommended by FAO/WHO for the older child should be used.

Folic Acid

It has long been recognised that folate deficiency is common in the developing world. About 20% of children in Jamaica and Kenya are folate deficient and similar results have been published from many countries [294, 351, 367-369].

Folic acid (the monoglutamate), which is the form added to food, is at least 85% available. Food folate is normally only 30 to 80% as efficiently absorbed as folic acid. Food folate occurs mainly with a long polyglutamate side chain that needs to be hydrolysed by a zinc dependent intestinal enzyme, conjugase, before absorption. There are inhibitors of this conjugase in many plant foods, for example human conjugase is inhibited 16-35% by beans and 28% by maize. Banana, tomato and orange juice are more potent inhibitors [370, 371]; this may be of relevance in plantain/banana eating cultures such as Uganda. Conjugase is defective in those who are on a deficient zinc intake. Although the food-folate availability from western diets is thus about 50%, it is likely to be considerably lower in those who eat maize or plantain based diets. This particular effect is not often considered when anti-nutritional factors in foods are examined.

Folate is readily oxidised in food in the presence of iron, heat or light. Cooking oxidises tetrahydrofolate to the dihydrofolate so that about half of the folate in cooked food is as 5'-methyl-5,6-FH₂. In the acid conditions of the stomach some of oxidised folate may isomerise to a form (5'-methyl-5,8-FH₂) which is totally unavailable. The utilisation of folate is dependent upon having an adequate iron, zinc and vitamin C status, nutrients that are frequently deficient in poor populations.

The recent FAO/WHO and IOM committees have established values that are substantially above those of previous committees (table 34). This is largely because of the recognition that homocysteine levels in plasma are a more sensitive test of the adequacy of folate status than those used previously. F100 and RUTF have 350 µg/1000kcal.

Because of the high level of deficiency of folate in malnourished children, the poor availability of natural folate from many diets and the effect of concomitant deficiencies on folate status the diet given to a malnourished child should contain substantially more folate than that of a healthy Western child, provided that there is also vitamin B12 fortification.

It is recommended, for a fortified food approach to have 350 µg/1000kcal (the same level as RUTF/F100). Where a food based approach is used there should be 220 µg/1000kcal in the diet; this is 30% above the level for a healthy child.

Ascorbic acid (Vitamin C)

Moderately malnourished children have had little fresh fruit or green vegetables in their diet for considerable periods so that their status is usually precarious. The bone changes seen in scurvy (scorbutic rosary), are common in malnourished children. These bony changes do not occur rapidly so that the severely malnourished child will have been taking a vitamin C deficient diet during the development of the condition, certainly when she was moderately malnourished. It is likely that the blue sclera seen frequently in many parts of Africa, are due to abnormalities of collagen formation, this could be due to chronic vitamin C (or copper) deficiency.

In northern Kenya epidemic scurvy occurs annually in the refugee camps. The problem is such that a special report was commissioned from the IOM to address this issue [279]. The IOM advised that the cooking losses were so substantial that food fortification was unlikely to help; however the foods tested contained high levels of iron added in an effort to combat anaemia.

Thus, in terms of setting vitamin C requirements for the moderately malnourished it is important to examine the availability and stability of vitamin C in the foods. The families of subsistence farmers who harvest once or twice per year and store their grain for prolonged periods are particularly at risk as food vitamin C is quickly destroyed as food is dried and stored. Similarly, pastoralist communities rarely have access to fruit and green vegetables⁴³.

As ascorbic acid can overcome the antagonistic effect of polyphenols, phytate and calcium phosphate on iron absorption; reducing the iron level and increasing the ascorbate level of supplementary foods may even have a beneficial effect on iron nutrition. The relatively high level of vitamin C in a spread given to Saharawi children may be partly responsible for its success in reversal of the anaemia, despite the relatively modest levels of iron in their diet [258].

Ascorbate is very vulnerable to oxidation (the dehydroascorbic acid is oxidised with irreversible opening of the lactone ring). It normally decreases rapidly in stored foods; oxidation is exaggerated by exposure to air, traces of iron, heat and is worse in a neutral or alkaline matrix. There are also

⁴³ Milk, particularly camel's milk, is a source of vitamin C.

ascorbate oxidases in many plant tissues. Rapid heating to levels which destroy these oxidases can help preserve vitamin C in diets.

Vitamin C is the major anti-oxidant of the aqueous body, it also “regenerates” oxidised vitamin E. However, when in the presence of free iron it becomes a pro-oxidant through its reductive activity (e.g. [372, 373]).

