Proposed recommended nutrient densities for moderately malnourished children

Michael H. Golden

Abstract

Recommended Nutrient Intakes (RNIs) are set for healthy individuals living in clean environments. There are no generally accepted RNIs 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; and second, for those who are to take mixtures of locally available foods over a longer term to treat or prevent moderate stunting and wasting. Because of the change in definition of severe malnutrition, much of the older literature is pertinent to the moderately wasted or stunted child. A factorial approach has been used in deriving the recommendations for both functional, protective nutrients (type I) and growth nutrients (type II).

Key words: Ascorbate, biotin, calcium, catch-up growth, cobalamin, convalescence, copper, DRV, essential fatty acid, folic acid, growth, iodine, iron, magnesium, malnutrition, manganese, niacin, nutrient density, nutrition, nutritional deficiency, nutritional requirements, pantothenic acid, phosphorus, potassium, protein, protein–energy malnutrition, pyridoxine, RDA, recommendations, riboflavin, RNI, selenium, sodium, stunting, sulfur, thiamine, vitamin A, vitamin D, vitamin E, vitamin K, wasting, zinc

The author is an Emeritus Professor, Department of Medicine and Therapeutics, University of Aberdeen, Aberdeen, Scotland.

Please direct queries to the author: Michael Golden, Pollgorm, Ardbane, Downings, Co. Donegal, Ireland; e-mail: mike@pollgorm.net.

This publication reflects the personal views of the author and does not necessarily represent the decisions or the policies of the World Health Organization.

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 to 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 [1] based upon weight-for-age to one based upon weight-for-height, reanalysis of the data shows that many of the studies of children with less than 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 are likely to apply to those with moderate as well as those with severe wasting.

In order to derive the requirements of 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 the requirement 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 more than 10 g/kg/day and returning the children to physiological normality.

The requirements for normal Western individuals (Recommended Nutrient Intake, RNI) were used as the minimum requirements. They were converted into nutrient:energy densities with the use of the energy

requirement for female children. The highest nutrient density among 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 5 g/kg/day. To this increments were added to allow those with mild nondehydrating diarrhea 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 and water, and recurrent infections such as malaria.

Two sets of requirements are suggested. First are the requirements for rehabilitation with the use of a variety of appropriately processed locally available foods; these are the minimum requirements, as it is unlikely that the optimal requirement for all nutrients can be consistently reached with unfortified local foods. Second are the optimal requirements proposed when special complementary, supplementary, or rehabilitation foods are being formulated to treat 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 and its peculiarities are considered. The nutrient:nutrient ratios were examined to ensure that the diet would not be unbalanced and that there would not be detrimental interactions between the nutrients.

The results are shown in **table 1**. The RNI values for healthy Western populations and the nutrient densities in the F100 formulation used for rehabilitation of the severely malnourished 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 emphasized that there are many uncertainties involved in deriving these first estimates of the

TABLE 1. RNIs for normal children, nutrient contents of F100 and RUTF (used for treating children with severe acute malnutrition [SAM]), and proposed RNIs for children with moderate acute malnutrition (MAM) living in contaminated environments, expressed as nutrient:energy densities (amount of nutrient/1,000 kcal)

Nutrient	Gravimetric unit	RNIs for normal children		F100 and RUTF for SAM	Proposed RNIs for MAM[a]				
		FAO	Other[b]		Food	Supplement	SI unit	Food	Supplement
Protein									
Protein	g	22.3	—	28.4	24	26	—	—	—
Nitrogen	g	3.6	—	4.6	3.9	4.2	mmol	275	300
Minerals									
Sodium	mg	—	978	434	550 maximum	550 maximum	mmol	24	24
Potassium	mg	—	1,099	2,400	1,400	1,600	mmol	36	41
Magnesium	mg	79	112	175	200	300	mmol	8.3	12.5
Phosphorus	mg	450	634	762	600	900	mmol	19	29
Sulfur[c]	mg	0	0	0	0	200	mmol	0	5.6
Zinc	mg	12.5	16.5	22.3	13	20	μmol	200	310
Calcium	mg	595	820	1,009	600	840	mmol	15	21
Copper	μg	—	892	2,749	680	890	μmol	11	14
Iron	mg	17.8	17.8	24[d]	9	18	μmol	160	320
Iodine	μg	201	201	190	200	200	μmol	1.6	1.6
Selenium	μg	17.8	29.7	55	30	55	nmol	380	700
Manganese	mg	—	1.2	0.69	1.2	1.2	μmol	22	22
Chromium	μg	—	10.8	0	0	11	nmol	0	210
Molybdenum	μg	—	16.6	0	0	16	nmol	0	170
Vitamins, water soluble									
Thiamine (vitamin B_1)	μg	523	523	700	600	1,000	mmol	2.0	3.3

continued

TABLE 1. RNIs for normal children, nutrient contents of F100 and RUTF (used for treating children with severe acute malnutrition [SAM]), and proposed RNIs for children with moderate acute malnutrition (MAM) living in contaminated environments, expressed as nutrient:energy densities (amount of nutrient/1,000 kcal) *(continued)*

Nutrient	Gravimetric unit	RNIs for normal children		F100 and RUTF for SAM	Proposed RNIs for MAM[a]				
		FAO	Other[b]		Food	Supplement	SI unit	Food	Supplement
Riboflavin (vitamin B_2)	µg	595	595	2,000	800	1,800	mmol	2.1	4.8
Pyridoxine (vitamin B_6)	µg	595	732	700	800	1,800	mmol	4.7	10.7
Cobalamin (vitamin B_{12})	ng	966	966	1,000	1,000	2,600	nmol	745	1,930
Folate	µg	167	167	350	220	350	nmol	500	795
Niacin	mg	6.4	8.4	10	8.5	18	µmol	70	145
Ascorbate (vitamin C)	mg	45	74	100	75	100	µmol	425	570
Pantothenic acid	mg	2.7	2.7	3	2.7	3	µmol	12.3	13.7
Biotin	µg	9.7	9.7	24	10	13	nmol	40	53
Vitamins, fat soluble									
Retinol (vitamin A)	µg	595	743	1,500	960	1,900	µmol	3.3	6.6
Cholecalciferol (vitamin D)	µg	7.4	10.9	30	7.4	11	nmol	19	29
Tocopherol (vitamin E)	mg	8.9	8.9	22	11.5	22	µmol	27	51
Phytomenadione (vitamin K)	µg	16.1	16.1	40	20	40	nmol	44	89
Essential fatty acids									
N-6 fatty acid	g	—	—	5	5	5	—	—	—
N-3 fatty acid	g	—	—	0.85	0.85	0.85	—	—	—
Others									
Choline	mg	—	223	—	223	223	—	—	—
Histidine	mg	—	430	—	430	430	—	—	—
Isoleucine	mg	—	575	—	575	575	—	—	—
Leucine	mg	—	1,245	—	1,245	1,245	—	—	—
Lysine	mg	—	1,190	—	1,190	1,190	—	—	—
Methionine + cystine	mg	—	575	—	575	575	—	—	—
Phenylalanine + tyrosine	mg	—	1,125	—	1,125	1,125	—	—	—
Threonine	mg	—	655	—	655	655	—	—	—
Tryptophan	mg	—	175	—	175	175	—	—	—
Valine	mg	—	776	—	776	776	—	—	—

FAO, Food and Agriculture Organization; RNI, Recommended Nutrient Intake; RUTF, ready-to-use therapeutic food

a. The recommendations for moderately malnourished children are divided into two components. The first component (Food) is the amount that should be in the diet when programs are based on a mixture of local foods to treat the moderately malnourished without general fortification of the diet. The second component (Supplement) is the suggested nutrient density that should be achieved in the diet when specially fortified supplementary foods are used in a program to treat moderately malnourished or convalescent children.

b. Highest of the values given by other authorities: see **table 45** for details.

c. The sulfur should be in addition to that derived from protein.

d. Iron is only added to RUTF, not to F100

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 taste, availability, dietary interaction, acid–base balance, efficacy, and cost, that should be taken into account in formulating any supplementary foods or fortification are considered. The effects of antinutrients 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 article by Michaelsen et al. [2].

A summary of the derived nutrient requirements is given in **table 1** expressed as nutrient densities (nutrient/1000 kcal). The derived nutrient requirements expressed in absolute units are given in the appendix (**table 46**).

Introduction

National and international 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 are retarded. In such circumstances, it is likely that the requirements for nutrients are higher than for those living in safe, secure environments. The reality is that the diets of these children are much poorer than those of children living without such stresses, where food comes from a wide variety of sources. When they get an infection and lose their appetite, 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 to 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 (low height-for-age) by the time they reach 2 years of 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 [3–5]. The Food and Agriculture Organization/World Health Organization (FAO/WHO) and the Institute of Medicine (IOM) have addressed this need in their reports 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 assess the diets of those who are living in stressful environments or are at risk for malnutrition. The recommendations for healthy Western populations are based upon relatively extensive experimental data; these RNIs give a necessary benchmark from which to start [6–14]. However, for many essential nutrients, there are major gaps in the data upon which the RNIs are based. This is particularly true when deficiency in the West is not encountered in the healthy (e.g., potassium, magnesium, phosphorus) or the emphasis is on excess intake (e.g., sodium); these nutrients become critically important when there are abnormal losses from the body, for example, with diarrhea or enteropathy, and in the malnourished. Deficiencies of these same nutrients are 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 consumed where malnutrition is common is unknown [15]. Furthermore, for children in the age group from 6 to 59 months, there are few direct experimental measurements, and RNIs have been assessed either by extrapolation from older age groups or from the composition of breastmilk [16]. The resulting judgments for normal children differ from committee to committee, sometimes quite dramatically.

Children who need to replenish the tissues that have been lost while developing moderate malnutrition or who need to have catch-up growth during convalescence from illness will have higher requirements for nutrients laid down in growing tissue than normal children. Children living in hostile environments will also require higher intakes 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 those required for maintenance in 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 enable functional tissue to be synthesized more rapidly than normal.

General considerations in the derivation of RNIs for moderately malnourished children

The effects of giving modern therapeutic diets to severely wasted children are dramatic. The children regain their appetites and ingest enough of the diet to gain weight at up to 20 times the normal rate of weight

gain; indeed, the Sphere Project standards require an average rate of weight gain of more than 8 g/kg/day [17]. However, with the older diets, when emphasis was placed upon energy density, the children did not regain physiological or immunological normality; thus, delayed hypersensitivity [18], thymic size [19], sodium pump function [20], glucose tolerance [21], renal concentrating ability [22], and muscle size [23] 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 [24–28] because the balance of nutrients was not correct to allow appropriate amounts of lean tissue to be synthesized. When the limiting "growth nutrient" was added to the diet, the children would regain more functional tissue and their physiology and immunity would improve [29–31], presumably until the next essential nutrient limited further growth. With the modern diets based upon the F100 formula, they regain physiological and biochemical normality [32, 33].

These observations raise a critical point. Weight gain, of itself, does not indicate a return to physiological, biochemical, immunological, or anatomical normality. Indeed, consuming "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* individual*; this was often the experience with the older diets used to treat malnutrition and with attempts to treat stunted children with energy supplements alone [34]. Indeed, many overweight children are stunted in height, indicating that they have had a chronic deficiency of nutrients required for growth [35, 36]. 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 [37–40] and the derivative ready-to-use therapeutic foods (RUTFs) [41]) gives 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 RNIs) and a severely malnourished child recovering in a hostile environment (F100 formula).

Variables determining the increments needed for the moderately malnourished child

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

- The amount of new tissue that needs to be synthesized to achieve a normal body composition;
- The time available for the child to recover;
- 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;
- The extent of any initial nutrient deficit or excess in the body tissues brought about by physiological adaptation to the malnourished state;
- Whether there are likely to be changes in nutrient availability due to intestinal abnormalities or ongoing pathological losses in the moderately malnourished child.

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

Nevertheless, there are considerable uncertainties in attempting to derive nutrient requirements for 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, and therefore Adequate Intakes (AIs), which are observed intakes of 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), and the effect of changes in intestinal function in children with moderate malnutrition on the absorption of nutrients from the diet, as well as the effect of intercurrent infections, diarrhea, 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 experts' opinions diverge. The present article is deliberately conservative. For example, even if a

* Obesity is only "overnutrition" in terms of energy. Obese 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 coincidental low intakes of essential nutrients results in many obese persons being undernourished. It is misleading to think of obesity as "overnutrition"; nutrition is much more than simple energy intake.

TABLE 2. Rates of weight gain required to catch up in weight over 14 to 40 days[a]

Category change		−3 to 0 z-scores	−3 to −1 z-scores	−3 to −2 z-scores	−2 to 0 z-scores	−2 to −1 z-scores	−1 to 0 z-scores
14 days	Male	16.9	11.1	5.5	11.4	5.7	5.8
	Female	18.3	12.0	5.9	12.4	6.1	6.3
20 days	Male	11.8	7.8	3.8	8.0	4.0	4.1
	Female	12.8	8.4	4.2	8.7	4.3	4.4
30 days	Male	7.9	5.2	2.6	5.3	2.6	2.7
	Female	8.5	5.6	2.8	5.8	2.9	3.0
40 days	Male	5.9	3.9	1.9	4.0	2.0	2.0
	Female	6.4	4.2	2.1	4.4	2.1	2.2

a. The rates of weight gain are expressed in g/kg/day, using the mean body weight as the denominator. The values are the means for children from 60 to 85 cm in height; within this height range, the maximum and minimum divergence of values ranged from 0.7% to 2.5% of the quoted value, respectively. All calculations are based on WHO 2005 standards. [42]

mean rate of weight gain of 5 g/kg/day is not frequently achieved in a group of children under traditional treatment, there will 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 levels that permit such a rate of recovery, and not to set them at levels that restrict 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 of functional tissue, setting the requirements at a level that would allow mainly for adipose tissue synthesis would fail to return some of the children to normality and might promote obesity. The RNIs, in the presence of such uncertainty, should be set at a level that will not compromise groups of children and yet are achievable both with mixtures of local foods and with fortified foods, where the fortification is not elevated to a level that would pose a hazard if the fortified food was taken exclusively. As with the RNIs for healthy children, setting the RNIs for malnourished children will necessarily involve value judgments 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 are 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 the fat tissues within a reasonable period 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 such children to regain their weight deficit in 30 days or less. If the deficit is between −2 z-scores (just moderately malnourished) and −1 z-score (the lower limit of normal and the upper limit for mild wasting), then the rate of weight gain required will be less than if a child is to gain weight from −3 z-scores to achieve the median weight-for-height of 0 z-scores. The rates of weight gain required to achieve different degrees of catch-up over periods of 14 to 40 days are shown in **table 2**.

In general, girls need to achieve a slightly higher rate of weight gain than boys. Since the definition of moderate malnutrition is from −2 to −3 z-scores, for a child of −2 z-scores to become normal (0 z-scores) or a child of −3 z-scores to achieve −1 z-score over a period of about 30 days, the rate of weight gain will need to be about 5.5 g/kg/day.* 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 5 g/kg/day.

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 should 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 achieve a shorter recovery period or a greater total weight gain) need to be achieved under special circumstances, then the nutrient composition of the diet should approach that of F100.

* If the same table is constructed with the weight at 0 z-scores used as the divisor, then the corresponding figure is about 4.9 g/kg median z-score/day.

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 synthesize 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/g.* Lean tissue contains between 18% and 20% solids,** and the rest is water. Thus, the energy deposited in lean tissue is about 0.8 kcal/g of tissue. It takes little energy to synthesize 1 g of adipose tissue, but to assemble 1 g of lean tissue requires about 1.0 kcal/g. Thus, 8 kcal/g are required to make adipose tissue and 1.8 kcal/g to make lean tissue. 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, at least 10% of the diet is usually malabsorbed in the recovering malnourished child without diarrhea, so the ingested energy required to synthesize 1 g of mixed tissue is about 5.5 kcal/g.

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 is also about 5 kcal/g of new tissue. In one elegant experiment in which the children's muscle mass was measured, Jackson et al. [44] were able to predict the proportion of newly synthesized 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 zinc deficiency itself causing intestinal dysfunction. As the zinc deficiency became more severe, energy was lost from the body by malabsorption. It should be noted that many of the reported studies of malnutrition were conducted before we understood the importance of nutrients such as zinc for the quality of the tissue synthesized. For the purposes of calculation of the requirements for tissue synthesis, a figure of 5 kcal/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 synthesized, 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, since skeletal accretion is relatively slow.

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

Stunting considerations

"Stunting" is a dynamic process. In order for a normal child to meet the criteria for moderate or severe stunting (< –2 and < –3 height-for-age z-scores, respectively), that child will have to have been growing at less than the rate of a normal child for some time. For example, if a normally grown 1-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 cutoff point to be defined as stunted until 2 years of age [55]. 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 countries*** [56]. 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,

* The Atwater factors, which are used to calculate metabolizable energy content of food, use 4 kcal/g for protein, because the urea that is excreted contains the residual energy from the protein. If the dietary energy intake is calculated with the use of bomb calorimetry factors instead of Atwater factors, then the energy content of protein is 5.6 kcal/g.

** The water content of lean tissue varies with the rate of growth or 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 a 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. [43]. This variable has not been taken into account in 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 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, and 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 occurring at different times of the year. It is possible that the weight gain was mainly accounted for by adipose tissue without either lean tissue or skeletal tissue growth. Unfortunately, body composition was not assessed.