The recent IOM committee report has considerably increased the RNI of vitamin C for the young child, for older children the levels are lower than those set by other committees (see table 35). It is unclear why these dramatic differences should be recommended.

Malnourished children are exposed to greatly increased oxidative stress compared to healthy Western individuals. For example, in setting the RNIs for vitamin C the IOM recommend a much higher value for smokers than for non-smokers. Similarly, patients with “oxidative” diseases such as rheumatoid arthritis have chronically low vitamin C levels and greatly increased rates of vitamin C disappearance after a test dose is given [374].

The highest values from the IOM committee are for the older infant at 74mg/1000kcal

Vitamin C is one of the more expensive ingredients in the mineral/vitamin mixes used to make fortified foods, nevertheless, it is clear that the vitamin C status of most moderately malnourished children is severely compromised and that they live under polluted unhygienic conditions. It is important not to have a high level of iron in any fortified food if vitamin C deficiency and pro-oxidant effects are to be avoided [373].

It is recommended that a level of 100mg/1000kcal of vitamin C be used for fortified foods. For a food based approach the IOM level of 75mg/1000kcal is appropriate.

Vitamin E

Vitamin E is the principal fat soluble antioxidant of the body. In particular, it protects cell membranes and the brain. It also prevents the essential fatty acids from being oxidised. Whenever it has been measured in malnutrition it has been found to be deficient [350, 375-384], no paper could be found where the vitamin E was normal in the malnourished. Vitamin E occurs with fat in the diet. There is no pro-vitamin E, in contrast to vitamin A, which can generate vitamin E so that a low fat diet will nearly always be deficient in vitamin E. Thus, where there is vitamin A deficiency, there is almost certainly concomitant vitamin E deficiency. Many seed oils are good sources of vitamin E. The typical diet of most moderately malnourished children is characterised by low levels of fat, and tropical oils have lower levels than temperate seed oils (e.g. coconut oil and red-palm oil are not good sources of vitamin E). Many commercial oils are fortified with synthetic antioxidants (BHT and BHA) because vitamin E is usually lost during refining. They do not contain sufficient vitamin E and the added antioxidants, although preventing the oil from becoming rancid, have no biological function; they cannot replace or minimise the requirement for vitamin E in the body. The requirement for vitamin E is greatly increased by any oxidative stress and by a high intake of poly-unsaturated fatty acids, which both increase vitamin E turnover and requirements. Vitamin E is critical for the proper functioning of the immune system as well as for maintenance of membrane integrity.

The differences in the committees are illustrated in table 36. The levels set recently by the

FAO/WHO are substantially higher than those of any other committee⁴⁴. Some committees set their values for vitamin E entirely in relation to the amount of poly unsaturated fatty acid recommended for the diet. This would not be appropriate for those living in the developing world.

However, higher values are suggested for the infant, where brain haemorrhage, haemolytic anaemia and oedema have been described in Western premature infants on a low vitamin E diet [385]. Apart from these catastrophic features, as with the other antioxidants, lesser levels of vitamin E deficiency do not show any characteristic signs or symptoms, apart perhaps from the host response to infections such as measles. There is a relatively low vitamin E content of most breast milk samples measured which can be greatly increased by dietary supplementation [386]. Breast milk vitamin E is lower in women exposed to the oxidant stress of smoking [387], presumably by increased metabolic destruction under such conditions. Women in countries such as Bangladesh [388] have low levels of vitamin E in breast milk.

The malnourished child is particularly prone to oxidant stress and has low levels of many of the antioxidants [275, 297, 389-392] including vitamin E.

There is an important interaction between vitamin E and selenium. Selenium is a critical nutrient that has been neglected but is involved in infection, virulence of organisms, emergence of new organisms, immune function and protection from oxidative stress. It is equally critical that there is sufficient vitamin E to augment selenium in these functions. To quote from Beck et al “*deficiencies in either Se or vitamin E results in specific viral mutations, changing relatively benign viruses into virulent ones*” [315]. In view of this it is critical that sufficient vitamin E is given to those living under unhygienic conditions and other environmental stresses.

The highest vitamin E recommended intake is set at 8.9mg/1000kcal. The level in F100/RUTF is 22mg/1000kcal, considerably above any of the committees’ recommendations. This level was set deliberately for the malnourished in view of their infective burden, exposure to oxidative stress and pre-existing deficiency.

In view of the low level of fat in the habitual and home diets of malnourished children and their heavy exposure to pollutants and infection the levels that are recommended for a Western healthy child are quite inadequate for the environment of these children.