TABLE 3. Experimental studies on the energy cost of tissue deposition

Subjects and author	Cost (kcal/g tissue)	Date	Ref.	Country	Notes
Recovering children with SAM on milk diet					
Ashworth	5.5	1968	[45]	Jamaica	Milk diet—with K and Mg only
Kerr 1	4.61	1973	[46]	Jamaica	Milk diet—with K and Mg only
Kerr 2	6.2	1973	[46]	Jamaica	Milk diet—with K and Mg only
Whitehead	3.5	1973	[47]	Uganda	
Spady	4.4	1976	[48]	Jamaica	Milk diet—with K and Mg only
Jackson	6.1	1977	[44]	Jamaica	Only 5 subjects—but had muscle mass measured
Golden	4.8	1981	[29]	Jamaica	Milk diet—early in recovery, mixed tissue synthesized
Morris	5.1 ± 0.5	1989	[32]	Jamaica	Standard milk-based diet with added minerals
Morris	4.8 ± 0.5	1989	[32]	Jamaica	F100 diet
Recovering children with SAM on type II–deficient diet					
Waterlow	6.56	1961	[49]	Jamaica	Original diets—deficient in several nutrients
MacLean	8.39	1980	[24]	Peru	Nitrogen balance shows only adipose tissue being made
Golden	6.9	1981	[30]	Jamaica	70% fat tissue synthesis—low-Zn diet
Golden	8.1	1981	[29]	Jamaica	Milk diet—late in recovery with probable limiting nutrients, fat being synthesized
Recovering children with SAM on soy-based diet					
Golden	6.5	1981	[29]	Jamaica	Soy-based diet—early in recovery
Golden	7.4	1981	[29]	Jamaica	Soy-based diet—late in recovery
Golden	15.5	1991	[50]	Jamaica	Soy-based diet (high phytate, mineral deficient)
Golden	7.4	1991	[50]	Jamaica	Soy-based diet plus Zn
Normal children					
Fomon	5.6	1971	[51]	USA	
Payne	5	1971	[52]	Review	
Reviews (various subjects)					
Roberts	2.4 to 6	1989	[53, 54]	Review	

SAM, severe acute malnutrition

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 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 farther behind the child is, the longer the child will have to maintain an accelerated rate of growth for full catch-up. Conversely, the earlier the age at which a child is identified to be stunting, the easier and more rapid is the reversal of stunting. 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 [55]. It is wrong to think that after the age of 2 or 3 years 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 [57, 58]. To prevent stunting, this improvement must occur over the time the child is actively stunting, which is during the first 2 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 [59], 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 [34]. Preventive

intervention should be strongly focused on the young child, certainly below the age of 2 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 receiving 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 with those of older children. For example, a child growing from 2 to 3 months of age gains about 1 mm per day. If a 24-month-old child gained height at 1 mm per day, 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 age*; 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 [60]. However, it is reasonable to suppose that gain in height of a taller, older child could occur at the same absolute rate as in 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 [61, 62]. Unfortunately, nearly all examples come from children over 24 months of age. However, older children with pituitary disorders treated with growth hormone, hypothyroid children treated with thyroxin, and children with celiac disease treated with a gluten-free diet all catch up, initially, at between three and four times the normal rate of height gain for their age [62, 63]. As these accelerated height gains are 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, although they are sustained for relatively short periods of time and have not been 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 [64]. For children recovering from shigellosis, Kabir et al. [65] reported that 33-month-old children (86 cm) gained 10.2 ± 4.4 mm (SD) during 21 days of convalescence. The average is about twice the normal (using WHO 2005 standards [42]) If we now take the mean plus 2 standard deviations (that is 10.2 plus twice 4.4 = 19 mm over 21 days), the rate of height gain was 0.9 mm/day, compared with a normal rate of height gain of 0.3 mm/day for children 86 cm in height (WHO 2005 [42]); it is even higher when compared with the normal rate of height gain of children 33 months of age. Thus, in Bangladesh, rates up to three times the normal rate of height gain were observed; given that these children were probably fed suboptimal diets with respect to the ratios of type II nutrients and that they 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 1 year has a normal height and has only been gaining 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 a rate that is 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 1, 2, or 3 height-for-age z-score units if the child is gaining at between two and four times the normal rate of height gain for her age. A child under 1 year of age can gain 1 z-score unit in 2 to 4 weeks. The severely stunted (–3 height-for-age z-scores) 6-month-old child could fully return to normal height-for-age (0 z-scores) in about 6

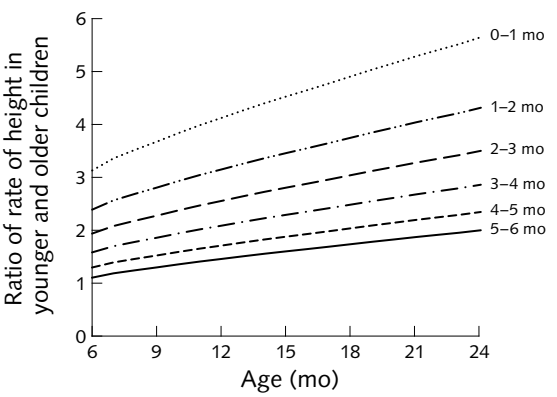

FIG. 1. Possible potential for catch-up in height. The absolute height increases of children from birth to 6 months, in 1-month intervals, were derived from the WHO 2006 standards. These were compared with the absolute monthly increases in height of children from 6 to 24 months. The graph shows the ratio of the absolute height gains (mm/mo) of younger to older children. For example, if a 24-month-old gained height at the same rate as a 0- to 1-month-old, she would gain height at 5.6 times the normal rate for her height and for her age (dotted line); if she gained height at the same rate as a 5- to 6-month-old, she would gain height at twice the normal rate for her height and age (solid line)

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

weeks. A 12-month-old child can catch up 1 z-score unit in about 3 weeks and fully catch up in height in about 2 months.

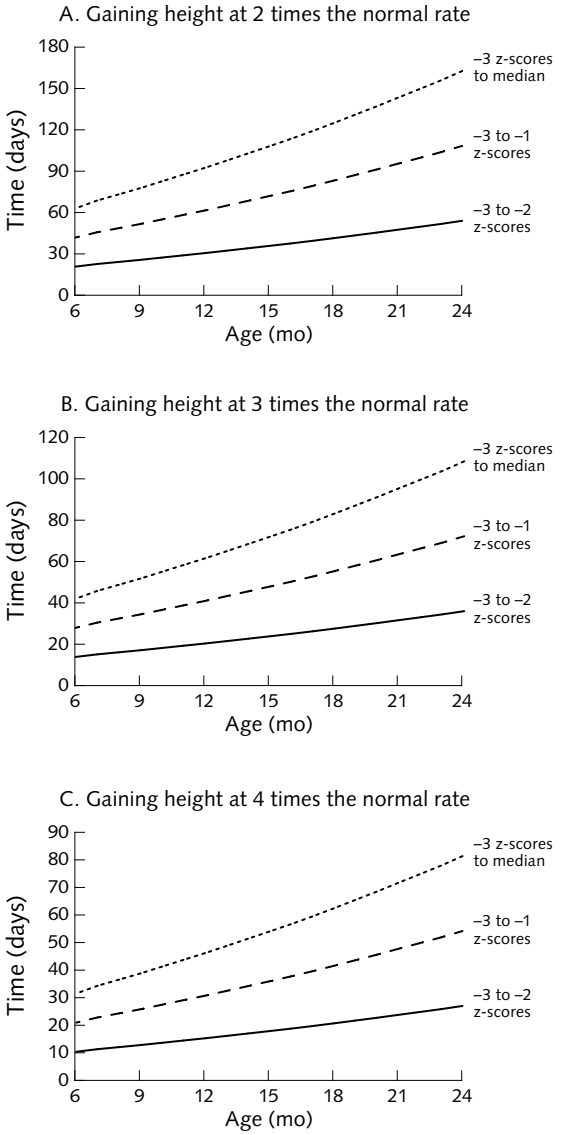

FIG. 2. Number of days it takes for children to gain 1, 2, or 3 z-score units in height if the rate of height gain is two (A), three (B), or four (C) times the normal rate (WHO 2005 standards) for children between 6 and 24 months of age. The time to gain 1 z-score unit (i.e., from –3 z to –2 z, from –2 z to –1 z, or from –1 z to the median height for age) is almost the same and can be read from the solid lines in the graphs for children gaining height at different rates. Similarly, the dashed lines give the time to gain 2 z-score units. For example a 6-month-old child catching up height at three times the normal rate will gain 2 z-score units of height-for-age in 28 days, and a 24-month-old child will take 72 days (dashed line in B)

Thus, although "stunting"* 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 from 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 catch-up in height 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 data). If they remained in the program, presumably they would fully reverse their stunting as well as their wasting.**

A child who is stunted, but not wasted, and 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 at normal weight-for-height. Thus, when the nutritional requirements for height gain are considered, 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 increase in height could cause a child with normal weight-for-height to become moderately wasted, despite the fact that the child was actually growing at an accelerated rate. This is occasionally seen in practice. It may occur when children are gaining height, because their diet becomes richer in growth nutrients but lower

* 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 between the process and the end result occurs because of this unfortunate nomenclature. "Stunting" is here used in the conventional, rather than the correct, way.

** The data of Golden and Walker [66] that suggested that children only gained height after they had reached their target weight-for-height were based on children who were 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. The weight gain of these children was due to 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 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.

in energy so that they "exchange" adipose tissue for lean and skeletal tissue [34]. Seasonal differences in weight and height growth can be explained in this way [56, 67].

In order to examine the nutrient requirements for the reversal of stunting,* 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 considered.

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 also needs to gain weight at an increased rate. A child 6 to 9 months of age who is gaining height at three times the normal rate will need an average weight gain of 4 g/kg/day 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 be reversed by the nutritional treatments. We should focus on the requirements for normal growth at an accelerated rate, rather than considering whether there are different nutrient requirements for ponderal and longitudinal growth.

Diets that do not produce height gain in children who are both stunted and wasted probably do not contain the appropriate amounts 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, synthesize 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 a gain in weight.

Are specific nutrients needed for reversal of stunting?

An increase of 1 cm in height should be accompanied by a weight gain of about 210 g.** 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 synthesize 210 g 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, sulfur, and probably magnesium. For other nutrients, if the requirements for bone formation are the same as or lower than those for soft tissue formation, the needs for accelerated longitudinal growth can be ignored.***

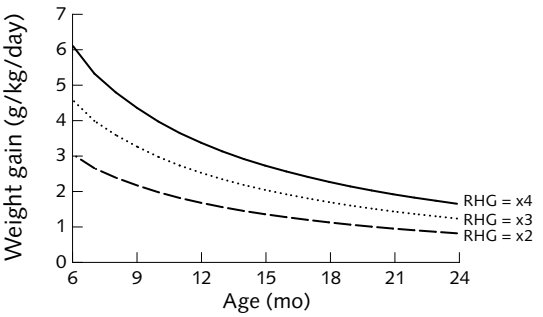

FIG. 3. Rates of weight gain that need to accompany accelerated height gain to maintain normal body proportions (weight-for-height). Based upon WHO 2005 standards. RHG, rate of height gain

The nutrients specifically required 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 remodeling of the osteoid of the mineralized cartilage. The nutrients needed for cartilage synthesis at the growth plates are thus the crucial factor in determining whether there is to be nutritional limitation of skeletal growth.

Cartilage is composed mainly of glycosaminoglycans such as chondroitin sulfate. These are highly branched carbohydrate chains attached to a small protein core. The characteristic of the carbohydrates moieties is that they are highly sulfated. The main essential nutrient needed in abundance to make cartilage is sulfur.**** Inorganic sulfate can be used; however, most of the sulfate in the body is derived from catabolism of the amino acids

* With regard to various deficits in weight-for-age seen in many populations, regression analysis of weight-for-age against 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 by the degree to which they are wasted. Low weight-for-age is thus dominated by the stunting component of growth.

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

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

**** In animal studies, bone growth is measured by the incorporation of radioactive sulfur into skeletal tissue [68, 69]. These assays, when used for factors in blood that stimulate bone growth, show low levels of these factors in malnourished children [70].

methionine and cystine.* Thus, there needs to be either adequate protein, relatively rich in sulfur amino acids, or inorganic sulfate 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 that of 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 cofactors for the maturation of collagen. Vitamin K is required for osteocalcin to "capture" calcium during bone formation. Magnesium is essential, 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 sulfur, phosphorus, calcium, magnesium, vitamin D, vitamin K, vitamin C, and copper.

The effect of nutrient deficiency on bone growth is illustrated by the classic experiments of McCance and Widdowson [71]. Their research shows three pigs born from the same litter. The large pig was given a normal diet, the smallest pig a restricted diet, and the medium pig was given a protein-deficient diet. The growth of the lower jaw of the protein-deficient pig 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 sulfur deficiency.**

In terms of ossified tissue, where calcium is the dominant nutrient, research by Hammond et al. shows the tibia and fibula of a feral pig, living wild, and the bones of a domestic pig from New Zealand (they are genetically similar, since there are no native wild pigs in New Zealand) [72]. The bones from the domestic pig are heavier and contain more calcium than the bones from the feral pig, but the feral pig's bones are longer. Calcium deficiency does not affect longitudinal growth. Calcium-deficient animals grow normally but have thin, weak bones. In contrast, growth ceases in animals with phosphorus deficiency. Even though calcium may not be important in stunting, children with moderate or severe malnutrition have thin, demineralized bones. Many have costochondral junction swelling, a sign of defective bone mineralization. This is likely to be due to either calcium or phosphorus deficiency.

Classification of the essential nutrients

About 40 nutrients are essential for health; each of them has to be in the diet that is supplied to children. If any one is not present in an adequate amount, 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, each one is likely to be critical for children who are living under conditions of environmental and infective stress and who have persistent or acute malnutrition. Essential nutrients are classified according to the response to a deficiency [59, 73]. Type I nutrients are those that are needed for particular biochemical functions in the body. If these nutrients are severely deficient, the child will develop specific symptoms and signs of deficiency; if their level is suboptimal, the child will be less healthy and will be susceptible to stress and infection. However, deficiency of these nutrients does not generally lead to growth failure, at least not until the deficiency results in overt clinical illness. Thus, children who are classified as of normal weight or even overweight, on the basis of weight-for-height, height-for-age, weight-for-age, or mid-upper-arm circumference (MUAC), may have quite severe deficiencies of any of the type I nutrients. Although this undernutrition 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 it will improve health and immune function. Deficiencies of several of these nutrients (iron, iodine, vitamin A) can be detected by convenient clinical features and tests, and therefore these nutrients have received most attention. For deficiencies of other type I nutrients, there are no pathognomonic clinical features and biochemical tests are inconvenient or expensive, so that deficiencies of these nutrients are frequently unrecognized until they are severe and life-threatening or cause an unfavorable outcome from intercurrent illness.

The type II nutrients are the growth nutrients. They

* 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 sulfates; and last, by the skeletal tissue to make cartilage. It is partly for this reason that gain in height presupposes the presence of sufficient sulfur-containing amino acids 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.

** The protein-deficient pig is also almost hairless. Hair proteins contain a high proportion of sulfur amino acids. There is disproportional growth failure in the different bones of stunted children. Among children who are stunted in height, the long bones are most affected, the spine is less affected, and the facial bones are least affected. 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 measurements of sitting height and leg length should be performed.

are the building blocks of tissue and are necessary for nearly all biochemical pathways. With deficient intake of any one of these nutrients, the child will not grow. A mild deficiency leads to stunting; with a more profound deficiency, or more commonly a pathological loss of the nutrient, there is also wasting. Because all tissues need these nutrients for cellular division and growth, those tissues 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 also have life spans of only a few days; therefore, a type II deficiency may aggravate or cause malabsorption and immune dysfunction. Because the moderately malnourished child (anthropometrically) has not grown, by definition there is a deficit* of *all* of the type II nutrients. This holds irrespective of whether the catabolic episode is due to an infection, a pathological loss, a specific type II nutrient deficiency, another cause of loss of appetite, or starvation. Since there are no body stores of these nutrients, apart from the functional tissues,** during tissue catabolism all the nutrients released from the tissue are lost from the body [75]. 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, since children with moderate malnutrition (stunting or wasting) have normally been consuming a diet deficient in many nutrients, including both type I and type II, multiple deficiencies are common. It would be inappropriate to give only the type II nutrients in an attempt to reverse wasting or stunting and ignore the high prevalence rates 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 to give zinc pills in the hope of finding the simple magic bullet. The history of parenteral nutrition provides a salutary lesson. 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 was thought to be adequate amounts, so that the diet was optimal, and then the nutrient of interest would be 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 of a particular nutrient, 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 slowed. 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 adventitial 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 from pantothenic acid deficiency among refugees in Afghanistan should not have happened [76].

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 the development of F100 and derivative foods used to treat severe malnutrition so successfully, and more recently to treat and prevent malnutrition in vulnerable populations [77]. It would be preferable to treat and prevent malnutrition with a mixture of local foods; if this is not possible, 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 (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 to recently have had, diarrhea. The moderately malnourished, therefore, do not start at the same baseline as those who are anthropometrically normal within the same population.

Anthropometric data on malnutrition have been used to calculate that about half of all child deaths are due to malnutrition [78]. These deaths are due 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 B_{12}, 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

* It is useful to differentiate a "deficit" from a "deficiency." A deficit denotes 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 [74]; similarly, a potassium, magnesium, or phosphorus deficit can be caused by protein deficiency [75].

** 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.

type I nutrient deficiencies (where there is no 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 articles specifically addressing the functional* and nutritional deficits of the 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 the Wellcome classification. The diagnosis of severe malnutrition at that time was less than 60% weight-for-age.** 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 –3 weight-for-height z-scores, 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 at the Tropical Metabolism Research Unit (TMRU), Jamaica (1980–90), and reported as "severely malnourished" shows that 61% had moderate wasting (< –2 to > –3 National Center for Health Statistics [NHCS] weight-for-height z-scores) and only 39% had severe wasting; when the same children were reassessed with the use of the WHO 2005 standards, 29% were still classified as moderately wasted. These children were severely stunted (60% < –3 z-scores, 32% < –4 z-scores, 16% < –5 z-scores). The same confusion about the definitions of "severe" and "moderate" malnutrition occurs even in recent publications (e.g., El Diop et al., 2003 [80], where half the severely malnourished children would be classified as moderately malnourished 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 reported separately 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, e.g., renal excretion of acid after an acid load [81] or cardiac output [82], shows that the moderately wasted children lie between the recovered children and the severely wasted children. However, there is considerable overlap between the degree of functional abnormality of moderately and severely wasted children.

Thus, it is proposed that the effects on weight-for-age criteria of physiological changes reported for children diagnosed as having severe malnutrition 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. Since most of these children are "uncomplicated" metabolically, they will have similar metabolic adaptations [83] to those reported. There is likely to have been an ascertainment bias toward 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 or her energy needs: when there is an energy deficit, the person feels hungry,*** and when sufficient energy is consumed, the person feels satiated. It is remarkable how precisely energy balance is maintained, even in the obese gaining weight (if an adult gains 5 kg in 1 year, energy intake and expenditure are 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 tastes learned from the mother during pregnancy and the family in infancy, modulated by taste appreciation, habituation, organoleptic properties, tradition, culture, and learned feelings of well-being associated with different foods

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

** Usually using the Harvard standards published in earlier editions of *Nelson's Textbook of Paediatrics* [79].

*** 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 a deficiency in many other nutrients giving rise to anorexia. Anorexia does not need to be major to lead to malnutrition. If mild anorexia leads to an energy intake of 90 kcal/kg/day and the requirement is 100 kcal/kg/day so that the shortfall is 10 kcal/kg/day, the child will lose about 2 g/kg/day (5 kcal/g). In 10 days, 2% of body weight will be lost, and in 3 months, the child will have lost 20% of body weight and will now be 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.

and aversions associated with coincident illness.

If the quantity of food a person eats is closely related to energy requirements (at any particular level of adaptation), that total quantity of food has to contain all the nutrients for health. If "empty calories" form a large proportion of the diet, 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 principal reasons that 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 [34]. A good diet is characterized by the consumption of a wide variety of different foods, with 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 characterized 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, 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 term.* As a diet becomes more restricted, 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 of 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 contain only half the required 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 consume traditional weaning foods as well as breastmilk. 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/day as biscuits that were nutritionally deficient in several type II nutrients. The supplement was detrimental for the adolescents, with a negative "dose" response, those receiving 300 kcal being the worst. Presumably, the home diet was marginal in these nutrients, and 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 well-being of the pupils [85].