Thus, for a fortified/complementary food approach it would be appropriate to have the same level of vitamin E as in RUTF. That is 22mg/1000kcal. This level cannot be reached using a food based approach. For a food based approach a level of increase of 30% over the requirement for a healthy child living in a hygienic environment would be appropriate; this would result in a requirement of 11.5mg/1000kcal.

Retinol (vitamin A)

Retinol deficiency is widespread in those parts of the world where moderate malnutrition is common. Its deficiency not only leads to blindness, but also to dysfunction of mucosal surfaces and the immune system. Vitamin A metabolites interact with the genome to control the sequence of expression various genes. Retinol is therefore of fundamental importance to the whole of the body and not only to eyesight, although this is used clinically to diagnose vitamin A deficiency. Vitamin

⁴⁴ It is now thought that the vitamin E RNI may have been set at too high a level for those in the USA (personal communication L.H Lindsey). However, it would be quite unacceptable to make a recommendation for the malnourished, who are ubiquitously deficient in vitamin E, which is at a lower level than that proposed officially for normal healthy children. No reports could be found that give data on the physiological requirements, turnover or biomarkers of vitamin E status from malnourished children, or those living in situations of infective and environmental stress apart from simple plasma vitamin E levels.

A supplementation has been shown in several trials to have a dramatic effect upon infectious disease and mortality rates under stable conditions [393-396]. Mortality from such conditions as measles is reduced substantially if the vitamin A status of the host is normal. In much of the developing world capsule distribution with vaccination is routine practice. These programs are successful. However, concern has arisen because of the teratogenic effects of vitamin A in high doses and the more recent demonstration that high doses of vitamin A are associated with an increased mortality and increased respiratory tract infection in children with severe clinical malnutrition [397, 398].

The highest RNI is for the young child and the lactating woman (table 37). It is quite unclear why the IOM recommendations differ so markedly between those for the infant and for the young child.

The data of Rothman et al [399] upon which the recommendations with respect to teratogenesis are set are shown in table 38, expressed as vitamin A:energy densities. The original units of the published paper are IU/d; these have been converted to $\mu\text{g}/\text{d}$ using a conversion factor of 1 IU-0.3 μg retinol and then to a density using the requirement for a non-pregnant⁴⁵ 31-50 year old female. This gives the most conservative figure for retinol: energy density. The results are not normally expressed in this way. It seems that there is no epidemiological evidence of a teratogenic effect, in a normally nourished population with presumably full vitamin A stores, when the amounts of Vitamin A ingested are up to 1875 $\mu\text{g}/1000\text{kcal}$.

Considering the widespread and severe effects of prior deficiency in the moderately malnourished children, their depleted hepatic stores and the low fat content of the diet on the one hand and the relative dangers of mothers in early pregnancy taking any product formulated using these recommendations exclusively on the other hand, it is reasonable to give as high a level of vitamin A in the diet that is possible without there being any evidence of an adverse effect if taken by pregnant women.

For this reason using a fortified food approach it is recommended that there be 1900 $\mu\text{g}/1000\text{kcal}$ retinol in the diet of moderately malnourished children. If a food based approach is used then an increase of 30% over the highest density recommended for a healthy western child would be appropriate. This would result in a density of 960 $\mu\text{g}/1000\text{kcal}$.

It is assumed that where a food based approach is being advocated that there will also be a vitamin A capsule distribution program for children at risk of vitamin A deficiency and for the moderately malnourished. If such programs are universally in place with a high and verified coverage, then the food based recommendations could be reduced to match the FAO/WHO recommendation of 600 $\mu\text{g}/1000\text{kcal}$.

Vitamin D

Signs of vitamin D deficiency commonly occur in children in hot, dry and dusty areas. That is so of a broad band from the Sahara to China and from the Urals to Ethiopia. Part of these signs may be due to phosphate, calcium or magnesium deficiency, particularly when associated with severe malnutrition (see sections on these nutrients). Nevertheless, classical rickets, responsive to vitamin D, does occur, particularly where the children are not exposed to sunlight for cultural reasons.

⁴⁵ The teratogenic effects occur early in pregnancy, before there is any substantial rise in energy requirement

Exclusively breast fed infants whose mothers have a low vitamin D status can develop vitamin D deficiency [400-402] or even overt rickets [403].

Although there is a lot of “light” in these countries the large amounts of atmospheric dust coming from the desert reflects most of the UV-B so that it is only when the sun is directly overhead that significant UV-B light is available (in Saudi Arabia monitoring UV showed a sharp peak from 1100h to 1300h and almost none outwith these times). During the middle of the day most are indoors or completely covered up. Thus, contrary to expectation, rickets is a relatively common condition of the desert areas. It is therefore necessary to ensure that the diet has adequate amounts of vitamin D. For adequate absorption, vitamin D, like other sterols⁴⁶ requires fat in the diet and no substantial small bowel bacterial overgrowth.