There is an important corollary of this concept. If only two foods are consumed and they each have the appropriate nutrient density to fully satisfy the nutrient requirements if consumed exclusively, then the nutritional requirements of the child will be fully met with *any* admixture of the two foods. For example, if only breastmilk** and a fully fortified complementary food of appropriate nutrient density and bioavailability are consumed, 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 breastmilk, there could be a smooth change in the proportions of breastmilk and complementary food consumed 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 [86, 87]. 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 [86]. Usually energy requirements are given separately for male and female children, 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

* Even human breastmilk has low levels of iron and copper. This is not at all harmful, since physiologically the fetus 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 [84]. Many moderately malnourished children have had either prematurity or intrauterine growth retardation; the additional requirements for those nutrients that have fetal stores and low breastmilk concentrations for this particular group of moderately malnourished infants are not considered in this report. The concentrations of other type I nutrients in breastmilk vary with the mother's status. The nutritional requirements of the lactating mother to enable her to provide milk with optimal amounts of nutrients are not considered in this report.

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

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 and sex group. However, the actual requirements of both energy and each nutrient (say nutrient X) for each individual vary within the population. If the requirements for energy and nutrient X vary completely independently, then to cover 97% of the population's requirements, when these requirements are expressed as nutrient:energy densities (amount of nutrient X per kilocalorie), 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 ratios) in the design of diets for the moderately malnourished, the following were considered:

1. 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.
2. For individuals of the same weight, most of the variation in requirements 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 lower requirements of energy and all other nutrients for maintenance than lean tissue; thus, with a higher proportion of the body as fat, all the nutritional requirements, when expressed per kilogram of body weight, are lower. Bone, 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 kilogram of 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 in similar proportions, so that expressing nutrient needs in relation to energy requirements will automatically compensate for these differences. The moderately malnourished child (wasted or 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 kilogram of body weight if there were no metabolic adaptation. This is sometimes found in practice in stunted children [88], despite presumed metabolic adaptation [83].
3. The basal metabolic rate is the major determinant of energy requirements. It varies from one individual to another, depending upon 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 energy increases; with adaptation to a chronically low intake, tissue turnover decreases [89]. To set requirements per unit of energy automatically compensates for such changes in metabolic state, 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. Setting requirements per unit of energy 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.
4. The energy requirements are clearly related to changes in physical activity. It is argued that the variance in basal metabolic rate itself covaries 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 losses, and therefore in requirements, of many nutrients, most frequently demonstrated by increases in urinary nitrogen with exercise. There are insufficient data on the exact nature of the changes in needs for energy and most other nutrients with changed physical activity, and what data there are come from adult athletes and not children or the malnourished. It may be that the incremental need for energy is somewhat higher than the incremental need for other nutrients. Nevertheless, most energy is consumed for basal and resting metabolism, and the variation in 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.

5. In children and the convalescent, there are also 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 required 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 amounts 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 who need to gain weight and height at accelerated rates. Furthermore, the relative energy and nutrient intakes required to support accelerated growth depend upon the type of new tissue that should be synthesized 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 will be lower; alternatively, if the child is to make lean tissue, the energy requirement will be relatively low and the nutrient requirement will be higher.

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

Nutrient:energy density requirements for normal people

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

- The FAO/WHO 2004 energy requirements [8];
- The WHO/FAO/UNU 2007 Protein requirements [90] ;
- The FAO/WHO/UNU 1985 Protein requirements [91];
- The FAO/WHO 2001 Human Mineral and Vitamin Requirements [7];
- The IOM series of publications [9–14]. The age ranges used for the IOM reports are not the same as those for the FAO/WHO requirements;
- The UK Dietary Reference Values (DRVs) 1991 [92]. Typical weights are given for the population groups.
- WHO/FAO/International Atomic Energy Agency (IAEA) 1996 for several trace elements [6].

For all calculations, the FAO/WHO 2004 energy requirements [8] have been used, with 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. Since these are slightly lower than the male child's energy requirements, the derived nutrient:energy ratio is marginally higher when calculated with the use of the female energy requirement.

For previous estimates of nutrient densities needed for stressed populations, either the old factorial data [3] or the values of the International Dietary Energy Consultancy Group (IDECG) [93] were used [4, 5]. Although the IDECG figures are lower than those derived before the doubly labeled water technique was 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, the nutrient:energy density for young children was computed and expressed as the amount of nutrient required per 1,000 kcal of diet. The resulting values are presented in **table 45** (see appendix).*

When there are major discrepancies between the different bodies that have made recommendations, those of FAO/WHO have been preferred. When 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, 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 antioxidant defense, and maintaining biomarkers within the physiological range.

Are the nutrient:energy density requirements derived for normal Western people applicable to the malnourished?

The conclusion is that the variations in requirements within a normal population are 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 they are expressed as nutrient densities, not in absolute amounts in relation to either height or age. If the child is to have accelerated

* When expressed as nutrient:energy densities, requirements are similar across the age groups from children to adults [4]. Thus, for nearly all age groups, and pregnant and lactating women, 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.

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 of energy, instead of in absolute amounts, is that when the foods comprising the diet are taken to satisfy the 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, 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 recovering severely and moderately wasted children. As the child with severe malnutrition gains weight, he or she 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 synthesized 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, the same diet as that 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:

» There is a reduction in the intestinal absorptive function of most people who live in poverty in a chronically contaminated environment. This is partly due to overgrowth of bacteria in the small intestine [94–102], which appears to be ubiquitous in the malnourished and present in all populations of such children who have been investigated. Most malnourished children spend a substantial proportion of their lives with at least mild diarrhea. This may, in part, be due to the prolonged high intake of lectins, saponins, and other antinutrients in the unrefined diet [103]. The levels of antinutrients allowable in foodstuffs have not been established by the *Codex Alimentarius*. This question is addressed by Michaelsen et al. [2]. 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 [104, 105] and gastric acid [106], and the bacterial overgrowth and the increased vulnerability of such an intestine to antinutrients and naturally occurring toxic factors in foods. Bioavailability studies have not normally been conducted in subjects with such fragile intestinal function.

» 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 [107–109]. There is a particular increase in the need for many of the antioxidant nutrients under conditions of both infection and 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 anemia associated with the use of biomass as fuel [110].

» The diets of most poor people are predominantly vegetarian. Because of the fiber and phytate within these foods, 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 feces, the available phosphorus will be lower than needed). Seeds have the correct nitrogen:potassium:magnesium:phosphorus ratio to make cytoplasm for the growing plant. If the phosphorus is malabsorbed because it is in the form of phytate, 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 phosphate from phytic acid (e.g., fermentation, germination, and

use of plant ash), the requirement for nutrients such as phosphate should be expressed in terms of *nonphytate* phosphorus. Nearly all food-composition tables give only 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 the moderately malnourished are to recuperate at a slower rate than the severely malnourished. If the moderately malnourished are to regain weight at the same rate as the severely malnourished then the nutrient:energy densities of the F100 formula is also appropriate for these children. 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. For weight gain, there is clearly no need to have the intake of any of the nutrients higher than those provided by F100, provided that the availability from the matrix is the same as that in F100; 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, and F100 and the differences between the RNIs for healthy children and the nutrient densities provided by F100.

All the values in the table are expressed per 1,000 kcal energy requirement (FAO) for 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 **table 45** (see appendix).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 ratios of the total requirements (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). Because 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 kilogram of initial body weight per day) when different types of tissue are being replaced in the body. At the left-hand side of the graph, 30% of the new tissue is lean tissue and 70% is adipose tissue, whereas at the right side of the graph, 80% of the new tissue is lean tissue and 20% is 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 whose muscle and skin* are wasted. During recovery to normal, both types of tissues have to be replaced. Measurements have shown that it is desirable to have a 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 5 g/kg/day and for them to replace their initial tissue deficits over about 30 days.

The graph (**fig. 6**) has been drawn using the data obtained from experimental studies on children recovering from malnutrition: the requirement for energy is 82 kcal/kg/day and the absorption of energy is 90% of that ingested, so that the child needs to ingest 91

* The skin is the largest organ of the body; it atrophies in malnutrition.

TABLE 4. RNIs for normal children compared with F100 formula diet[a]

Nutrient	RNI (FAO)	Other (IOM/UK/ WHO)	F100 and RUTF	F100 minus FAO	% Difference	F100 minus other	% Difference
Protein (g)	22.3	21.2	28.4	6.1	*29*	7.2	*34*
Protein (%kcal)	8.9	8.6	11.1	2.2	*26*	2.5	*30*
Sodium (mg)	529 UK	978	434	−95	*−10*	−544	*−56*
Potassium (mg)	1,099 UK	2,934	2,403	1,304	*44*	−531	*−18*
Chlorine (mg)	—	1,467	1,831	—	—	364	*25*
Magnesium (mg)	79	112	175	96	*85*	63	*56*
Phosphorus (mg)	450	634	762	312	*49*	128	*20*
Calcium (mg)	595	820	1,008	413	*50*	188	*23*
Zinc (mg)	12.5	16.5	22.3	9.8	*60*	5.8	*35*
Copper (μg)	332	892	2,749	2,417	*271*	1,857	*208*
Iron (mg)	18	16	24	6.2	*38*	7.6	*46*
Iodine (μg)	201	193	188	−13.1	*−7*	−5.1	*−3*
Selenium (μg)	17.8	29.7	54.8	37.0	*125*	25.1	*84*
Fluorine (μg)	—	740	NA	—	—	—	—
Manganese (μg)	—	1,170	690	—	—	−480	*−41*
Chromium (μg)	—	10.8	NA	—	—	—	—
Molybdenum (μg)	—	16.6	NA	—	—	—	—
Vitamin B_1 (μg)	523	525	700	177	*34*	175	*33*
Vitamin B_2 (μg)	595	628	2,000	1,405	*224*	1,372	*218*
Vitamin B_6 (μg)	595	732	700	105	*14*	−32	*−4*
Vitamin B_{12} (ng)	966	864	1,000	34	*4*	136	*16*
Folate (μg)	167	147	350	183	*124*	203	*138*
Niacin (μg)	6,239	8,368	10,000	3,761	*45*	1,632	*20*
Vitamin C (mg)	45	74	100	55	*75*	26	*35*
Pantothenic acid (mg)	2.7	2.7	3	0.3	*12*	0.3	*12*
Biotin (μg)	9.7	9.7	10.0	0.3	*4*	0.3	*4*
Choline (mg)	—	223	—	—	—	—	—
Vitamin A (μg)	595	743	1,500	905	*122*	757	*102*
Vitamin D (μg)	7.4	10.9	30.0	23	*206*	19	*174*
Vitamin E (mg)	8.9	5.2	22.0	12	*231*	17	*321*
Vitamin K (μg)	16	40	40.0	24	*60*	0	*1*

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake; UK, United Kingdom; WHO, World Health Organization

a. All values are expressed per 1,000 kcal female FAO energy requirement. Italicized numbers indicate a unit change to percentage.

kcal/kg/day* [48, 111, 112]. If each gram of new lean tissue consumes 2.8 kcal and each gram of new adipose tissue consumes 8 kcal, then the equation for energy requirement is

$$\text{Energy} = [82+ (2.8 * \text{lean} + 8 * (1 - \text{lean})) * \text{RWG}] / 0.9 \text{ kcal/kg/day}$$

(see legend to **table 5** for detailed explanation of the equation). For example, if the rate of weight gain (RWG) is to be 5 g/kg/day and the tissue is 70% lean tissue, then the equation becomes

$$\text{Energy} = [82 + (2.8 * 0.7 + 8 * 0.3) * 5] / 0.9 = 115 \text{ kcal/kg/day.}$$

For each of the growth nutrients, similar equations were derived from the amounts needed to maintain body weight, and then the increments were 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 normal calculation for energy requirement for maintenance uses 100 kcal/kg/day 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 spilled. To obtain the amount of the final diet that should be offered to malnourished children, it is important to reinstate an increment for spillage.

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**.

Estimation of individual nutrients' RNIs for moderately malnourished children

Type II nutrients

Protein

The protein energy content of breastmilk is about 15 g/1,000 kcal (6% of energy). This protein is perfectly balanced to meet requirements; however, a proportion is immunoglobulin A, which is not absorbed, so that the available protein is less than 6% of dietary energy. Using cow's milk protein, F100 contains 28 g/1,000 kcal (11.2% of energy). This is sufficient for rapid catch-up growth at over 20 g/kg/day 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 definitions of the age groups used by different authorities in this and subsequent tables are given in **table 45** (see appendix).

The highest figure is 22.3 g/1,000 kcal (FAO 1985 [91]), which should cover 97.5% of normal children's requirements. More recently, WHO/FAO/United Nations University (UNU) [90](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 0.6 g/kg/day [113]. This does not allow for any individual variation. Furthermore, with this intake, severely malnourished children cannot resynthesize liver proteins [114], indicating that this figure, derived from nitrogen balance data, is an underestimate of the true maintenance requirement. The minimum requirement for normal children is about 1.2 g/kg; this is the amount of protein supplied by F75, the diet used for severely malnourished children on admission. The protein content is about 20% (wet weight) in lean tissue [115] and 2% in fat tissue. During rapid weight gain, the additional protein is used to make new tissue with about 60% efficiency [116]. It is assumed that 90% of the protein is absorbed. To attain a rate of weight gain of 5 g/kg/day with 70% of the new tissue as lean tissue would require 23.3 g/1,000 kcal (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 that 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.

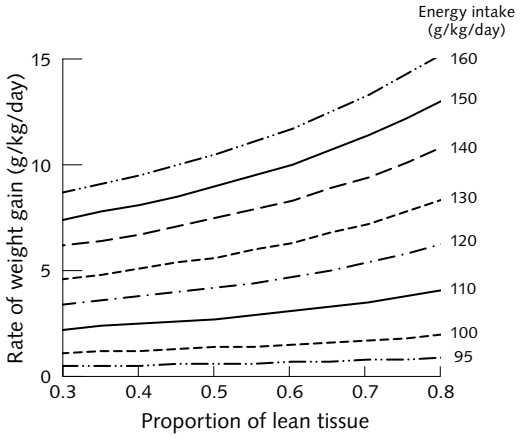

FIG. 6. Weight gain expected in relation to the proportion of lean tissue being synthesized for different energy intakes. For example, if a child is taking 140 kcal/kg/day and 80% of the new tissue is lean tissue, she should gain weight at 10.9 g/kg/day; if only 30% of the new tissue is lean and the rest is adipose tissue, the rate of weight gain should be 6.2 g/kg/day

In the past, increasing the protein content of diets and relief foods used in the 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 [117, 118]. When the diet is imbalanced, the excess protein will be broken down to energy and the nitrogen will be excreted.

It has been found that high-protein diets can be detrimental in severe malnutrition. This is thought to be for two reasons. First, whenever there is any compromise in hepatic function, additional protein that cannot be utilized for tissue synthesis has to be broken down by the liver and excreted; this process requires energy, which may be compromised in malnutrition [119], and generates an acid load [120, 121]. In experimental animals, a high protein load given in the presence of a dysfunctional liver can precipitate acute hepatic failure. When the protein cannot be adequately metabolized by the liver, a situation similar to an inborn error of amino acid metabolism occurs (malnourished children have acquired errors of amino acid metabolism [122–126]). 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 that 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

TABLE 5. Summary equations used to derive energy and nutrient requirements for catch-up weight gain[a]

Nutrient	Unit	Maintenance (units/kg body wt/day)	Deficit increment (units/kg body wt/day)	Diarrhea increment (units/kg body wt/day)	Lean tissue (units/g tissue)	Adipose tissue (units/g tissue)	Efficiency of use (%)	Absorption (%)
Energy	kcal	82	0	0	2.8	8	100	90
Protein	g	1.2	0	0	0.2	0.02	60	90
Potassium	mg	70	18	47	3.6	0.4	100	90
Sodium	mg	10	−17.5	27	1.4	0.7	100	100
Magnesium	mg	14.4	4.8	7.2	0.24	0.024	100	30–60
Phosphorus	mg	34	14.5	68	1.86	0.3	100	60
Zinc[b]	µg	33	340, 570	110	81	8.1	100	15, 35, 56

a. The general form of the formula used was

Nutrient = [maintenance + deficit + diarrhea + ({(C-lean * P-lean) + (C-fat *(1 – P-lean))}*RWG)* efficiency] / absorption.

The units are energy or nutrient/kg/day.
Where:

Maintenance is the minimum amount of *absorbed* (not ingested) nutrient or energy needed for balance (units/kg/day). *Deficit* is the tissue deficit that has to be replaced *in the existing tissues of the body*, calculated from the measured reduction in tissue wet-weight concentration (usually from muscle biopsy) of the nutrient per kilogram (not adjusted for changes in body composition due to malnutrition) and converted into a daily additional requirement on the basis that the deficit in the child's existing tissue is to be made good in 30 days. That is (normal-concentration * deficit-proportion/30); for example, if the normal potassium level is 2,340 mg/kg and there is a 23% deficit, then the daily increment added for the deficit is 2,340 * 0.23/30 = 18 mg/kg/day. *Diarrhea* is the *additional* amount of the nutrient, over and above the maintenance requirement, that is lost when the child has one or two nondehydrating loose stools per day, converted into a daily loss per kilogram of body weight. *C-lean* is the concentration of the nutrient or energy in normal lean tissue (nutrient per gram of tissue). *P-lean* is the proportion of new tissue synthesized that is lean tissue. *C-fat* is the concentration of the nutrient or energy in adipose tissue. (*1 minus P-lean*) is the proportion of new tissue that is adipose tissue. *RWG* is the rate of weight gain (g/kg/day); this has been taken to be 5 g/kg/day for most analyses. *Efficiency* is a factor to allow for the efficiency of conversion of the absorbed nutrient into tissue. It is assumed to be 100% for most nutrients that are recycled in the body. This factor is only applied to the nutrient laid down in new tissue; it is assumed that a reduced efficiency is already incorporated into estimates of the maintenance requirement. How the efficiency changes with clinical state or in making good a deficit is unknown, and efficiency is therefore assumed to be 100%; if it were less, this would have the effect of increasing the nutrient requirement. *Absorption* is the proportion of the nutrient or energy ingested that is absorbed into the body (availability).

At any particular rate of weight gain and tissue composition, the derived value for the nutrient requirement was divided by the derived value for energy requirement (nutrient/kg/day divided by energy/kg/day = nutrient/energy) to obtain the nutrient:energy density; it was expressed as amount of nutrient per 1,000 kcal required in the diet of moderately malnourished children to promote rapid growth.

Most of the values in the table come from single studies in patients with a spectrum ranging from moderate to severe malnutrition. Many of these studies are old and use relatively inaccurate analytical techniques. The confidence intervals around the values, and hence the derived requirements, are correspondingly wide; see text under each nutrient for references.

b. Two figures are given for zinc deficit and three for availability. These represent different estimates of the deficit and the change in availability from diets of different matrices. See section on Zinc.

to one-third of body water per day [127]. A high-protein diet is a reason for a high water requirement and can even lead to hyperosmolar dehydration. Because both of 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 protein recommendations for normal children are 21 g/1,000 kcal and 22 g/1,000 kcal, respectively; F100 contains 28.4 g/1,000 kcal but is designed to sustain a higher rate of weight gain than that under consideration for the moderately malnourished. The present calculations suggest that an intake of high-quality protein of 23.3 g/1,000 kcal would be adequate for the moderately wasted or stunted child.

It is therefore proposed that the diet should contain 24 g of protein with a quality of at least 70% of reference protein per 1,000 kcal. 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 26 g/1,000 kcal to account for the uncertainties of the calculations and any additional needs of stunted children. It is recommended that protein sources rich in the sulfur amino acids should be used preferentially in stunted populations.

The appendix (**table 45**) gives the amino acid requirements per 1,000 kcal for normal children. There are insufficient data to make recommendations for individual amino acids for the moderately malnourished child. Nevertheless, the nutrient density of essential amino acids in the diets of moderately malnourished children should not fall below the requirements for normal children.

Sulfur

There are important uses for amino acids beyond the synthesis of protein. In particular, the metabolite sulfate

TABLE 6. RNI protein requirements expressed as nutrient densities and proportion of energy

Unit	Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
g/1,000 kcal	FAO 1985	22.3	20.1	15.2	14.6
g/1,000 kcal	FAO 2007	15.0	15.6	12.8	13.5
g/1,000 kcal	IOM	—	16.4	12.7	13.7
g/1,000 kcal	UK	21.4	21.2	15.2	14.8
%kcal	FAO	8.9	8.0	6.1	5.8
%kcal	IOM	—	6.5	5.1	5.5
%kcal	UK	8.6	8.5	6.1	5.9

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake; UK, United Kingdom

TABLE 7. Protein:energy ratio for children gaining tissue with between 30% and 80% lean tissue at different rates[a]

% lean	1 g/kg/day	2 g/kg/day	3 g/kg/day	5 g/kg/day	10 g/kg/day	15 g/kg/day
30	15.0	15.2	15.5	15.9	16.6	17.1
35	15.2	15.6	16.1	16.8	18.0	18.7
40	15.4	16.1	16.6	17.6	19.4	20.5
45	15.6	16.5	17.2	18.5	20.8	22.3
50	15.8	16.9	17.8	19.4	22.3	24.2
55	16.0	17.3	18.4	20.3	23.9	26.2
60	16.3	17.7	19.0	21.3	25.5	28.4
65	16.5	18.2	19.7	22.3	27.2	30.6
70	16.7	18.6	20.3	23.3	28.9	32.9
75	16.9	19.0	20.9	24.3	30.8	35.4
80	17.2	19.5	21.6	25.4	32.7	38.0

a. Note that with low rates of weight gain and 30% lean tissue deposition, the ratio approximates that of the IOM calculations.

is used to synthesize 3'-phosphoadenosine 5'-phosphosulfate (PAPS). This is the high-energy sulfate compound used to make glycosaminoglycans for basement membranes and cartilage. The sulfate is derived mainly from the amino acids cystine and methionine. There is experimental evidence that addition of inorganic sulfate can alleviate some of the requirements for these amino acids, in both animals and humans [12], and sulfate added to a protein-deficient diet can result in a growth response. On the other hand, excess sulfate in the diet is not absorbed and can give rise to an osmotic diarrhea (magnesium sulfate is used as a laxative). The average intake of sulfur from all sources by children up to 5 years of age in the United States is between 0.5 and 1.5 g/day [12], which is high in comparison with the IOM requirement for sulfur amino acids of 575 mg/1,000 kcal; this equates to about 170 mg of sulfur per 1,000 kcal.

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

There is a further reason why sulfur-generating amino acids are important in a hostile environment. Many relatively hydrophobic toxins and drugs are eliminated by conjugation with sulfate in the liver for elimination in the bile. Other xenobiotics and products of free-radical damage are covalently bound with the sulfhydryl moiety of glutathione and eliminated in the urine as mercapturic acids; their excretion is elevated in the malnourished child [128]. If there is a high exposure to such toxins (smoke, food toxins, and bacterial products), additional sulfur-containing amino acids, over and above those needed for protein and glycosaminoglycan synthesis, need to be supplied.

Low levels of sulfate are excreted by children on a typical African diet [129] and those with malnutrition [130, 131], and these children have undersulfation of glycosaminoglycans [132–134]. Adequately sulfated glycosaminoglycans may be particularly important to prevent viral infection [135, 136]

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 the diet of these children should contain additional sulfate. The amount is uncertain but is clearly an important research topic. **It is suggested that about 200 mg of sulfur per 1,000 kcal, as sulfate, be incorporated in the diet, *in addition* to the sulfur 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 potassium requirements in 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 do.* In particular, there is a major depletion of potassium in all malnourished patients [137–146]. 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 malnutrition; it has even been suggested that the administration of heroic amounts of potassium lowers mortality** [147]. Some committees have suggested minimum intakes or AIs for Western populations. The uncertainly is reflected in the marked difference in the published figures (**table 8**). The 10th edition of the US Recommended Dietary Allowances (RDAs) [148] gives minimum values of 800 to 1,000 mg/1,000 kcal. The UK safe allowance is 1,100 mg/1,000 kcal. The recent IOM recommendations are considerably higher than this, going up to nearly 3 g/1,000 kcal for a 1- to 3-year-old child. The IOM figure is very high and is in disagreement with all other estimates of the 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 1,100 mg/1,000 kcal will be used.

The amount of potassium in F100, 2,400 mg (61 mmol)/1,000 kcal, is adequate to replete body potassium in the severely malnourished in about 2 weeks [149] and support rapid weight gain. Thus, this amount could be considered as the upper boundary for the moderately malnourished. No tolerable upper limit has been determined for potassium in any of the publications, but a proportion of children have impaired renal function in malnutrition [22, 81, 150–154]; 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 diarrhea 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 the following factors need to be taken into account:

Normal potassium losses. On a diet containing 780 mg (20 mmol) of potassium per day, adults lost 10,000 mg (250 mmol) of potassium from their bodies, 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 [155] (despite considerable sodium retention and alkalosis [156]). The minimum daily fecal losses were about 400 mg (10 mmol), and the renal losses were 200 to 400 mg (5 to 10 mmol). Such experimental deficiency studies have never been performed in children.

In malnourished children *without* diarrhea, but with an adequate potassium intake, the stool output was 23 ± 10 (SD) mg/kg/day (0.6 ± 0.25 mmol/kg/day) [157]. These children all had low total body potassium content and could be said to be "adapted" in a similar way to Squires and Huth's adults [155]. This would then perhaps give a minimum stool output with an upper 97.5% limit of 43 mg (1.1 mmol) per kilogram of body weight per day.

The minimum urinary losses are unknown. Normally about 3% of filtered potassium is excreted, which corresponds to about 1,000 mg (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/day (0.7 to 2.3 mmol/kg/day), which is consistent with the figure in adults when converted to body surface

* Potassium deficiency is especially likely in patients with diarrhea, diuretic-induced renal losses, anorexia, and any abnormalities of the sodium pump or cell membrane, such as those present in moderate and severe wasting.

** There is one report that severely malnourished children have a better outcome with the administration of higher amounts of potassium [147], 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 hyperkalemia 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 the diet of children recovering from malnutrition in Kivu, Democratic Republic of the Congo, resulting in an increased potassium intake.

TABLE 8. Potassium AIs (mg/1,000 kcal)

Nutrient	Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
Potassium	IOM	—	1,041	2,934	2,737
Potassium (min)	UK	1,099	1,001	818	821

AI, adequate intake; IOM, Institute of Medicine; UK, United Kingdom

area. It is reasonable to assume that the lower bound of this range corresponds with the minimum amount of potassium that 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 with fecal and urinary losses.

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

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

Potassium is the major cation in normal feces; it is exchanged for sodium mainly in the colon. In diarrhea this exchange is less than perfect, so that with increasing volume of diarrhea the sodium concentration increases and the potassium concentration decreases [158, 159]. Although the concentration of potassium may decrease, this is more than offset by the increased volume of diarrhea, so that there is a substantial increase in the amount of potassium lost in all forms of diarrhea. 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 diarrhea there is equimolar potassium and sodium, and in normal stool potassium reaches 90 mM concentration. Thus, although the mean stool potassium output of a malnourished child without diarrhea was quite modest, with one or two loose stools (which are usual in malnourished children) the output increased to 62 ± 23 mg (1.6 ± 0.6 mmol)/kg/day [157]. In acute diarrhea the output can be considerably higher. Ruz and Solomons [160] published an equation for children with diarrhea, which indicates that the output is related to fecal volume by the relationship

$$\text{Potassium (mg/kg/h)} = 3.11 + 0.96 * \text{fecal volume (mL/kg/h)}.$$

The average weight of each diarrheal stool from a malnourished child of 6 kg is about 30 g; if a child has two such stools per day (not sufficient to be diagnosed as acute diarrhea), there will be a loss of 10 g/kg/day of stool, and the fecal output of potassium will increase to 90 mg/kg/day 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 diarrhea should be treated with rehydration therapy; the dietary recommendations do not cover such needs. Nevertheless, two "loose stools" that do not result in dehydration 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 diarrhea that is 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 potassium content is about 3,590 mg/kg (92 mmol/kg) in muscle and about 350 mg/kg (9 mmol/kg) in fat tissue, so that the total body potassium content is about 2,340 mg/kg (60 mmol/kg).

The increment in energy requirement over the basal requirement is greater than the increment in potassium requirement over the basal requirement, 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 synthesized, much more potassium is needed than when adipose tissue is laid down. At rates of weight gain up to 5 g/kg/day, 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 effect of the type of 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 [139, 144, 146, 161]; this is brought about by slowing down of the sodium pump, which normally maintains a high potassium concentration inside the cell [162, 163]. 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 to 7 weeks of undernutrition to fully

develop. It is likely that the moderately malnourished child will have been underfed for at least this length of time.

The deficit is 23%, based on measurements of total body potassium, and about 11%, based on fat-free dried muscle biopsies. The tissue deficit of potassium is thus greater than that of protein.

If we assume that there is a 23% deficit in the tissue, which has to be made up in 30 days, then there is a requirement of an additional 18 mg (0.46 mmol)/kg/day (calculated as 60*0.23/30 mmol/kg/day, where there are 60 mmol/kg, a 23% deficit 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 reasons for the high content of potassium in F100 and F75 (2,400 mg/1,000 kcal) are that the tissue deficit has to be corrected more rapidly in severely malnourished children, particularly in those with kwashiorkor (7 to 14 days), and that the mortality rate appears to be lower with high intakes of potassium.

We should assume that the moderately malnourished child will have up to three loose (not watery) stools daily and that we need to repair the tissue deficit in about 30 days. **In this case, the potassium intake should be 1,600 mg/1,000 kcal. 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 1,400 mg/1,000 kcal.** On a local diet, the child will then need additional potassium if there are loose stools (even without clinical diarrhea).

Magnesium

In general, the need for magnesium in the food for moderately malnourished children has been largely ignored. There is a large tissue magnesium deficit in children with malnutrition, including those with moderate malnutrition. Children remain in strongly positive magnesium balance throughout recovery, and even at the time of their full recovery, after they have regained weight to reach normal weight-for-height, the magnitude of the positive balance of magnesium (avid retention in the body) is impressive and worrying [164–170]. Even current best-practice therapeutic care seems unable to fully replenish the magnesium deficit of severely or moderately malnourished patients within the time required to regain normal weight.

It is unclear whether this strongly positive balance is due to sequestration of magnesium into bone with increased bone turnover during convalescence [171], but the amount of magnesium sequestered 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) is markedly decreased by magnesium depletion [172, 173]. Magnesium depletion, in particular, is thought to exacerbate the osteoporosis and osteomalacia of celiac disease and Crohn's disease and may be partly responsible for the osteoporosis of malnutrition. Frequently, patients who have been treated for hypocalcemia 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 hypercalcemia [174]; the correction of magnesium deficiency *must* accompany or precede the 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 presence of a continuing magnesium deficit; it is likely that the delay in return of intracellular potassium concentrations to normal is related to the difficulty of 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), the potassium status of adults taking diuretics returns to normal [175]. This is probably because magnesium is an important cofactor controlling the sodium pump [176].

There is also evidence that thiamine deficiency cannot be corrected in the presence of a magnesium

TABLE 9. Basal potassium requirements and effect of stool losses and a tissue deficit (mg/kg/day)

Variable	Urine/stool	Urine plus stool[a]	Urine and, stool plus Deficit[b]
Basal urine	27	—	—
Normal stool	43	70	88
1 loose stool	82	110	128
2 loose stools	90	117	135
3 loose stools	98	125	143

a. The sum of urine and stool losses
b. The sum of urine and stool losses and the required intake to replete the deficit

TABLE 10. Potassium requirements of moderately malnourished children (mg/1,000 kcal)[a]

Variable	No tissue deficit	Tissue deficit
Basal, normal stool	770	967
Basal, 1 loose stool	1,203	1,400
Basal, 2 loose stools	1,288	1,485
Basal, 3 loose stools	1,374	1,571

a. See **table 5** for calculations.

deficiency [177]. 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 presence of a magnesium deficiency also make adequate magnesium, in an available form, a critical nutrient for the stunted child.

The starting point for the requirements is only 79 mg/1,000 kcal for normal individuals, according to the FAO. The IOM has set the requirements at 112 mg/1,000 kcal, whereas the UK DRV for younger children is 121 mg/1,000 kcal (**table 11**). This large discrepancy between the committees reflects the paucity of experimental data on magnesium requirements in normal children.

The magnesium level in F100 is 175 mg/1,000 kcal. 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 the availability of magnesium from the diet. This is the major factor in determining magnesium balance. Its absorption is adversely affected by fiber, phytate, and oxalic acid [9] (which are present in many foods, particularly wild foods). In addition, there may be an inhibitory effect of a high-fat diet, since the magnesium salts of the fatty acids that are released during digestion are all insoluble; this effect has not been adequately investigated [178]. It is probable that the magnesium present in breastmilk is particularly available (60% to 70%). The average availability from a mixed Western diet in adults consuming sufficient magnesium to maintain balance is about 50%. The availability falls to 35% with a high-fiber diet [9]. It is assumed that the amount of fiber in the diet will be less in therapeutic diets than in the usual diets consumed in the developing world; if this is not the case, 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 fecal magnesium output is between 7 and 12 mg/kg/day [179, 180], with an absorption of dietary magnesium of about 30%. The normal kidney can conserve magnesium efficiently; nevertheless, in balance studies of malnourished subjects with gross magnesium deficiency, the lowest observed urinary magnesium output was 1 mg/kg/day, with most of the subjects excreting more than 2.5 mg/kg/day without supplementation. The absorption of magnesium is under physiological control and related to the intake. Normal adults with normal intestinal function consuming a low-fiber diet with high magnesium content absorb less than 25% of magnesium; absorption increases to 75% when the magnesium 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. The graphs 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 synthesized does have an effect, but at rates of weight gain below 5 g/kg/day 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 effects of growth and the type of soft tissue that is required to be synthesized are thus not relevant to this analysis and will not be presented.

Malnutrition. The magnesium 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 magnesium level of 220 to 240 mg/kg wet weight of lean tissue to less than half this value (100 mg/kg) [167, 168]. During conventional recovery on a milk-based diet without additional magnesium, this value increased only marginally (to 135 mg/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 (0.07 mg/mg); the malnourished child has a ratio of 0.09 on admission, which 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 to synthesize 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).

To make up a magnesium deficit of 100 mg (4.1 mmol)/kg of lean tissue in 30 days, a person with 70% lean tissue would have to consume an additional 2.3 mg/kg/day of magnesium to allow for soft tissue

TABLE 11. Magnesium requirements for normal children (mg/1,000 kcal)

Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
FAO	—	79	63	59
IOM	—	112	78	94
UK	121	114	89	88

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; UK, United Kingdom

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 4.6 mg/kg/day.

Diarrhea. There are substantial increases in magnesium losses with diarrhea. Western gastroenterologists cite magnesium deficiency as being the most frequent and troublesome deficiency in such diseases as Crohn's disease [181–183]. If we assume the minimum fecal output of magnesium as 7.3 mg (0.3 mmol)/kg/day in malnutrition, as in normal people, and we also assume that malnourished patients without magnesium supplementation, who are at the upper end of the range of magnesium outputs, have mild diarrhea, then the fecal output during the sort of diarrhea that is likely to be found in moderately malnourished children will be at least twice that found in nondiarrheal states, i.e., 14.6 mg (0.6mmol)/kg/day.

Magnesium requirements. With the use of the parameters listed in **table 12**, the requirements for magnesium under various conditions can be computed using the form of the equation given in **table 5**, substituting the values for magnesium. Fecal 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, the effect of diarrhea will 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 fecal loss be 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/1,000 kcal for fortified diets. Despite the lack of specific data on magnesium metabolism with F100, in view of the positive results obtained from giving F100 to malnourished children, for food-based diets it would be reasonable to reduce intake to a minimum of 200 mg/1,000 kcal for planning purposes; however, if the diet has a high fiber or phytate content or if diarrhea is anticipated, the intake should be increased.**

Discussion. The values recommended are higher than those derived for F100 (175 mg/1,000 kcal). In designing that diet, it was assumed that the magnesium would have 70% availability from a milk-based diet without fiber or phytate, and the tissue deficit was underestimated with regard to the data of Montgomery [168] but was in accord with the results published from Thailand by Caddell [164]. To assess the F100 formula, biochemical parameters, weight gain, and lean tissue growth were considered; magnesium retention, bone health, and 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 effects of availability, diarrhea, and the initial deficit need to be considered in defining the magnesium 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 [184–186]. Bone turnover increases dramatically during therapeutic feeding [171] 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 that need to be considered in the design of the magnesium requirements.

Many magnesium salts give an unpleasant taste to foods when they are present in high concentrations. In order to improve the acceptability of any fortified foods, the salt will have to be chosen with care. "Food-grade" magnesium citrate has a neutral taste and is used in F100; it lacks the deliquescent properties of magnesium chloride and the cathartic effects of magnesium sulfate. Other salts of magnesium have been used; magnesium diglycinate appears to be better tolerated than other magnesium salts and is well absorbed in patients with poor intestinal function [187], but there

TABLE 12. Parameters used in assessing magnesium requirements in moderate malnutrition

Absorption 30% to 60%	mg	mmol
Normal muscle (unit/kg)	240	10
Normal fat (unit/kg)	24	1
Malnourished children's muscle (unit/kg)	96	4
Recovered children's muscle (unit/kg)	132	5.5
Deficit corrected over 30 days (unit/kg/day)	4.8	0.2
Urine losses (unit/kg/day)	2.4	0.1
Fecal losses (unit/kg/day)	7.2	0.3
Fecal losses, mild loose stools (unit/kg/day)	14.4	0.6
Fecal losses, diarrhea (unit/kg/day)	28.8	1.2

is limited experience with its use.

Children with malnutrition often have low or absent gastric acid [106, 188–191]. 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 Medical Research Council unit in Uganda [192]. Organic salts of magnesium are more available than inorganic salts [193–195]

Magnesium is a weak cation with a poor absorption. When it is given as the salt of a strong anion that is absorbed, the salt will cause a metabolic acidosis. This was shown in severely malnourished children treated with magnesium chloride, some of whom died [196]. The magnesium should always be given as the salt of a weak anion such as citrate or diglycinate.