Table 39 shows the recommendations for healthy normal children.

The requirements are quite variable between committees and age groups. The IOM reduced the recommended intakes to about half those of the US, 10th edition RDAs, and this has been endorsed by FAO.

For a supplementary food approach it is appropriate to focus on the 6-12 month old child, who is least likely to be exposed to sunlight and has the highest requirements. Therefore it is recommended that 11µg/1000kcal be present in the diet. For a food based approach, the FAO/WHO level of 7.4µg/1000kcal may be used.

Vitamin K

Vitamin K is mainly obtained from dark green leafy vegetables. Sufficient is presumably not taken by malnourished children. Measurement of the carboxylation of the clotting factors in severe malnutrition shows that up to 20% of patients have evidence of mild vitamin K deficiency (unpublished). Vitamin K is synthesised by the bacteria in the large intestine and it was previously thought that this supplied sufficient vitamin K during adult life. It may be that the small intestinal bacterial overgrowth in malnutrition protects against vitamin K deficiency. Patients on antibiotics that suppress intestinal flora require a dietary source of preformed vitamin K⁴⁷, so that during treatment, when antibiotics are given the diet should contain adequate amounts of vitamin K.

However, recent evidence shows that there may be insufficient synthesis as shown by under carboxylation of osteocalcin (a sign of vitamin K deficiency) in many Westerners with osteoporosis [405]. Furthermore, there are seasonal changes in vitamin K status in the West, [406] probably related to seasonal availability of fresh green vegetables [407].

There does not seem to be any data on the normal vitamin K status of African or Asian populations or moderately malnourished children.

The level of vitamin K in F100/RUTF is 40µg/1000kcal. This is at the level recently proposed by the IOM for older children, and is higher than the FAO/WHO recommendation (table 40). The reason for the discrepancy is unclear. The reason for the almost tenfold change in the IOM recommendation between the younger and older child seems inexplicable, the documents do not comment upon this.

⁴⁶ So called “swelling lipids” (monoglycerides, phospholipids, fatty acids) are required to expand the bile salt micelles in order to achieve adequate absorption of highly hydrophobic compounds such as many sterols. The bacteria overgrowing the intestine in malnutrition deconjugate bile salts and could drastically reduce vitamin D availability [210] [404].

⁴⁷ Prophylaxis in patients with HIV using cotrimoxazole, does not cause suppression of intestinal bacteria

Because of the low levels of dark-green leafy vegetables, and hence vitamin K, in the diets of moderately malnourished children they should be given the amounts in RUTF/F100 and as recommended by the IOM of **40µg/1000kcal of vitamin K. For a food based approach then a level of 20µg/1000kcal as the FAO/WHO requirement plus 30% would probably be adequate**

Biotin

Biotin is normally already present in the diet in what are thought to be adequate amounts, although there is considerable variation from one food to another and relatively few foods have been analysed. Where uncooked egg protein to be used in formulating foods for malnourished children additional biotin is essential to “neutralise” the anti-biotin antinutrient, avidin, contained in the egg [408].

Biotin deficient infants on prolonged parenteral nutrition have a particular facial distribution of fat, skin lesions similar to zinc deficiency, candidiasis, flat affect and are withdrawn; this is similar to both the features of kwashiorkor and severe zinc deficiency. There is thus a possibility of clinical confusion and misdiagnosis; biotin deficiency is rarely considered. However, the most characteristic feature of biotin deficiency is complete hair loss, a phenomenon that is also common in malnourished children. Biotin deficiency has not been looked for in moderately malnourished children, so their status is unknown. The plasma levels are lower in severely malnourished children and biotin supplementation improves their levels of biotin dependent enzymes [409-411]. It has been postulated that the abnormal fatty acid profile of malnourished children is related to biotin deficiency [412].

F100 (24µg/1000kcal⁴⁸) contains a high concentration of Biotin. Relative to the current recommendations and with the uncertainty surrounding the requirements it would appear that the levels in F100 may be excessive. The recommendations for normal children are given in table 41; the IOM and FAO/WHO levels are identical.