Although magnesium is relatively nontoxic 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 sulfate) have been used to induce diarrhea and for the treatment of constipation. There should not be sufficient magnesium in the diet to exacerbate any diarrhea. Although this is largely a theoretical argument, because the doses used as a cathartic are high [197], 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 hexaphosphate). This is used by plants to store phosphorus for use after germination. During plant growth, the phytate is mobilized 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 the protoplasm of plants, animals, and humans. If the phytic acid is not absorbed, the available nitrogen:phosphorus ratio derived from the foodstuff will be unbalanced because of 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 requirements as a result of consumption of dairy products; people in some cultures obtain phosphorus and other minerals from chewing bones.

TABLE 13. Potential magnesium requirements (mg/1,000 kcal)[a]

	Absorption (%)			
Condition	30	40	50	60
No tissue deficit	246	224	211	202
With tissue deficit	342	277	237	211
With some loose stools	421	356	316	290
With several loose stools	580	514	474	448

a. See **table 5** for calculations.

The situation is different with the moderately malnourished child. Nearly every malnourished child has physical signs of bony changes (swelling of the costochondral junction) [37], and x-rays show demineralization of the bones. These changes are not adequately explained by vitamin D deficiency, the classic cause of rickets. These common clinical findings in the developing world are now being described in Western children who develop phosphorus-deficiency rickets secondary to chronic ingestion of some antacids (aluminum, magnesium, and calcium salts) that make phosphorus unavailable [198, 199]. Clinical phosphate deficiency is extremely common in malnutrition [200, 201], even in malnourished adults in Western hospitals [202], and is closely related to prognosis [203]. Correction of phosphate deficiency is likely to partly account for the success of cow's milk, a particularly rich source of available phosphorus, in the treatment of malnutrition. No extraneous phosphorus is 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 their phosphorus content and availability. Calcium phosphate ($Ca_3(PO_4)_2$) is often used; it is very insoluble and should not be the phosphate (or calcium) salt chosen for diets for children with malnutrition. If diets for the moderately malnourished child are being assessed for phosphorus adequacy, 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 provide 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, for whom 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 5.6 g/kg and the adult 12 g/

kg [204]. The additional phosphate in adults is in bone and brain. **Table 14** shows the phosphorus content of tissues [205].

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 [206]; indeed, it may be that a high dietary intake of protein or carbohydrates, which require phosphate for their initial metabolism, can cause severe metabolic damage or even death in the presence of a phosphate deficiency by acute consumption of hepatic ATP [207–210].

In view of the relative unavailability of the phosphorus from phytic acid (if 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 contents 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, since much of the phosphate comes from a mixed diet containing dairy products. The availability of phosphates is 55% to 70% in Western adults and 65% to 90% in infants [9]. There have been few studies of phosphate availability or status among people living in developing countries consuming their habitual, restricted, vegetarian diets to guide the formulation of requirements.

There appears to be considerable variation between the committees setting the RNIs (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 United Kingdom set the highest requirements for infants.

Parameters. In malnourished children, the average minimum amount of phosphorus needed for phosphorus balance is 28 mg (0.9 mmol)/kg/day [211]. However, the IOM rejected phosphorus balance as a way of assessing the phosphorus requirement, because when the subjects are just "in balance," they have a lower than normal plasma phosphate concentration. The IOM suggests 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 also is subject to metabolic, hormonal, and renal modulation.

For the purposes of setting the requirements for the moderately malnourished child, 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, 34 mg/kg/day is set as the maintenance requirement. The tissue content is 1,860 mg (60 mmol) per kilogram 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 [212] (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 [213]. Thus, it will be assumed that the soft tissue deficit of phosphorus in moderate malnutrition is 435 mg (14 mmol)/kg (21%), which is of a similar magnitude to the deficit of potassium and magnesium. If the soft tissue deficit of phosphorus is to be made up in 30 days, there will need to be an additional retention of 14.5 mg (0.47 mmol)/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

TABLE 14. Phosphorus content of tissues

Tissue	Age group	Phosphorus (mg/kg)
Whole body	Infant	5,600
Whole body	Adult	12,000
Muscle	Infant	2,010
Muscle	Adult	1,820
Liver	Infant	2,560
Liver	Adult	2,670
Kidney	Adult	1,780
Spleen	Adult	2,200
Lung	Infant	1,360
Lung	Adult	1,610
Brain	Infant	1,670
Brain	Adult	3,380
Skin	Infant	1,080
Skin	Adult	430
Tissue mean	All	1,880

TABLE 15. Phosphorus RNIs (mg/1,000 kcal)

Authority	7–9 mo	10–12 mo / 7–12 mo	1–3 yr	4–6 yr
IOM	—	409	450	360
UK	634	578	285	263

IOM, Institute of Medicine; RNI, Recommended Nutrient Intake; UK, United Kingdom

because of defects in bile salt metabolism [214].

For the moderately malnourished child, a phosphorus availability of 60% is assumed on the basis that the availability 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**).

Diarrhea. 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 be able to excrete sufficient dihydrogen phosphate in the urine to eliminate the hydrogen ions without compromising phosphorus status. With marginal levels of phosphorus in the diet acidosis itself can induce phosphate deficiency. When there is a relative phosphate deficiency, acidosis cannot be corrected.* Thus, conditions such as diarrhea, 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 diarrhea because of the acidosis; there is also an increase in fecal phosphate loss in diarrhea, 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 diarrhea will be achieved when the daily phosphate losses are doubled. No data to address the increment in phosphate losses with diarrhea in the moderately malnourished were found. The assumption of a doubling of fecal 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 fecal output is about twice as great in the malnourished as in the recovered state.

Phosphorus metabolism in malnutrition 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.

* The magnesium chloride-induced acidosis only occurred when the children were on a maintenance diet similar to F75; when the growth diet, which is rich in phosphorus (with the same phosphorus density as F100), was given, the acidosis disappeared and a high urinary titratable acidity and excretion of dihydrogen phosphate occurred [196].

TABLE 16. Parameters used to assess phosphorus requirements

Availability	60%
Balance	34 mg/kg/day
Tissue	1.860 mg/kg
Diarrhea	68 mg/kg/day
Deficit	434 mg/kg
Replace in 30 days	14.5 mg/kg/day

Growth. The specific requirements of phosphorus for growth are similar to those of 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 with and without diarrhea.

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 child, for continuing skeletal growth or for accelerated height gain in the stunted child. Because of the additional requirement for bone formation, it is suggested that the phosphorus requirement for the moderately malnourished child should equal or even exceed that for the severely malnourished child. This is because the moderately malnourished child will be consuming the diet for much longer than the time normally taken to treat the severely malnourished child in order to enable reversal of stunting, during which the moderately malnourished child may have repeated episodes of acidosis and diarrhea.

It is suggested that the phytate fraction should be measured in foods used for calculation of diets for the moderately malnourished. The phytate fractions should be given 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 900 mg (29 mmol) per 1,000 kcal of *nonphytate* phosphorus when the diet is fortified, and a minimum of 600 mg/1,000 kcal in a diet based on only locally available foods.

Many inorganic phosphorus compounds are marginally soluble and are likely to be unavailable if they are 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. Preventing calcium phosphate from precipitating in artificially formulated diets containing the full calcium and phosphorus requirement, without using milk, presents a difficult technical problem [215] 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 zinc is always less than that of protein, and therefore it is difficult to become protein deficient without being first zinc deficient [216]. Therefore, 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 diarrhea and to have a major effect upon the recuperation of patients. Zinc is also critical for the immune response. The congenital condition acrodermatitis enteropathica, which is due to a defect in zinc absorption, is characterized by immune dysfunction and diarrhea, as well as by skin lesions and failure to grow. These same conditions characterize 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 United States showed that zinc was the limiting nutrient in the diets of children enrolled in the Head Start program, and zinc deficiency resulted in progressive stunting [217]. Even early types of infant formulas contained insufficient zinc for growth. Feeding recovering malnourished children with infant formula brands based upon soy protein led to clinical zinc deficiency that resulted in abnormalities of immune function, body composition, thymic regrowth, and the sodium pump [19, 29, 218, 219]. It is imperative that the diets of moderately malnourished children contain adequate amounts of available zinc.

Phytic acid is a strong chelator of zinc. This chelation is greatly exacerbated by the presence of excess calcium, and the diet should not contain excess calcium if phytate is present [220, 221]. 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 [222], which presumably releases zinc locked in bone.

Because of the strong association between the dietary matrix and zinc status, FAO/WHO [7] and WHO [6], 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, and therefore urinary excretion can be quantitatively ignored.

Table 19 shows the zinc requirements recommended by the various expert committees. The Western committees have proposed a zinc intake of about 5 mg/1,000 kcal or less for children. The RNI has been considerably reduced by the IOM from the previous US recommendations [148], possibly because of domestic concerns about induced copper deficiency with high zinc intakes. Nevertheless, this large variation is mainly due to differences in assumed availability. The dietary zinc requirement published by FAO for infants consuming cereal diets typical of developing countries is over 12 mg/1,000 kcal, and the previous recommendation of the WHO/FAO/IAEA committee was 16 mg/1,000 kcal. These recommendations are for normal children consuming unknown diets. It is clear that the matrix has a dominant effect upon zinc availability and thus upon zinc dietary requirements.

TABLE 17. Phosphorus balance in malnourished children (mg/kg/day)

Variable	Admission	Day 10–20	Day 30–50
Intake	162.0	161.0	153.0
Urine	9.7	25.7	35.7
Feces	104.0	67.0	56.0
Balance	48.2	68.8	61.4

Source: Linder, 1963 [179].

Zinc losses. Fecal zinc excretion can fall to low values in zinc deficiency, and the absorbed amount of zinc needed for "maintenance" is only 0.033 mg/kg/day [6]. 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. The normal zinc concentration in muscle is about 81 mg/kg [25]. This content of zinc in soft tissue is high compared with 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, relatively large amounts of zinc are liberated from the tissues as a result of the catabolism of muscle [223]. Anorexia is a primary and cardinal feature of persons consuming a low-zinc diet [224]. In dietary surveys, the resulting low energy intake is often interpreted as an "energy deficiency," when the prime cause is poor appetite due to an inadequate supply of available zinc [74]. With an intake less than that required for maintenance, the zinc that is released from the catabolized tissue alleviates the deficiency and relieves the anorexia somewhat, at the expense of continued gradual weight loss [225]. It is critical that there be sufficient available zinc in the diet to prevent this anorexia from occurring and to support at least normal rates of growth.

TABLE 18. Phosphorus requirements for moderately malnourished children (mg/1,000 kcal)[a]

	Rate of weight gain (g/kg/day)		
% lean tissue	2	5	10
No phosphorus deficit or diarrhea			
50	354	339	323
60	364	360	356
70	375	383	393
21% soft tissue phosphorus deficit			
50	585	534	476
60	599	560	517
70	612	589	561
21% soft tissue phosphorus deficit and loose stools			
50	918	814	698
60	936	849	749
70	954	886	804

a. See **table 5** for calculations.

Malnutrition. In severe or moderate malnutrition, muscle zinc concentration falls from about 81 to 64 mg/kg [25]. This deficit is of the same order of magnitude as that 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 17 mg/kg. This tissue deficit has to be made good in about 30 days, which will require an additional retention of 0.57 mg/kg/day, 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 synthesized has relatively little effect upon the zinc:energy requirement within the range of 50% to 70% lean tissue synthesized, 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.

Diarrhea. Not only is zinc deficiency a cause of diarrhea, but also substantial zinc is lost in the diarrheal stool. The zinc output in the feces increased threefold from 0.050 to 0.160 mg/kg/day with diarrhea [226]. 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 diarrhea. For that reason, no allowance will be made for diarrhea in calculation of the zinc:energy ratio required. The resulting calculations are shown in **table 20**.

Discussion. **Table 20** shows the effect of the three different availabilities of zinc at different rates of weight gain without an initial deficit or with a deficit of either 8 g/kg or of 17 mg/kg that is to be made good in 30 days. Shown are the necessary zinc:energy densities per 1,000 kcal and the absolute zinc intake required in milligrams per kilogram per day.

Breastmilk has about 1.7 mg of zinc/1,000 kcal; this corresponds in the table to a rate of weight gain of 1 g/kg/day with a highly available source of zinc. The effects 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 of 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 [75]. The RNIs for normal children living on a Western diet are completely inadequate for a wasted or stunted child receiving a cereal- or pulse-based diet. Even children consuming a strict vegetarian diet in the Netherlands grow similarly to children in the developing world [227], indicating that the infective burden or care practices are not the dominant causes of malnutrition

TABLE 19. Zinc RNIs (mg/1,000 kcal)

Authority[a]	7–9 mo	10–12 mo/ 6–12 mo	1–3 yr	4–6 yr
FAO (high)	—	3.7	2.5	2.5
FAO (moderate)	—	6.1	4.3	4.1
FAO (low)	—	12.5	10.8	9.1
IOM	—	4.5	2.9	3.6
UK	7.7	7.0	5.1	4.9
WHO (high)	—	4.9	3.5	3.1
WHO (moderate)	—	8.3	5.8	5.2
WHO (low)	—	16.5	11.5	10.4

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake; UK, United Kingdom; WHO, World Health Organization

a. High, moderate, and low refer to the availability of zinc from different types of diet.

in those receiving traditional weaning diets.

RUTF and F100, which are special milk-based diets for the severely malnourished, have more than 10 times the concentration of zinc found in breastmilk; with the high availability from such a diet, this amount allows repletion of the deficit and rates of weight gain of well over 10 g/kg/day. 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 consuming RUTF at home with considerable amounts of high-phytate other foods, zinc may become the limiting nutrient in recovery unless the foods are consumed at different times of the day. The instructions for consuming such foods should include advice that they be consumed 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 zinc 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: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 presence of antinutrients, the appropriate absorbed copper:zinc ratio might be achieved with lower dietary ratios if the antinutrients specifically affect zinc absorption.* It is important to collect data to address this interaction in the malnourished child. Thus, it is not feasible for a child in an already depleted state to have meaningful catch-up growth on a diet with low zinc availability.

A minimum of 13 mg zinc/1,000 kcal should be given when the zinc in 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, the minimum should be increased to 20 mg/1,000 kcal.

When very high levels of zinc are given (> 6 mg/kg/day), there is a danger of toxicity, with increased mortality [228], although in the study of Doherty et al. [228], no copper supplements were given.** 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; incorporation of the zinc in the diet obviates the problem of toxicity,

TABLE 20. Assessment of zinc requirements with various availabilities and rates of weight gain[a]

Zinc availability[b]	Deficit (mg/kg)	RWG (g/kg/day)	Zinc requirement	
			mg/1,000 kcal	mg/kg/day
High	0	0	0.6	0.06
High	0	2	1.9	0.19
High	0	5	3.4	0.40
High	0	10	5.2	0.74
Moderate	0	0	1.0	0.09
Moderate	0	2	3.1	0.31
Moderate	0	5	5.4	0.64
Moderate	0	10	8.3	1.18
Low	0	0	2.4	0.22
Low	0	2	7.2	0.73
Low	0	5	12.7	1.49
Low	0	10	19.3	2.75
High	8	0	6.2	0.56
High	8	2	6.9	0.70
High	8	5	7.7	0.90
High	8	10	8.7	1.24
Moderate	8	0	9.9	0.90
Moderate	8	2	11.0	1.12
Moderate	8	5	12.4	1.45
Moderate	8	10	13.9	1.99
Low	8	0	23.1	2.11
Low	8	2	25.8	2.61
Low	8	5	28.8	3.37
Low	8	10	32.5	4.64
High	17	0	11.8	1.07
High	17	2	11.9	1.21
High	17	5	12.1	1.41
High	17	10	12.2	1.75
Moderate	17	0	18.8	1.71
Moderate	17	2	19.0	1.93
Moderate	17	5	19.3	2.26
Moderate	17	10	19.6	2.80
Low	17	0	43.9	4.00
Low	17	2	44.4	4.51
Low	17	5	45.0	5.27
Low	17	10	45.7	6.53

RWG, rate of weight gain

a. See **table 5** for calculations.

b. Availability: high, 56%; moderate, 35%; low, 15%.

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

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

as those who have poor appetites and are not gaining weight will consume less of the diet and hence the supplement. When children are gaining weight rapidly and are sequestering nutrients into tissue, their intakes not only of zinc but also of copper and other nutrients will increase. With F100, consumed at 100 kcal/kg/day, the intake of zinc is 2.3 mg/kg/day; when the child is gaining weight rapidly on the same diet and takes 200 kcal/kg/day, the zinc intake will be 4.6 mg/kg/day. Children very rarely consume more than this amount of food. This fundamental difference between giving a nutrient as a pharmaceutical on a body weight or age basis* and incorporating it in a diet an appropriate amount is critical when treating children with all forms of malnutrition. This is the main conceptual change in treatment with the use of diets such as F100 from the earlier practice of giving individual supplements on the basis of body weight.

Phytase

The availability of zinc, calcium, iron, phosphorus, magnesium, and even protein [229] can be considerably enhanced by adding commercially available microbial phytase to diets [2]; this has been confirmed in humans with respect to iron [230]. Addition of phytase has been successful in the nutrition of monogastric farm animals but has not yet been used for human feeding. The addition of phytase to the diet would prevent the need to reject bulk ingredients that lead to low availability of the affected nutrients from the diet. The levels of microbial phytase that have been found to lead to a linear increase in growth and nutrient utilization are up to about 2,000 units** per kilogram of feedstuff (about 500 units/1,000 kcal). 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. Enzymatic breakdown can be effected either through externally added microbial phytase in the case of formulated foods or by fermentation or germination in the case of local food use. Even simple soaking can halve the phytic acid content [231]. It would be useful to study traditional methods of food preparation among populations living where different foodstuffs originated [59, 232].

Sodium

Sodium is the main electrolyte in the extracellular fluid. Normally there is an extraordinary capacity to conserve sodium. Adults without pathological losses can maintain sodium balance on intakes of 70 to 460 mg/day, and there are healthy populations that have a mean adult intake of about 920 mg/day. It is almost impossible to induce sodium deficiency without a pathological loss; this was achieved by McCance [233] by induction of excess sweating in volunteers. Normal intake far exceeds the minimum requirements for healthy people in nearly every country (**table 21**). The minimum maintenance amount for the malnourished child is unknown; since there is excess sodium in the body that has to be lost during recovery, there is probably little requirement in the absence of ongoing pathological losses. For the normal, healthy child, no experimental data on minimum requirements during salt restriction were found. The minimum requirement has been set at 10 mg/kg/day 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 monosodium 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 that were formulated to treat renal failure before the development of dialysis treatment were very low in sodium, tasteless, and very difficult to eat [234].

Diarrhea. Although the capacity to conserve sodium in health is remarkable, considerable losses can occur in pathological states. The most common is infective diarrhea*** [235, 236].

It is assumed that acute episodes of watery diarrhea will be treated with oral rehydration solution (ORS). Nevertheless, there will commonly be lesser degrees of "loose stools" in the moderately malnourished.

The concentration of sodium in diarrheal stool from a malnourished child is less than in stool from a normal child producing the same volume of stool. In malnourished children without any diarrhea, the sodium output was 0.9 mg/g stool, rising to 10.1 ± 8.7 mg/g stool in malnourished children with nondehydrating diarrhea

* 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 that the zinc:copper ratio may be changed, resulting in acute copper deficiency. There is also the danger of giving the tablets to a patient in an acute catabolic state when large amounts of zinc are being released from the tissues [223] and sequestered in the liver or lost from the body. Physiologically the body reduces plasma zinc during infections, since high zinc concentrations can blunt the immune response (see references in Doherty et al. [228]). These dangers are not present when the zinc is incorporated into the diet. There is no need to give higher amounts of zinc than those found in F100 (supplying 2 to 5 mg/kg/day, depending upon the intake), unless the matrix of the diet decreases zinc availability substantially, or to give additional zinc to those in an acute catabolic state (when the appetite is suppressed).

** One unit is defined as the amount of enzyme that releases 1 μmol of inorganic phosphate per minute from 5.1mmol sodium phytate at pH 5.5 and 37°C.

*** Far less sodium is lost in osmotic diarrhea, in which the main osmolytes in the stool are the substances that are malabsorbed.

TABLE 21. Sodium AIs (mg/1,000 kcal)

Nutrient	Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
Sodium	IOM	—	550	978	864
Sodium (min)	UK	503	491	529	518

AI, Adequate Intake; IOM, Institute of Medicine; UK, United Kingdom

that did not require special administration of electrolytes [157]. The output would then be up to 27 mg/kg/day (97% CI). This is thus the *minimum* requirement for sodium to cover mild diarrhea in the moderately malnourished.

The stool sodium output of normal children with infective diarrhea is higher than that of malnourished children with diarrhea. The sodium output, in mg/kg/h, amounts to about 1.43 + 1.45 multiplied by the stool volume in ml/kg/h [160].

Malnutrition. Sodium is unlike other nutrients in malnutrition, in that the total body sodium *increases* considerably instead of decreasing. This increase is probably secondary to a slowing of the sodium pump or potassium depletion, with a consequent rise in intracellular sodium [163, 237, 238]. During treatment, this sodium has to come out of the cells and be excreted; if this occurs rapidly, the patient may die from acute heart failure [239]. For this reason, sodium should be *restricted* in the diets of the moderately malnourished. When a malnourished child has 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, the increase is on the order of 50% to 60% on a dry weight basis, but because the tissue is more hydrous than normal, the increase amounts to between 20% and 34% on a wet weight basis (**table 22**).

The tissue sodium concentration is about 1,380 mg/kg. Thus, during the first 30 days when a moderately malnourished child is convalescent, there is a need to *lose* the additional sodium at a rate of about 17.5 mg/kg/day. The severely malnourished child is particularly sensitive to increased sodium intake, and treatment of the malnourished child with diarrhea presents a major problem [22]. However, because of their sodium-retaining state, the diarrheal stools of malnourished children contain less sodium than the diarrheal stools of normal children, so that the stool losses of sodium are less in malnourished than in normal children. However, the diets based on the RNIs will be consumed by normal as well as by malnourished children and also by children after they have reversed their physiological abnormalities. An association between stunting and abnormal sodium homeostasis is unexplored. Nevertheless, if the normally nourished have no diarrhea and normal physiology, their sodium needs will be adequately satisfied by a low-sodium 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 sodium needs computed for normal children, those with malnutrition, and those with stool losses of 27 or 62 mg/kg/day.

If only normally nourished children were to consume a diet, the sodium recommended intakes could be set at a level that would improve organoleptic properties and give some protection against diarrhea. However, the requirements for a moderately malnourished child should be set a far lower level than those for a normal child. In areas where kwashiorkor occurs in some children, the nutritional deficiencies and physiological changes that lead to edema appear in many of the wasted children, albeit to a lesser extent than in kwashiorkor. Moderately malnourished children in these areas should not be given high-sodium diets.

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

Nevertheless, **a maximum sodium level of about 550 mg/1,000 kcal would also satisfy the normal child with mild diarrhea who is not gaining weight, as well as the malnourished child with additional losses;** it is twice the concentration found in breastmilk. Higher concentrations should not be given to children who are living in kwashiorkor areas or who are severely malnourished. It would be inappropriate to design a diet for moderate malnutrition that would be dangerous if it were consumed by the severely wasted child.

An important further disadvantage to increasing sodium intake is that it increases the renal solute load that will need to be excreted and thus increases 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 water 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 when the environment is neither very humid nor very dry.

TABLE 22. Sodium content of muscle biopsies of children with severe acute malnutrition (SAM) and normal or recovered children

Normal or recovered children (mg/kg wet wt)	SAM (mg/kg wet wt)	Increase (%)	Reference
1,408	1,693	20	Nichols, 1972 [240]
1,349	1,654	23	Vis, 1965 [241]
945	1,267	34	Metcoff, 1966 [242]
1,010	1,357	34	Frenk, 1957 [243]

One of the main reasons why breastmilk is low in protein and electrolytes is to maintain as low a renal solute load as possible. The renal osmotic load from breastmilk is 145 mOsm/1,000 kcal [244].

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

If the recommendations are followed so that 26 g of protein per 1,000 kcal is consumed, of which 90% is absorbed, 135 mOsm/1,000 kcal urea will be generated. Similarly, potassium will generate 82 mOsm/1,000 kcal, sodium 48 mOsm/1,000 kcal, and magnesium 12 mOsm/1,000 kcal, 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 small* [245–248].

The total renal solute load that will be generated will thus be about 280 mOsm/1,000 kcal (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 breastmilk. Insensible water loss is dependent upon the temperature and the metabolic heat produced that needs to be dissipated; in general, at thermoneutrality, the insensible water loss is about 25 g/kg/day but rises exponentially as environmental temperature approaches or exceeds body temperature.

Renal concentrating ability is severely compromised in malnourished children, including those with moderate malnutrition and those who recovered on the older diets, so that the maximum that can be achieved by many children is about 400 mOsm/L, and some children cannot concentrate their urine at all [81]. If a young child is consuming 100 kcal/kg/day, contributing 28 mOsm that needs to be excreted and losing 25 g of water/kg/day through insensible loss, then the minimum water that needs to be consumed, if the urine concentration is not to go above 400 mOsm/L, is 100 mL/kg/day. If only the diet is being consumed, the energy density cannot be higher than 1 kcal/mL without the danger of hypernatremic/ hyperosmolar dehydration, and the protein and electrolyte concentrations of the diet need to be limited to levels that do not pose a threat of hypernatremic dehydration due to water deficiency [247, 249–252]. Of course if additional water is consumed with or after meals, the foods of the

TABLE 23. Sodium requirements in relation to stool losses, rate of weight gain, and nutritional status[a]

Nutritional status	Stool losses[b]	RWG (g/kg/day)	Sodium requirement (mg/1,000 kcal)
Normal	Normal	0	227
	Normal	2	221
	Normal	5	213
	Mild loose	0	530
	Mild loose	2	493
	Mild loose	5	449
	Moderate loose	0	909
	Moderate loose	2	833
	Moderate loose	5	744
Malnourished	Normal	0	0
	Normal	2	17
	Normal	5	36
	Normal	10	59
	Mild loose	0	303
	Mild loose	2	289
	Mild loose	5	272
	Mild loose	10	252
	Moderate loose	0	682
	Moderate loose	2	629
	Moderate loose	5	567
	Moderate loose	10	493
Sodium contents (mg/1,000 kcal)			
US RDA			978
UK DRV			529
Breastmilk			257
F100			434

RWG, rate of weight gain; US RDA, US Recommended Dietary Allowance; UK DRV, United Kingdom Dietary Reference Value

a. See **table 5** for calculations.

b. Stool losses: mild loose, 27 mg/kg/day; moderate loose, 62 mg/kg/day.

* 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 (0.9 mOsm/g lean tissue); this is offset to some extent by failure to generate metabolic water from oxidation of ingested fat and carbohydrate (1.07 and 0.55 mL/g, respectively) when it is deposited in tissue instead of being burned. The reason 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.

diet can be more energy dense. In other words, with the recommended protein and electrolyte content, if the child's diet consists only of porridge, either the energy density must not rise above 1,000 kcal/L of wet porridge or additional water must be given. The addition of oil to the diet will not alleviate the need for additional water and may aggravate the danger of water deficiency because the the energy density of the diet is thereby increased and less of the diet will be consumed to satisfy energy needs so that there will be less ingested water available for excretion of the osmolytes present in the diet.

If the temperature is above thermoneutrality (28° to 32°C), the humidity is low, the child has a fever, or the child is malnourished (and therefore the ability of the kidney to concentrate may not rise above 300 mOsm/L), then either the energy density of the porridge needs to be reduced or additional water must be consumed. 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 for young children excessively energy dense. In Tchad in May (with a daytime temperature of 45°C and a relative humidity of less than 15%), the water turnover of malnourished children was one-third of total body water per day [127]. The danger of having an excessively energy dense diet is particularly the case in infants 6 to 12 months of age, who 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, since 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 diarrhea. 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 for type I nutrients are not the same as those for type II nutrients. Here, the maintenance or replenishment of body stores and the specific functions the nutrients play need to be considered. The requirements for these nutrients are likely to be affected particularly by the environment and the 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 are not dependent upon the balance of the type II nutrients (see the balance studies of Rudman et al. [75]). If we only consider soft tissue regeneration, the requirement for calcium, unlike that for phosphorus, 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 malnourished, wasted children. Nevertheless, all malnourished subjects have substantial osteoporosis [184, 185, 253]. 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. In malnourished children, the intracellular content of calcium is effectively zero and the extracellular level is normal. Even though the bone mineral deficit has not been quantified when the requirements for phosphorus or magnesium have been set, it is desirable that there be adequate calcium to maintain positive balance, and the phosphate:calcium ratio should be such that there is no danger of induction of hypocalcemic tetany.

The total body calcium even of normal children living in the developing world is low, and their diet is normally low in calcium [254]. Even though calcium may not be directly involved in the promotion of longitudinal growth, calcium is vital to give adequate density to the bone and prevent deformity or calcium-deficiency rickets [255, 256], particularly when the diet or supplementary food is maize based [257]. 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 allow normal bone density to be restored and maintained.

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

A phosphorus requirement of 900 mg (29 mmol)/1,000 kcal has been set (600 mg 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 be maintained within the range of 0.7 to 1.3 for all children over 6 months of age. **Therefore, 840 mg (21 mmol)/1,000 kcal 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 600 mg/1,000 kcal.**

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 whether the food-based recommendation will supply sufficient calcium to replenish bone mineral [258]. Food constituents such as oxalate that inhibit inorganic calcium absorption do not affect the absorption of calcium from milk [259]. Although in normal adults calcium from inorganic sources is as available as calcium from milk [260], 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 1,000 mg/1,000 kcal; on this diet, severely malnourished children have an increased bone turnover [171] and nonedematous 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 rations for malnourished children, iron has received the most attention, and its nutrition has been extensively researched. The RNIs are based upon firm and extensive research data [11]. 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 those in the population who are severely anemic. 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 utilization and hemoglobin synthesis than by simply increasing the dose of iron. The results of one study on Saharawi stunted children are particularly illuminating; anemia responded to, and severe anemia was eliminated by, a more balanced diet [261]. Adding riboflavin to the diet had a greater effect upon ferritin levels than increasing the level of iron to the therapeutic range [262–264]; it would appear that anemia in the moderately malnourished child is usually a multimicronutrient disorder and not simple iron deficiency. There is evidence of deficiencies of many hematinics in the malnourished child: 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 hemoglobinopathies or glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Indeed, there are multiple causes of anemia in the malnourished child. There are also metabolic effects that lead to unresponsiveness of the bone marrow [265], despite high levels of erythropoietin [266].

TABLE 24. Calcium RNIs for normal children (mg/1,000 kcal)

Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
FAO	—	595	523	483
IOM	—	401	489	576
UK	820	747	369	340

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake; UK, United Kingdom

It is well known that iron deficiency is particularly common in the developing world. However, it is rarely appreciated that iron deficiency mainly affects normally grown children. In most malnourished children, including those with severe or moderate wasting or kwashiorkor, the storage levels of iron are *increased*, not decreased, even in the presence of quite severe anemia [267–276]; the increase appears to increase mortality [271, 277, 278], particularly if therapeutic iron is given [279]. There are therefore cogent reasons not to have a high iron nutrient density in diets designed for the malnourished child, particularly in areas where kwashiorkor is common. It is a mistake to assume that the anemia usually present in the malnourished child is due to simple iron deficiency alone. Treating non-iron-deficient anemia with iron or even anemia due to multiple deficiencies with iron alone, in these circumstances, may increase the mortality rate. It is for this reason that no iron is 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 1 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 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 labor [280, 281]. 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, 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 food to become rancid more quickly but 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 [282], 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 increased mortality [283]. Although the study of Sazawal et al. [283] 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, there is some evidence that excess iron, as well as iron deficiency, is associated with increased infection apart from malaria [284], although 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 on one hand and not either causing or exacerbating dietary vitamin deficiency (particularly scurvy) or giving excess to the malnourished or the iron replete within the population on the other hand.

Fifth, iron overload also occurs in populations that ferment food in iron cooking pots [285]. Iron overload can also occur in patients with hemoglobinopathies, which are common in malarious areas.

Sixth, iron readily forms totally insoluble complexes with selenium, particularly in anaerobic environments such as the intestine or some soils; thus, high iron intakes may precipitate selenium deficiency when selenium intake is marginal [286]. This nutrition–nutrient interaction does not seem to have been considered in the list of detrimental effects of the use of foods designed for the moderately malnourished as therapeutic vehicles.

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

Table 25 gives the iron requirements for normal children consuming 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 of iron (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 8.9 mg/1,000 kcal would be required.

In view of the uncertainty about whether the iron content of the diet should be increased to treat anemia or decreased to avoid 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 18 mg/1,000 kcal should be present; however, whenever possible, diets with low iron availability should not be formulated for treatment of the moderately malnourished. For a food-based approach and for most formulated diets, it is important that the basic ingredients be such that the iron is more available, in which case a level of 9 mg/1,000 kcal should be used.

For special groups, such as pregnant women, it is difficult to achieve a high enough iron concentration in a poor diet 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 were used for groups with particularly high requirements, such as the use of micronutrient powders or spreads that should contain high levels of all hematinics. In formulating recommendations for iron contents in diets for general use by moderately wasted or stunted children, the needs of special groups and the use of food as a therapeutic vehicle should not be a consideration, any more than in the case of other nutrients whose deficiency is common. Thus, with respect to iron, no special provision need be made for children who are malnourished, have diarrhea, have an infection, or are convalescing from illness.

The form of iron in the food is important. Iron destroys many vitamins that are vulnerable to oxidation, including vitamin C, and it greatly decreases the shelf-life of products. For these reasons, it is strongly recommended that iron should be physically encapsulated (with material that is removed in the intestine of moderately malnourished children) or be in the form of amino acid complexes or iron-ethylenediaminetetraacetate (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 encapsulated iron or iron provided as amino acid complexes or iron-EDTA 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 as those for iron apply to copper that is added to the diet in terms of using a stable but

TABLE 25. Iron RNIs at various levels of availability (mg/1,000 kcal)

Availability	Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
Fe (15%)	FAO	—	5.9	4.2	4.8
Fe (12%)	FAO	—	7.4	5.2	5.6
Fe (10%)	FAO	—	8.9	6.3	7.2
Fe (5%)	FAO	—	17.8	13.6	14.5
Fe (not given)	IOM	—	16.4	6.8	7.2
Fe (not given)	UK	12.2	11.1	7.0	4.6

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake; UK, United Kingdom

available chelate and exploring microencapsulation technology.* 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 [287]. Clinical copper deficiency occurs particularly in the Andes [288]. Copper deficiency causes anemia, neutropenia, and osteoporosis; copper is also critical for collagen maturation. Copper deficiency is particularly associated with persistent diarrhea. Malnourished children who receive adequate copper are less likely to get an infection during recovery [289].

On the other hand, copper toxicity used to occur in some parts of India and Bangladesh where milk is fermented in brass vessels that can release sufficiently high levels of this element to produce cirrhosis of the liver [290, 291]. This is no longer a common problem, since most cooking vessels now used are aluminum, and should not be a consideration in formulating the diets. Animal milks, including human milk, are particularly low in copper (experimental animals fed exclusively on milk develop clinical copper deficiency). Physiologically, infants are born with a large store of copper in their liver (in a special fetal protein called mitochondrocuprin). Its function is to provide sufficient copper to last from birth to weaning. The breastmilk 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 colonization of the child's intestine by bacteria [84]. 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 diarrhea.

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 copper 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 metallothionine,** 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 deficiency*** and should not fall below 1:20.****

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 for copper are shown in **table 26**. There is no FAO/WHO recommendation. The level set by the IOM and the United Kingdom is between 300 and 500 µg. However, with a recommended zinc intake of 20 mg/1,000 kcal, if a ratio of 1:10 is to be achieved, the intake of copper would need to be increased considerably above the recommended RNIs. Such an intake could be regarded as 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 diarrhea in moderately malnourished children, the relatively high prevalence of copper deficiency in the malnourished, and the lack of any programs in which additional copper is likely to be added to the diet, it is proposed that the **copper density be set at 890 µg/1,000 kcal for a fortified diet and at 680 µg/1,000 kcal 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 copper 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 be present in the diet to avoid this interaction.

Molybdenum in the diet, particularly in the presence of sulfur-containing amino acids or other sulfur compounds, renders copper totally unavailable by precipitation as copper thiomolybdate in the lumen of the intestine [292, 293]. Indeed, soluble thiomolybdates are now used as drugs to treat copper toxicity in

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

** Metallothionine is exceptionally rich in sulfur amino acids; the relatively low levels of sulfur amino acids in malnutrition may limit metallothionine synthesis and ameliorate the interaction between zinc intake and copper absorption in these circumstances.

*** Whether the reverse interaction also occurs, as a result of metallothionine induction, is unknown.

**** This will normally occur temporarily when zinc supplements are given to children after diarrhea, 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.

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 humans. One of the main determinants of copper status will be the dietary molybdenum intake. In turn, the availability of molybdenum from the soil is dependent not only on 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, widespread copper deficiency was induced in the human and animal population (Colin Mills, personal communication). 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 sulfur amino acids should be used. On the other hand molybdenum is an essential element, and sufficient has to be present in the diet (see Molybdenum, below).

TABLE 26. Copper RNIs μg/1,000 kcal)

Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
IOM	—	327	332	317
UK	496	452	399	429
WHO	—	892	586	459

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake; UK, United Kingdom

Selenium

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

It is unfortunate that the inclusion of selenium has been overlooked, since 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 soil,* so that all plant foods that are grown in these areas will be low in selenium. Although selenium is in the same class of the periodic table as sulfur, the chemistry of selenium is quite distinct from that of sulfur. The soil chemistry of selenium is critical in this process. As the soil Eh (reduction-oxidation potential) goes from an oxidizing 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 are 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 National Research Council [286] for a full description of selenium soil chemistry with references).

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 [295–298]. 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 cause selenium deficiency in fully breastfed infants; the milk samples have no antioxidant power at all [299].