In view of the poor diet of malnourished children, and evidence for deficiency [410], it is recommended for fortification programs that the diet should contain 13µg/1000kcal; for food based approaches to treating the moderately malnourished an intake of 10µg/1000kcal is appropriate

Pantothenic acid

There has been one report of epidemic pantothenic acid deficiency in malnourished refugees [74]. This occurred in Afghanistan among malnourished peoples that were given highly refined wheat flour and the other ingredients of the food basket suffered a pipeline break. The patients presented with crippling burning foot syndrome which was only partially relieved by administering pantothenic acid; the supplementation totally prevented any new cases from developing.

Pantothenic acid is present in the surrounding membranes of most seed plants and it was this particular circumstance of taking highly refined flour that seems to have precipitated widespread clinical deficiency, similar to that seen in the Japanese POW camps during the Second World War.

⁴⁸ In some tables and documents there appears to be a transcription error. The original level set was 100nmol/1000kcal (biotin has a molecular weight of 244), which is equivalent to 24ug/1000kcal. The transcription error has resulted in F100 having 100ug instead of 100nmol. This is not at all deleterious.

Although it is likely that the basic ingredients of the diet will have sufficient pantothenic acid, fortified foods should always contain additional pantothenic acid to ensure adequacy of the moderately malnourished. F100/RUTF contains 3mg/1000kcal. The RNIs are shown in table 42.

A supplementary food approach should contain 3mg/1000kcal and a food based approach 2.7mg/1000kcal.

Essential Fatty Acids

Essential Fatty acids are important for brain and neural tissue development. The data for abnormal development of children on a low essential fatty acid intake in the Western World is becoming clear, now that more sophisticated methods for examining neural development have been established. This is covered in detail in the companion paper by Michaelsen et al [1].

Malnourished children have low levels of essential fatty acids, particularly n-3 fatty acids. They also appear to have defects in metabolism of the parent essential fatty acids to more unsaturated and elongated fatty acid derivatives [413-420]. There are also alterations in neurological function in malnourished children that are physiologically similar to those seen in essential fatty acid deficiency, but the relationship of these to essential fatty acid deficiency, although probable has not been confirmed.

The most salient clinical feature of EFA deficiency is a dry flaky skin. This is common in moderately malnourished children; mothers whose children are treated with highly fortified lipid based spreads almost all comment on the change in the texture and appearance of their children's skin. The levels recommended are those found in RUTF and F100.

There is substantial transdermal absorption of essential fatty acids and in many cultures the mothers anoint their children with local oils, which may affect the essential fatty acid status. It is the practice in India to massage children with mustard seed oil. This is a particularly rich source of essential fatty acids and vitamin E; it is noteworthy that the malnourished children in India rarely have the same skin lesions or perineal dermatitis that are widespread in African malnourished children. In the absence of essential fatty acids from the diet, in the event of clinical deficiency or where there is a problem with fat absorption (any cause of malabsorption syndrome), then EFA deficiency can be treated and prevented by anointing the child's skin with oils containing the EFAs.

The recommendations are that:

The omega-6 fatty acid series should comprise at least 4.5% of energy which is 5g/1000kcal.

The omega-3 fatty acid series should comprise at least 0.5% of energy which is 0.85g/1000kcal.

The total fat content of the diet used to treat moderately malnourished children should be 35% to 45% of the dietary energy.

Manganese, Chromium, Molybdenum Fluorine

There are far fewer data on the quantities of these essential nutrients required in the normal, moderately or severely malnourished child.

It is recommended that pending more definitive data that the highest IOM requirements be adopted as the interim recommendations for the moderately malnourished child, with the reservations discussed below (table 43).

FLUORINE. There are large areas of Africa where the major problem is fluorosis. This occurs throughout the whole of the Rift valley area. There are also areas of India with endemic fluorosis. It is not recommended that additional fluorine be added to any complementary or other food for use in these areas.

Fluorine – complementary food addition of 0mg/1000kcal.

MANGANESE. Manganese deficiency in animals gives rise to obesity, teratogenic abnormalities of the inner ear, and epilepsy. Human epileptics have low levels of manganese [421]. It is also associated with iron metabolism. Gross clinical deficiency in parenterally fed adults is associated with anaemia and skin lesions.

RUTF has 0.7mg/1000kcal Manganese. The levels of manganese in the blood of malnourished children is about half of that in control children in each of the studies that have reported levels [422-424]. It would appear to be important to add manganese to the diets of the malnourished. However, no supplementation studies in the malnourished child could be found.

It is recommended that the manganese intake be increased to that recommended by the IOM of 1.2mg/1000kcal

CHROMIUM. Chromium has been implicated in carbohydrate metabolism. The levels are low in children with severe malnutrition and they appear to have improved glucose tolerance with chromium supplementation [425, 426]; this is also seen in malnourished adults [427]. The chemical form of chromium appears to be important. Most inorganic chromium is unavailable and some valencies of the metal (for example the tri-oxide) are toxic. In view of the reports of chromium deficiency in malnutrition and their glucose intolerance, adequate chromium should be in the diets of malnourished children. However, there is insufficient data to determine the appropriate dose to recommend. Thus, it is recommended that chromium be added to the diets at the level of adequate intakes reported by the IOM. This would result in an intake of 11microgram/1000kcal.

MOLYBDENUM. Molybdenum is an essential co-factor in several enzymes involved with energy metabolism and the metabolism of sulphite. There do not seem to be reports of clinical deficiency in man, although there are reports in farm animals. There seems to be a problem in some areas of nutrient-nutrient interactions from high levels of dietary molybdenum (induction of copper deficiency). It is not recommended that molybdenum be added to the diet in excess of the adequate intakes reported by the IOM, until the extent and frequency of deficient or excessive intakes is defined. This would result in an intake of 16 microgram/1000kcal.

Choline

Deficiency in animals gives neurological abnormalities and fatty liver. Both these conditions occur in the malnourished child and their pathogenesis is at present unexplained. On the current diets which do not contain any added choline, even in children gaining weight rapidly with a high lipid intake, the fat in the liver is very slow to dissipate [428, 429]. Fatty liver is common in marasmus as well as kwashiorkor [429] in contrast to traditional teaching. It is possible that choline deficiency could be associated with this abnormal fat accumulation, and the failure of it to dissipate due failure to incorporate choline into the current diets. On the other hand, a small early study of the effect of choline and betaine on fatty liver of kwashiorkor (assessed by liver biopsy) failed to show fat mobilisation [274].

The role of choline deficiency in malnutrition awaits further work. In the mean time it is recommended that the IOM RNI be followed of 220mg/1000kcal.

Tolerable upper limits of nutrients for the malnourished.

There is considerable uncertainty about the safe upper limit for many of the nutrients recommended for addition to the diets normal healthy individuals; however, they are in general conservative.

For moderately malnourished children who have abnormalities of intestinal, liver, and renal function, which may affect the absorption, metabolism and disposal of nutrients, there are no data upon which to confidently establish tolerable upper limits. Malnourished children have tissue deficits of most nutrients (except sodium and usually iron) that need to be made good; they need to have sufficient nutrients in the diet to sustain accelerated weight and height gain. This is a totally different situation from the factors that the committees who established the upper limit recommendations took into account. Their levels were set to take into account members of the general public who are already replete, may be in the upper section of the intake distribution or may through individual idiosyncrasy be sensitive to a particular nutrient. With the moderately malnourished, a similar argument has been advanced for restricting sodium and iron in the diets and indeed, setting tolerable upper limits for these two nutrients, in particular, that are more stringent than for the general healthy child living in the developed world. Individuals with other disorders, such as diabetes, cirrhosis, renal failure, hypertension, or an inborn error of metabolism, also have specific changes made to the recommendations to accommodate their clinical conditions that are not addressed by the committees setting tolerable upper limits.

A further consideration is that the safe upper limits are set for *individual* nutrients on the basis that there might be adverse nutrient: nutrient interactions if a particular nutrient was taken to excess without increments in the interacting nutrient. For example the upper limit of zinc is set to avoid induction of copper deficiency if copper intake is marginal; similarly the upper limit of folate is set to avoid neurological damage if B12 intake has been deficient. Such considerations do not obtain when a food, that aims to include all essential nutrients in sufficient amounts, and with the correct balance to avoid such interactions, is formulated and given as a complete diet or as a part of a diet which has added *balanced* and complete fortification to compensate for dietary deficiency in the remainder of the diet. When various portions of a supplementary food are taken each of the interacting nutrients are then taken in appropriate ratios. This argument does not apply to a food based approach where the chosen diet may not contain sufficient of one of the interacting nutrients.

Indeed, it is likely that the balance of nutrients is as important as the absolute amounts of each nutrient. Thus, we have considered protein: energy ratios, essential amino acid ratios, copper: zinc interaction and calcium: phosphorus ratios. However, there are many other important balances that should be considered. For example, potassium: sodium: nitrogen: phosphorus: zinc ratios, iron: manganese, iron: selenium and copper: molybdenum: sulphur interactions. Such interactions are important and single nutrient supplementation, if used at all, should always take such interactions into consideration.

A WHO/FAO workshop addressed the problem of defining upper limits for inadequately nourished and diseased populations [430]; the report (section 3.1.2 and section 9) contains the following statements:

“...estimates of upper levels of intake derived for adequately nourished and 'generally healthy' populations may not be appropriate for—or may need adjustments to be useful to—(sub)populations that are nutrient deficient and/or are generally subject to disease conditions such as malaria”.