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 [278, 300]. 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 [301]. Malnourished children are exposed to increased oxidative stress 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 [128]. Therefore, an adequate selenium intake is critical for the protection of children.

Second, selenium, through a compound known as thioredoxin, is responsible for the maintenance of the redox state of cells [302]. Without adequate functioning of this compound, most of the control processes in the body are compromised [303]. This includes the leakage of sodium into cells and of potassium out of cells, as well as cardiac and renal function. Indeed, it is postulated that many of the differences between the reactions of malnourished children and well-fed Western children to infections (e.g., measles mortality) may be related to selenium status [300]. Of particular interest is the finding that selenium added *in vitro* increases thioredoxin, which can reduce the HIV virus replication rate up to 10-fold [304].

Third, selenium is responsible for the conversion of thyroid hormone (T4) to its active metabolite (T3). In

* 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 United Kingdom, and parts of the United States. Most of the developing world has not been surveyed. In Jamaica, the selenium concentration in free-range hen's eggs were used as a proxy for environmental selenium deficiency, which was found to be widespread [294].

areas where there is combined iodine and selenium deficiency, massive goiters occur, whereas in areas with iodine deficiency alone, the goiters are smaller [305]. Such large goiters are predictably characteristic of much of Africa. Large doses of iodine can overcome lack of the T3 hormone, even in the presence of a selenium deficiency, but where the intake of iodine is marginal, 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, coexisting 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 (coxsackievirus was the first to be studied, as its 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 [306, 307]. This will then be passed to the next individual, who will contract 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 West. 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. Selenium deficiency may also be a reason why resistance to antibiotics and antimalarials arises 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 [308–319]. Selenium deficiency causes mutations not only in viruses but also in bacteria such as *Mycobacterium tuberculosis*. The appearance of 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 have been 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 100 μg/day augmented immune function and led to more rapid removal of poliovirus (vaccine strain) from the blood and lower mutation rates of the poliovirus [320].

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 [321–327]. 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, where 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) [328].

The grains from some parts of the United States, particularly maize, are largely selenium deficient [286]. 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 and RUTF is 55 μg/1,000 kcal. This is because selenium deficiency is so common in malnourished children and malnourished children have active infections and nutritional immunoincompetence and are living in highly stressful environments; the requirements for such nutrients are likely to be higher for those in the developing world than for 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 [7]. Selenium levels in human milk vary considerably, depending upon the mother's selenium status. Thus, human milk concentrations cannot be used as a guide unless we are sure that the mother's selenium status was adequate at the time of sampling. The average selenium level in human milk is about 29 μg/1,000 kcal.

The selenium contents of many of the foods and ingredients currently used to treat moderately malnourished children are low. Furthermore, there are major gaps in food-composition tables, with selenium concentrations rarely given; 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 the plants 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, which is found in selenized yeast, is often used to supplement diets because of its low toxicity. However, its metabolism in the malnourished child is completely different from that of both inorganic selenium and methionine [329]. 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 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 contain 55 µg/1,000 kcal 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 µg/1,000 kcal 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/1,000 kcal 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 followed in areas where the bedrock and plants are high in selenium (e.g., some parts of Venezuela). When we consider the nutrient contents of foods in terms of nutrient:energy density, it is clear that this problem is not of major concern. Thus, the selenium:energy ratio of the habitual foods of the population living in seleniferous areas will far exceed the densities proposed. Thus, when a fortified food containing the recommended densities of selenium is consumed in place of a local food, the total intake of selenium will fall.*

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

Iodine

Iodine deficiency is recognized 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 iodization 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 presence 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, since some within the population may not consume or receive iodized 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 it would lead to toxicity or "double dosing" if consumed exclusively.

The whole idea of expressing nutrient requirements as densities is to enable us to design a diet that 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 consumed by the moderately malnourished at a level that will result in a normal iodine intake when the foods are ingested to meet energy requirements. Any iodine that comes from salt will then be in 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 recommendation may have been made partly in view of the recognized widespread deficiency of iodine and partly to compensate for the low levels of iodine in the breastmilk of iodine-deficient mothers.

However, in view of the widespread occurrence of iodine deficiency, the need to provide the infant with sufficient iodine from 6 months of age, 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

TABLE 27. Selenium AIs (µg/1,000 kcal)

Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
FAO	—	14.9	17.8	16.9
IOM	—	29.7	19.6	21.6
UK	15.6	14.2	15.7	15.0
WHO	—	17.8	20.9	19.3

AI, Adequate Intake; FAO, Food and Agriculture Organization; IOM, Institute of Medicine; UK, United Kingdom; WHO, World Health Organization

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

added, it is **proposed that the RNI of iodine for the moderately malnourished child should be set at 200 µg/1,000 kcal.**

For a food-based approach to treating the moderately malnourished child, 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 iodized salt is available in the area. The level recommended will not lead to thyrotoxicosis, even if modest amounts of iodized salt are taken along with the fortified food. F100 contains 190 µg iodine/1,000 kcal and human milk from an iodine-sufficient population about 170 µg/1,000 kcal.

Thiamine

Thiamine requirements are traditionally closely linked to energy and are calculated as nutrient densities before conversion 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 beriberi and Korsakoff–Wernicke syndrome in adults; the corresponding syndromes in children are meningoencephalitis, aphonic beri-beri, and cardiac failure. Deficiency is particularly found in poor populations that have been eating polished rice. The thiamine concentration in breastmilk rises and falls with the thiamine status of the mother, so that fully breastfed infants can die from thiamine deficiency when the mother is symptomless. Many of these deaths are misdiagnosed [330].

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 breastfeeding mother is not related to the risk to her child. Deficiency is particularly likely in adults with a high alcohol intake, which may affect breastmilk being consumed by malnourished children.

Thiamine in food is unstable at neutral and alkaline pH values, and it is readily destroyed by oxidation (e.g., by iron) and heat [10]. Cooking typically leads to losses of up to 60%. It is particularly susceptible to destruction by sulfite and chlorine. Sodium hypochlorite (or metabisulfite) is commonly added as a disinfectant to water and food used to prepare meals for malnourished children; if this water is used to prepare the food without previous exposure to air, the likelihood of thiamine deficiency is increased. A high intake of sulfate, which can be reduced to sulfite by bacteria in the mouth and intestine, can also compromise thiamine status. Sulfites 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 chewing betel nut as well as eating raw fish will magnify the chances of thiamine deficiency [331].

The biological half-life of thiamine is 9 to 18 days. Malnourished children who start with a poor thiamine status are likely to become overtly deficient within 2 weeks.

Thiamine is not toxic, even in very high doses.

The recommendations for thiamine are generally between 400 and 500 µg/1,000 kcal. There is little spread between the authorities, probably because they all relate thiamine requirements to energy intake in the same way (**table 29**). The FAO/WHO recommendation for normal 1- to 3-year-old children is 523 µg/1,000 kcal. F100 contains 700 µg/1,000 kcal.

Many of the moderately malnourished children treated according to these recommendations are likely to belong to rice-eating populations and will already be depleted of thiamine. It would be prudent to ensure that malnourished children consume thiamine at levels higher than those recommended for normal children.

Because losses of up to 60% may occur 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 complementary or fortified food should contain 1,000 µg of thiamine/1,000 kcal. 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 µg/1,000 kcal.**

Riboflavin

Meat, milk, and green leafy vegetables are the main dietary sources of riboflavin. These foods are not consumed commonly or sufficiently by malnourished children or by 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 [332], and similar results have been found in most developing countries [264]. In India, Indonesia, and elsewhere, riboflavin deficiency is a major cause of mild anemia, and hemoglobin levels do not return to normal in these

TABLE 28. Iodine RNIs (µg/1,000 kcal)

Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
FAO	—	201	78	89
IOM	—	193	88	65
UK	94	85	73	75
WHO	—	74	94	72

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake; UK, United Kingdom; WHO, World Health Organization

populations with the administration of iron unless riboflavin, which is needed for iron utilization, is also administered. Riboflavin deficiency is also a cause of poor intestinal absorption [333, 334].

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 cofactor in glutathione reductase, an enzyme that is essential for 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 classic overt riboflavin deficiency [335, 336].

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 riboflavin important in those exposed to oxidative stress, but also oxidation either in the food or in the body will greatly increase the loss of riboflavin. As with vitamin C, destruction during cooking may be partly due to the high iron content in the diets, such as CSB, used as relief rations and for treatment of moderate malnutrition.

There is remarkable consistency across age groups, physiological states, and different committees in the recommendations for riboflavin (**table 30**), with levels around 600 μg/1,000 kcal for normal people living in uncontaminated environments.

Normal subjects who were fed 550 μg of riboflavin/day (approximately 250 μg/1,000 kcal) for 4 months developed overt clinical signs of deficiency [337, 338]. This early work on human deficiency shows that the margin between adequacy and clinical deficiency is quite narrow. The level giving clinical deficiency approaches the IOM value for 4- to 8-year-old children when allowance is made for a 10% standard deviation. It is possible that with more stringent ways of assessing the riboflavin intake required to remain healthy, 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, whenever investigations have been carried out, a high prevalence of biochemical deficiency has been found 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.

TABLE 29. Thiamine (vitamin B_1) RNIs (μg/1,000 kcal)

Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
FAO	—	446	523	483
IOM	—	446	489	432
UK	312	427	523	525

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake

TABLE 30. Riboflavin (vitamin B_2) RNIs (μg/1,000 kcal)

Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
FAO	—	595	523	483
IOM	—	595	489	432
UK	625	569	628	600

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake; UK, United Kingdom

Most of the present products used to treat the moderately malnourished have well in excess of each of the committee's requirements for riboflavin (800 to 3,000 μg/1,000 kcal). Because of riboflavin's critical role in oxidative stress, the riboflavin content of RUTF/F100 is 2000 μg/1,000 kcal. Other nutrients that are important for oxidative protection and whose half-lives have 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, below).

The moderately malnourished are exposed to considerable environmental and infective oxidative stress at least as great as in the United States, 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 1,800 μg/1,000 kcal for the moderately malnourished child when a fortified-food approach is used (riboflavin is nontoxic even in very high doses and is relatively inexpensive). When a food-based approach is used for the moderately malnourished child, the RNI for healthy children is inadequate, and a level of 800 μg/1,000 kcal 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 [339–344]. 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 alkalinizing culinary techniques of Central America. It should be emphasized that pellagra is not due simply to a lack of niacin in the diet. Rather, it is a multinutrient deficiency syndrome in which 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 [345]. Although about 60

mg of tryptophan will give rise to 1 mg of niacin, there is a large interindividual variation in the efficiency of this conversion, the hormonal, genetic, and biochemical bases of which are incompletely understood. Although pellagra can be treated with therapeutic doses of niacin, this conversion is vital to maintain niacin status with 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 pellagra.* For this reason, there is uncertainty about each of the factors affecting niacin status of individuals: the total amount of niacin required for normal metabolism: the commonly used conversion factor of 60 mg tryptophan generating 1 mg of niacin: and, the extent of interindividual variation (particularly in females and in pregnancy); the experimental basis is not sufficiently firm to set population requirements confidently. How these values 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 of pellagra are caused by lack of antioxidant protection against ultraviolet light energy (a free-radical initiator); this is thought to be because of inability to regenerate enough 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 patients with pellagra 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 defenses are otherwise adequate or sunlight exposure is minimal. Typically, the skin that is not directly traumatized 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 they are switched to a pellagragenic diet, it has been observed that fat people tend to show symptoms before thin people. Within a family, adults, particularly women,** tend to develop the skin lesions. Other family members who eat the same diet and have similar niacin:energy requirements are not so diagnosed; indeed, the lesions that constitute the case definition of pellagra are said not to occur in younger children. Thus, children and others may be susceptible to the other features of niacin deficiency (diarrhea 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" [349]).

It is unknown how frequently diarrhea among 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 diarrhea are misdiagnosed needs to be entertained. If this is so, then the prevalence of niacin deficiency and the public health measures that should be instituted will be more important than currently assumed.

Niacin is stable during storage and with normal methods of food preparation (moist heat). It is present in many foods covalently bound to small peptides and carbohydrates and is 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 for niacin are consistent across age and physiological states, with between 6 and 7 mg/1,000 kcal being required by normal, healthy children (**table 31**).

Higher amounts are added to foods used for rehabilitating the moderately malnourished. Because maize is frequently the staple food of malnourished children and maize itself is often a basic ingredient in many diets used for the moderately malnourished (e.g., corn-soy blend and Unimix), niacin levels for these children should be substantially above the requirements for normal children. F100 has 10 mg of niacin/1,000 kcal but also contains high-quality milk as its base, with adequate levels of tryptophan.

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 consumed by moderately malnourished children.

It is therefore recommended that if a fortified-food approach is used, there should be a threefold

* This occurs in Hartnup disease (from renal loss of amino acids) and in persons with carcinoid tumors (from consumption of tryptophan to synthesize serotonin, the product of this tumor), both of which result in increased tryptophan loss from the body but have no influence on preformed niacin metabolism.

** Female sex hormones reduce the conversion of tryptophan to niacin [346–348]. It is likely that the conversion factor of 60 mg tryptophan:1 mg niacin is less efficient for postpubertal females and is particularly compromised in pregnancy.

increase in niacin for the moderately malnourished child to 18 mg/1,000 kcal. For a food-based approach, the FAO/WHO level for 4- to 6-year-old children should be increased by about 30% to 8.5 mg/1,000 kcal. This level is approximately the level set by the UK DRV committee and should allow for the replenishment of niacin stores.

TABLE 31. Niacin RNIs (μg/1,000 kcal)

Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
FAO	—	5,947	6,276	6,439
IOM	—	5,947	5,867	5,763
UK	6,245	7,112	8,368	8,252

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake; UK, United Kingdom

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 (seborrheic dermatitis, anemia, 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 pediatric 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. It is of great interest that one study of breastmilk pyridoxine in Nepalese women showed it to be about 10% of that in American women [350, 351]. Thus, there may be widespread unrecognized compromised pyridoxine status.

Animal sources of pyridoxine are highly available, but in plants a variable proportion is in the form of glycosides (20% in rice, 28% in wheat, and 15% to 57% in beans). These forms are not as biologically available as animal sources of pyridoxine (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 25 days. There are no convenient field tests of pyridoxine status, so that with the lack of clinical signs, its deficiency is normally not recognized.

It is important that pyridoxine status may affect the behavior of both the mother and the infant; a low pyridoxine status is related to poor mother–infant interaction [352]. Abnormal behavior is frequently seen in both malnourished infants and their mothers. If this is partly due to deficiency of a simple vitamin, supplementation with the vitamin 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.

Pyridoxine requirements are fairly uniform across committees and age ranges as compared with those of other nutrients. The highest requirements for normal people are those from FAO/WHO (**table 32**).

The levels of pyroxidine that have been included in foods for malnourished children are much higher than these values. This is appropriate for several reasons: there is likely to be a pre-existing deficiency in children whose intakes have been largely from whole-grain cereals (nearly all the developing world) and pulses; breastmilk pyridoxine is low in the beneficiary populations wherever it has been measured; the availability of pyroxidine from most diets will be lower than that assumed by the committees making recommendations for developed countries; many cases that do occur will not be correctly diagnosed, so that deficiency will be unrecognized; the body stores of pyridoxine are depleted in the moderately malnourished child and they should be made good; the pyridoxine status may become precarious if the child will subsequently be consuming a diet based upon maize, beans, and oil; and 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 pyridoxine requirement be set at 1,800 μg (1.8 mg)/1,000 kcal for a fortified-food approach. When mixed diets are being designed from local foods, a level of 800 μg/1,000 kcal should be adequate, unless the children are receiving milled whole cereals, in which case the level should be increased to 1,000 μg/1,000 kcal.

Cobalamin (vitamin B_{12})

Vitamin B_{12} does not occur in plants. The populations where moderate malnutrition is common are almost entirely vegetarian by necessity. Surprisingly, the circulating levels of vitamin B_{12} in severely malnourished children are not low [297, 353–358]. This may be because concomitant liver injury releases cobalamin

into the circulation [358, 359]. The levels have not been examined with modern methods, and liver stores have not been measured. Ruminants get their vitamin B_{12} from bacterial and protozoal synthesis in the rumen. Synthesis of vitamin B_{12} may be one beneficial effect of small-bowel bacterial overgrowth when the dietary intake is very low [360, 361], but intestinal bacteria also convert dietary vitamin B_{12} into nutritionally inert metabolites [362, 363], so that the net effect of small-bowel bacterial overgrowth is normally detrimental.

There are normally large stores of vitamin B_{12} in the liver, so that clinical deficiency can take many years of depletion to develop in adults. However, the finding that the breastmilk levels in Guatemala were low is of concern [364]. As with pyridoxine deficiency, there seem to be behavioral changes in the mother–child relationship with vitamin B_{12} deficiency [365]. Young children of vitamin B_{12}–deficient mothers often have depleted liver stores and are more anemic than those of normal mothers. The diets that are usually given to malnourished children are almost devoid of vitamin B_{12}. Because of its long half-life, many consider that vitamin B_{12} status will remain stable over the course of treatment of moderate malnutrition. This is to ignore the likelihood of a pre-existing marginal vitamin B_{12} status in a child with a vegetarian mother consuming an exclusively cereal-based diet. It would be prudent during treatment of moderate malnutrition to ensure that adequate liver stores are established to maintain the child until family food containing animal products is consumed.

The absorption of vitamin B_{12} is particularly complicated; it 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 B_{12} absorption, so that patients with malabsorption frequently present with vitamin B_{12} deficiency [366]. Malabsorption causes vitamin B_{12} deficiency much more quickly than does dietary deficiency, because the enterohepatic circulation of vitamin B_{12} is disrupted. For these reasons, it is necessary to have adequate vitamin B_{12} in the recommendations for moderately malnourished children, despite the long half-life of vitamin B_{12} and the large hepatic store in a healthy Western child.

Persons who are marginal in vitamin B_{12} and are given large folic acid supplements will first present with severe and irreversible neurological disease rather than the normal presentation of anemia [367–369], although the evidence comes mainly from the older literature; the levels of folate intake recommended have not been shown to precipitate B_{12}-deficient neurological disease [370], although it remains a theoretical possibility [371]. In the presence of vitamin B_{12} 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, along with iron, to pregnant women) in largely vegetarian populations without attention to their vitamin B_{12} status.These people could develop irreversible spinal cord damage or dementia. For populations consuming the typical developing-country diet, all programs that supplement with folic acid should also include vitamin B_{12}.

TABLE 32. Pyridoxine (vitamin B_6) RNIs (μg/1,000 kcal)

Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
FAO	—	595	523	483
IOM	—	446	489	432
UK	468	569	732	675

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake; UK, United Kingdom

The RNIs for vitamin B_{12} are given in **table 33**.

Vitamin B_{12} is not toxic, even at high levels, and is stable in foods.

It would be wise to take the opportunity of giving moderately malnourished children under treatment sufficient vitamin B_{12} to replete their hepatic stores. Vitamin B_{12} is the only essential nutrient that is known to be completely absent from the exclusively plant-based diet of most malnourished children.