“The Group came to the conclusion that the appropriateness of a UL established for adequately nourished (sub)populations cannot be assumed to transfer to inadequately nourished (sub)populations. ...the Group considered it likely that inadequately nourished (sub)populations would need a different set

of ULs because of important differences in metabolism and the vulnerability that can result from these differences. However, the Group also concluded that too little is known about the effects of inadequate nutrition on the absorption, distribution, metabolism, and elimination of nutrient substances to allow specification of considerations relevant to adjusting ULs to make them appropriate for inadequately nourished (sub)populations.”

The statements and examples given in this report are germane to consideration of the nutrient requirements of the moderately malnourished. In setting the requirements and the upper limits it is clear that there is a major problem with the amount, quality and external validity of the evidence at hand.

Nevertheless, it is appropriate to consider the tolerable upper limits for normal healthy individuals and to justify any deviation for the moderately malnourished child.

Table 44 gives the tolerable upper levels recommended by IOM for healthy individuals in comparison with the amounts recommended for moderately malnourished children. The recommendations are expressed both in terms of absolute amounts and nutrient densities.

The recommendations for the malnourished exceed the tolerable upper limits recommended by the IOM for four nutrients, when expressed in absolute amounts or as nutrient densities. They are magnesium, zinc, folic acid and retinol.

It should be noted that the upper limits are set for children within a certain age group. The malnourished child is likely to be lighter and smaller than the children for whom the limits were set. On the other hand they are also likely to take commensurately less of the diet, so that although the nutrient densities have been set on the basis of the energy requirements of normal children, and the nutrient intakes of normal children, if less of the food is actually taken by the children they are less likely to reach the upper tolerable intake.

Magnesium

The tolerable upper limit has been set on the basis of the cathartic effect of pharmacological administration of some magnesium salts to adults, with extrapolation to children on a simple weight basis. The report states “*magnesium ingested as a component of food or food fortificants has not been reported to cause ...mild osmotic diarrhoea even when large amounts are ingested*”.

In view of:

- the persistently high positive magnesium balance in malnourished children,
- the neglected requirements for skeletal growth,
- the lack of any osmotic diarrhoea from F100,
- the fact that supplements of magnesium chloride, citrate, acetate and oxide have been used in the treatment of complicated severe malnutrition for many years (at doses of 24 mg/kg/d),
- the lack of any data from children showing an adverse effect
- the extrapolation from healthy adult recommendations on a simple weight basis rather than the more conventional surface area or metabolic weight basis which would increase the tolerable upper limit for children considerably, and
- the fact that the recommendation only applies to pharmacological supplementation and not food incorporated magnesium

it is suggested that the amount of magnesium to be incorporated into the diet of moderately

malnourished children should properly exceed the IOM upper tolerable limit for supplemental magnesium.

Zinc

The largest discrepancy is seen with zinc; therefore it is worth examining the basis for the tolerable upper limit in relation to the recommendations for the malnourished child.

It is clear from the report that “*the upper level is not meant to apply to individuals who are receiving zinc under medical supervision*”; it could be argued that the moderately malnourished child is indeed in need of therapeutic quantities of zinc. However, we need to consider what will happen if foods formulated with the present recommendations are taken by normal healthy individuals.

There were no reports found of adverse effects of zinc intakes that exceed the upper limit when the zinc was naturally occurring in food.

The cited adverse effects are suppression of the immune response, changes in HDL cholesterol, interference with iron absorption and reduction of copper status. The immune suppression only occurred with massive doses of zinc for prolonged periods and the cholesterol changes were inconsistent and ignored by the IOM committee.

The effect of zinc on iron absorption was only observed when the zinc: iron ratio exceeds 3:1 and the two metals are given together in water. When they are given with a meal, no effect of the zinc on iron absorption is observed [431]. When the zinc: iron ratio is increased to 5:1 there is a marked effect upon iron absorption (56% decline), but when the same doses of zinc and iron were given with a “hamburger meal” no effect was seen. As it is proposed that zinc and iron are always incorporated into the diet together and that the zinc: iron ratio should be well within the limits where no interaction is observed, this adverse consideration does not apply to the present recommendations for the moderately malnourished.

The most important effect of zinc appears to be on copper status. It is critical to point out that all the studies that have examined the effect of zinc on copper status have given zinc alone without incorporation of any copper into the supplement.

The upper limit was set on the basis of the study by Walravens and Hambidge [432] who gave 4 mg/ litre zinc to supplement a breast milk substitute, giving a total intake of 5.8mg. This was given to 34 infants from just after birth for six months. There was no effect upon plasma copper or any other observed adverse effect. It is important to note that physiologically infants have stores of copper laid down during late pregnancy that can supply the infant’s requirement for copper until 6 months of age; therefore this study may not be appropriate to make any judgement about the effect of zinc on copper status in the infant. Second, there was no attempt to give additional copper to these infants (correctly). This study has been used as the level at which there is “no observed adverse effect” of zinc supplementation and the upper tolerable limit set accordingly. The dose of zinc used appears to have been arbitrary and higher levels have not been tested to ascertain if there are no observable effects.

No comparable studies in children, over the age of 6 months, who have either had higher doses of zinc for prolonged periods and have copper status assessed, were found.

On the other hand very large numbers of children have been given much higher zinc supplements, albeit for short periods of time, whilst recuperating from acute diarrhoea without adverse effects on copper status having been reported (however, it is not clear from the reports if the effect upon copper status was appropriately examined in most studies).

F100 supplies about 20mg of zinc per 1000kcal, and has been given to severely malnourished

children for up to two months without there being any adverse effect on copper status, albeit copper has routinely been also added to the diet in a ratio of zinc: copper of 10:1 in order to obviate the known interaction of zinc and copper.

In none of the studies, examined by the IOM committee and reporting an adverse effect of zinc on copper status, were copper and zinc supplements given simultaneously. Dual supplementation is routine in all diets used to treat the malnourished.

It is concluded that copper should always be incorporated into any diet or medicament that is supplemented with therapeutic doses of zinc. When this is done the present IOM tolerable upper limit for zinc should be adjusted to allow sufficient zinc to be incorporated into the diets of malnourished children to properly support accelerated lean tissue synthesis and their immunological and functional recovery; zinc deficiency in this particular group of children is widespread and would not be alleviated if the tolerable upper limit set for the USA was applied to diets designed for the malnourished.

Folic Acid

Folate only exceeds the IOM upper tolerable limit in the older child by a marginal amount. The limit has been set on the basis that high doses of folic acid can exacerbate and mask the neurological manifestations of vitamin B12 deficiency. The level has been set at a deliberately conservative amount because there is commonly vitamin B12 deficiency in the elderly in developed countries. This is important. It also applies to populations subsisting on largely vegetarian diets, such as the moderately malnourished. There appears to be widespread marginal status of vitamin B12 in the population. The reasons for the conservative upper tolerable limit are obviated if vitamin B12 is given in adequate doses along with the folic acid. In principle if a diet is being fortified with folate, particularly if this fortification approaches or exceeds the tolerable upper limit, then vitamin B12 should always be incorporated into the diet along with folic acid. This is the case with the present recommendations. It should be routine practice to add vitamin B12 to all medicaments and diets which are fortified with folic acid and given to populations at risk of vitamin B12 deficiency.

Vitamin A

Vitamin A toxicity in children causes increased intracranial pressure and bone changes. They occur when children are given in excess of 5500 μ g per day for prolonged periods [433].

There is widespread vitamin A deficiency in much of the world and massive doses of vitamin A are distributed intermittently in capsule form to most children in the developing world. The cumulative dose does not exceed the toxic dose reported by Persson for children, although he only described 5 cases of intoxication.

In view of the limited number of studies on vitamin A toxicity in children (that have been designed to study toxicity) the upper tolerable limit has been set by the IOM by extrapolation from adult values, on a simple weight basis. This is conservative and if the extrapolation was on the basis of metabolic weight, liver size or surface area the tolerable intake would be higher.

In view of the high level of deficiency in moderately malnourished children and the increased mortality in deficient children in the developing world, it is important to have sufficient vitamin A in the diet to counteract this widespread deficiency. The question does arise about children receiving large doses of vitamin A from multiple sources. The dietary intake recommended should take into account the presence of capsule distribution in the area of distribution.

Appendix 1. Nutrient densities for normal healthy children (RNI and Adequate Intakes) 6 month to 5 years of age by age group, expressed as nutrient per 1000 Kcal, using the FAO/WHO mean female energy requirement as the denominator for the particular age range quoted by each authority.

Appendix 2.

Proposed nutrient intakes for moderately malnourished children (MAM) expressed as absolute amounts for comparison with the standard FAO/WHO RNIs and AIs for normal healthy children. The values recommended, expressed in nutrient: energy densities, have been "back-converted" to absolute amounts using the average energy requirement for females children within the age range quoted, and rounded.

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