As most moderately malnourished children will be under treatment for a relatively short time, it is recommended that 2.6 μg/1,000 kcal be set as the recommended intake of vitamin B_{12} when a fortified or complementary food program is designed. For a food-based approach, a level of 1.0 μg/1,000 kcal, as recommended by FAO/WHO for the older child, should be used.

Folic acid

It has long been recognized 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 [297, 356, 372–374].

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 hydrolyzed 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 by 16% to 35% by beans and by 28% by maize. Banana, tomato, and orange juice are more potent inhibitors [375, 376]; this may be of relevance in plantain- or banana-eating cultures such as Uganda. Conjugase is defective in persons with a deficient zinc intake. Although the availability of food folate from Western diets is about 50%, it is likely to be considerably lower from maize- or plantain-based diets. Inhibition of conjugase by specific foods is not often considered when

antinutritional factors in foods are examined.

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

The recent FAO/WHO and IOM committees have established folate requirements that are substantially above those of previous committees (**table 34**). This is largely because of the recognition that homocysteine level in plasma is a more sensitive test of the adequacy of folate status than those used previously. F100 and RUTF have folate concentrations of 350 μg/1,000 kcal.

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 B_{12} fortification.

For a fortified-food approach, a folate level of 350 μg/1,000 kcal (the same level as that in RUTF and F100) is recommended. When a food-based approach is used, the folate level in the diet should be 220 μg/1,000 kcal; this is 30% above the level for a healthy child.

Ascorbic acid (vitamin C)

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

TABLE 33. Cobalamin (vitamin B_{12}) RNIs (ng/1,000 kcal)[a]

Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
FAO	—	743	941	966
IOM	—	743	880	864
UK	625	569	523	600

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake; UK, United Kingdom

a. It is currently thought that the vitamin B_{12} RNIs may have to be revised upwards (L.H. Allen, personal communication).

TABLE 34. Folate RNIs (μg/1,000 kcal)

Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
FAO	—	119	167	161
IOM	—	119	147	144
UK	78	71	73	75

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake; UK, United Kingdom

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 [282]. 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 anemia.

Thus, in 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, since food vitamin C is quickly destroyed as food is dried and stored. Similarly, pastoralist communities rarely have access to fruits and green vegetables.*

Since 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 anemia, despite the relatively modest levels of iron in their diet [261].

Ascorbate is very vulnerable to oxidation (the dehydroascorbic acid is oxidized with irreversible opening of the lactone ring). It normally decreases rapidly in stored foods; oxidation is enhanced by exposure to air, traces of iron, or heat and is worse in a neutral or alkaline matrix. There are also ascorbate oxidases in many plant tissues. Rapid heating to levels that destroy these oxidases can help preserve vitamin C in diets.

Vitamin C is the major antioxidant of the aqueous body; it also regenerates oxidized vitamin E. However, in the presence of free iron it becomes a pro-oxidant through its reductive activity [377, 378].

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 (**table 35**). It is unclear why these dramatic differences should be recommended.

Malnourished children are exposed to greatly increased oxidative stress as compared with healthy Western children. For example, in setting the RNIs for

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

vitamin C, the IOM recommends a much higher value for smokers than for nonsmokers. Similarly, patients with "oxidative" diseases such as rheumatoid arthritis have chronically low vitamin C levels and greatly increased rates of disappearance of vitamin C after a test dose is given [379].

The highest recommended value of vitamin C from the IOM committee is 74 mg/1,000 kcal for the older infant.

Vitamin C is one of the more expensive ingredients in the mineral and 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 [378].

It is recommended that a vitamin C level of 100 mg/1,000 kcal be used for fortified foods. For a food-based approach, the IOM level of 75 mg/1,000 kcal 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 oxidized. Whenever vitamin E has been measured in malnourished subjects, it has been found to be deficient [355, 380–389]; no article could be found in which vitamin E levels were normal in malnourished subjects. Vitamin E occurs with fat in the diet. In contrast to vitamin A, there is no provitamin that can generate vitamin E, so that a low-fat diet will nearly always be deficient in vitamin E. Thus, when 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 characterized by low levels of fat, and tropical oils have lower levels of vitamin E 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 (butylated hydroxytoluene [BHT] and butylated hydroxyanisole [BHA]) because vitamin E is usually lost during refining. They do not contain sufficient vitamin E, and the added antioxidants, although they prevent the oil from becoming rancid, have no biological function; they cannot replace or minimize 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 polyunsaturated fatty acids, which increase both 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 between the recommendations of the different committees are illustrated in **table 36**. The levels of vitamin E set recently by FAO/WHO are substantially higher than those of any other committee.* Some committees set their values for vitamin E entirely in relation to the amount of polyunsaturated fatty acid recommended for the diet. This would not be appropriate for people living in the developing world.

However, higher levels of vitamin E are suggested for infants, because brain hemorrhage, hemolytic anemia, and edema have been described in Western premature infants on a low vitamin E diet [390]. Apart from these catastrophic effects, lesser levels of vitamin E deficiency, like lesser levels of the other antioxidants, are not associated with any characteristic signs or symptoms, apart perhaps from the host response to infections such as measles. Most breastmilk samples measured have a relatively low vitamin E content, which can be greatly increased by dietary supplementation [391]. Breastmilk vitamin E is lower in women exposed to the oxidant stress of smoking [392], presumably as a result of increased metabolic destruction under such conditions. Women in countries such as Bangladesh [393] have low levels of vitamin E in their breastmilk.

The malnourished child is particularly prone to oxidant stress and has low levels of many of the antioxidants [278, 300, 394–397], including vitamin E.

There is an important interaction between vitamin E and selenium. Selenium is a critical nutrient that has been neglected but that is involved in infection, virulence of organisms, emergence of new organisms, immune function, and protection from oxidative stress. It is equally critical that there be sufficient vitamin E to augment selenium in these functions. According to Beck, "deficiencies in either Se or vitamin E results in specific viral mutations, changing relatively benign viruses into virulent ones" [318]. In view of this, it is critical that sufficient vitamin E be given to those living under unhygienic conditions and other

TABLE 35. Ascorbic acid (vitamin C) RNIs (mg/1,000 kcal)

Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
FAO	—	44.6	31.4	24.1
IOM	—	74.3	14.7	18.0
UK	39.0	35.6	31.4	22.5

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake; UK, United Kingdom

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

environmental stresses.

The highest recommended intake of vitamin E is set at 8.9 mg/1,000 kcal. The level in F100 and RUTF is 22 mg/1,000 kcal, 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 vitamin E 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 healthy Western children are quite inadequate for these children.

Thus, for a fortified or complementary food approach, it would be appropriate to have the same level of vitamin E as in RUTF (22 mg/1,000 kcal). This level cannot be reached by a food-based approach. For a food-based approach, an 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 11.5 mg/1,000 kcal.

Retinol (vitamin A)

Retinol deficiency is widespread in those parts of the world where moderate malnutrition is common. Its deficiency leads not only 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 of various genes. Retinol is therefore of fundamental importance to the whole of the body and not only to eyesight, although eye signs and symptoms are used clinically to diagnose vitamin A deficiency. Vitamin A supplementation has been shown in several trials to have a dramatic effect upon rates of infectious disease and mortality under stable conditions [398–401]. 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, distribution of vitamin A capsules with vaccination is routine practice. These programs are successful. However, concern has arisen about the teratogenic effects of vitamin A in high doses and the more recent demonstration that high doses of vitamin A are associated with increased mortality and increased respiratory tract infection in children with severe clinical malnutrition [402, 403].

The highest RNIs are for young children (**table 37**) and lactating mothers**.** It is quite unclear why the IOM recommendations for infants and young children differ so markedly from each other.

TABLE 36. Vitamin E RNIs (mg/1,000 kcal)

Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
FAO	—	8.92	5.87	5.04
IOM	—	4.01	5.23	4.02

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake

TABLE 37. Vitamin A RNIs (μg/1,000 kcal)

Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
FAO	—	595	418	362
IOM	—	743	293	288
UK	546	498	418	375

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake; UK, United Kingdom

The data of Rothman et al. [404] upon which the recommendations with respect to teratogenesis are based are shown in **table 38**, expressed as vitamin A:energy densities. The original units of the published article are IU per day; these have been converted to micrograms per day by using a conversion factor of 1 IU = 0.3 μg of retinol and then to a density by using the requirement for a nonpregnant* 31- to 50-year-old woman. 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 1,875 μg/1,000 kcal.

Considering the widespread and severe effects of prior deficiency in moderately malnourished children, their depleted hepatic stores, and the low fat content of the diet on the one hand, and the relative dangers to mothers who exclusively consume any product formulated according to the recommendations made in this paper in early pregnancy on the other hand, it is reasonable to provide as high a level of vitamin A in the diet as possible without reaching a level where there is any evidence of an adverse effect if the diet is consumed by pregnant women. For this reason, **with the use of a fortified-food approach, it is recommended that the diet of moderately malnourished children contain 1,900 μg of retinol/1,000 kcal.** If a food-based approach is used, an increase of 30% over the highest density recommended for a healthy Western child would be appropriate. This would result in a retinol density of 960 μg/1,000 kcal.

It is assumed that when a food-based approach is being advocated, there will also be a vitamin A capsule distribution program for children at risk for vitamin A deficiency and for the moderately malnourished. If such programs are universally in place with a high and verified coverage, the food-based recommendations can be reduced to match the FAO/WHO recommendation of 600 μg/1,000 kcal.

Vitamin D

Signs of vitamin D deficiency commonly occur in

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

TABLE 38. Vitamin A teratogenicity[a]

Intake — µg/day	Intake— µg/1,000 kcal	No. of pregnancies	Neural tube defects—no. (%)	All congenital defects—no. (%)
0–1,500	< 625	6,410	33 (0.51)	86 (1.34)
1,500–3,000	625–1,250	12,688	59 (0.47)	196 (1.54)
3,000–4,500	1,250–1,875	3,150	20 (0.63)	42 (1.33)
> 4,500	> 1,875	500	9 (1.80)	15 (3.00)

Recalculated from Rothman et al. [404] to express the intake in terms of nutrient densities. Intakes per unit of energy were calculated on the basis of an intake of 2,400 kcal/day for an early pregnancy in an older woman.

children in hot, dry, and dusty areas. These conditions typically occur in a broad band from the Sahara to China and from the Urals to Ethiopia. Some of these signs may be due to phosphate, calcium, or magnesium deficiency, particularly when the deficiency is 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. Exclusively breastfed infants whose mothers have a low vitamin D status can develop vitamin D deficiency [405–407] or even overt rickets [408].

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

Table 39 shows the vitamin D recommendations for normal, healthy children.

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

For a supplementary-food approach, it is appropriate to focus on the 6- to 12-month-old child, who is least likely to be exposed to sunlight and has the highest requirements. Therefore, **it is recommended that 11 µg of vitamin D/1,000 kcal be present in the diet**. For a food-based approach, the FAO/WHO level of 7.4 µg/1,000 kcal may be used.

* So-called "swelling lipids" (monoglycerides, phospholipids, and 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 [214, 409].

Vitamin K

Vitamin K is obtained mainly from dark-green leafy vegetables. Malnourished children presumably do not consume sufficient dark-green leafy vegetables. 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 synthesized by 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 taking antibiotics that suppress intestinal flora require a dietary source of preformed vitamin K,** and therefore when antibiotics are given the diet should contain adequate amounts of vitamin K.

However, recent evidence shows that there may be insufficient synthesis of vitamin K in many Westerners with osteoporosis, as shown by undercarboxylation of osteocalcin (a sign of vitamin K deficiency) [410]. Furthermore, there are seasonal changes in vitamin K status in the West [411], probably related to seasonal availability of fresh green vegetables [412].

There do 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 and RUTF is 40 µg/1,000 kcal. 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 difference between the IOM recommendations for younger and older children seems inexplicable; the documents do not comment upon this.

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 of vitamin K in RUTF and F100 (40 µg/1,000 kcal)**, as recommended by the IOM. For a food-based approach, a level of 20 µg/1,000 kcal (the FAO/WHO requirement plus 30%) would probably be adequate.

** Prophylaxis with cotrimoxazole in patients with HIV does not cause suppression of intestinal bacteria.

TABLE 39. Vitamin D RNIs (μg/1,000 kcal)

Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
FAO	—	7.43	5.23	4.02
IOM	—	7.43	4.89	3.60
UK	10.93	9.96	7.32	0.00

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake; UK, United Kingdom

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 analyzed. When uncooked egg protein is used in formulating foods for malnourished children, additional biotin is essential to neutralize the antibiotin antinutrient, avidin, contained in the egg [413].

Biotin-deficient infants on prolonged parenteral nutrition have a particular facial distribution of fat, skin lesions similar to those associated with zinc deficiency, candidiasis, and flat affect and are withdrawn; these features are similar to those of both 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 biotin status is unknown. The plasma levels are lower in severely malnourished children, and biotin supplementation improves their levels of biotin-dependent enzymes [414–416]. It has been postulated that the abnormal fatty acid profile of malnourished children is related to biotin deficiency [417].

F100 contains a high concentration of biotin (24 μg/1,000 kcal*). 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 the evidence for biotin deficiency in malnourished children [415], **it is recommended for fortification programs that the diet should contain 13 μg of biotin/1,000 kcal**; for food-based approaches to treating the moderately malnourished, an intake of 10 μg/1,000 kcal is appropriate

* In some tables and documents, there appears to be a transcription error. The original biotin level set for F100 was 100 nmol/1,000 kcal (biotin has a molecular weight of 244), which is equivalent to 24 μg/1,000 kcal. Because of the transcription error, the biotin content of F100 is given as 100 μg/1,000 kcal instead of 100 nmol/1,000 kcal. The high level in F100 is not deleterious in any way.

TABLE 40. Vitamin K RNIs (μg/1,000 kcal)

Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
FAO	—	14.87	15.69	16.10
IOM	—	3.72	29.34	39.62

FAO, Food and Agriculture Organization; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake

Pantothenic acid

There has been one report of epidemic pantothenic acid deficiency in malnourished refugees [76]. This occurred in Afghanistan among malnourished people who were given highly refined wheat flour but did not receive the other ingredients of the food basket because of a pipeline break. The patients presented with crippling burning foot syndrome, which was only partially relieved by administration of 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 consuming highly refined flour that seems to have precipitated widespread clinical deficiency, similar to that seen in Japanese prisoner-of-war camps during the Second World War. 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 an adequate intake for moderately malnourished children. F100/RUTF contain 3 mg of pantothenic acid/1,000 kcal. The RNIs are shown in **table 42**.

The diet for a supplementary-food approach should contain 3 mg of pantothenic acid/1,000 kcal and that for a food-based approach 2.7 mg/1,000 kcal.

Essential fatty acids

Essential fatty acids are important for brain and neural tissue development. The evidence for abnormal development of children on a low intake of essential fatty acids in the Western world is becoming clear, now that more sophisticated methods of examining neural development have been established. This is covered in detail in the companion article in this issue by Michaelsen et al. [2].

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 [418–425]. 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 alterations to essential fatty acid deficiency, although probable, has not been confirmed.

The most salient clinical feature of essential fatty acid deficiency is a dry, flaky skin. This is common in moderately malnourished children; mothers whose children are treated with highly fortified lipid-based spreads

TABLE 41. Biotin AIs (μg/1,000 kcal)

Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
FAO	—	8.92	8.37	9.66
IOM	—	8.92	8.37	9.66

AI, Adequate Intake; FAO, Food and Agriculture Organization; IOM, Institute of Medicine

TABLE 42. Pantothenic acid AIs (mg/1,000 kcal)

Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
FAO	—	2.68	2.09	2.41
IOM	—	2.68	1.96	2.16

AI, Adequate Intake; FAO, Food and Agriculture Organization; IOM, Institute of Medicine

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 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 when there is a problem with fat absorption (due to malabsorption syndrome of any cause), essential fatty acid deficiency can be treated and prevented by anointing the child's skin with oils containing the essential fatty acids.

The recommendations are that the omega-6 fatty acid series should comprise at least 4.5% of energy (5 g/1,000 kcal), the omega-3 fatty acid series should comprise at least 0.5% of energy (0.85 g/1,000 kcal), and the total fat content of the diet used to treat moderately malnourished children should provide 35% to 45% of the dietary energy.

Manganese, chromium, molybdenum, and fluorine

There are far fewer data on the quantities of these essential nutrients required in the normal, moderately malnourished, or severely malnourished child. It is recommended that pending more definitive data, 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 0 mg/1,000 kcal.

Manganese. Manganese deficiency in animals gives rise to obesity, teratogenic abnormalities of the inner ear, and epilepsy. Human epileptics have low levels of manganese [426]. Manganese is also associated with iron metabolism. Gross clinical deficiency of manganese in parenterally fed adults is associated with anemia and skin lesions.

The manganese content of RUTF is 0.7 mg/1,000 kcal.* The levels of manganese in the blood of malnourished children were about half of those in control children in all studies that reported manganese levels [427–429]. It would appear to be important to add manganese to the diets of malnourished children. However, no studies of manganese supplementation in malnourished children could be found.

It is recommended that the manganese intake be increased to that recommended by the IOM (1.2 mg/1,000 kcal).

Chromium. Chromium has been implicated in carbohydrate metabolism. The levels are low in children with severe malnutrition. Chromium supplementation appears to improve glucose tolerance in malnourished children [430, 431] and adults [432]. The chemical form of chromium appears to be important. Most inorganic chromium is unavailable, and some valencies of the metal (for example the trioxide) are toxic. In view of the reports of chromium deficiency and glucose intolerance in malnourished children, their diets should contain adequate chromium. However, there are insufficient data to determine the appropriate dose to recommend. Thus, it is recommended that chromium be added to the diets at the level of AIs reported by the IOM. This would result in an intake of 11 μg/1,000 kcal.

Molybdenum. Molybdenum is an essential cofactor in several enzymes involved with energy metabolism and the metabolism of sulfite. There do not seem to be reports of clinical deficiency in humans, although there are reports from farm animals. There seems to be a problem in some areas of nutrient–nutrient interactions with 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 intake reported by the IOM until the extent and frequency of deficient or excessive intakes are defined. The present recommendation is thus 16 μg molybdenum/1,000 kcal.

* Manganese was inadvertently omitted from the F100 specifications. This omission was corrected when the derivative RUTFs were formulated.

TABLE 43. AIs of fluorine, manganese, chromium, and molybdenum, expressed per 1,000 kcal

Nutrient	Unit	Authority	7–9 mo	10–12 mo	1–3 yr	4–6 yr
Fluorine	mg	IOM	—	0.74	0.68	0.72
Manganese	mg	IOM	—	0.89	1.17	1.08
Chromium	μg	IOM	—	8.18	10.76	10.80
Molybdenum	μg	IOM	—	4.46	16.62	15.85

AI, Adequate Intake; IOM, Institute of Medicine

Choline

Choline deficiency in animals gives neurological abnormalities and fatty liver. Both of 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, the fat in the liver is very slow to dissipate, even in children gaining weight rapidly with a high lipid intake [433, 434]. Fatty liver is common in marasmus as well as in kwashiorkor [434], in contrast to traditional teaching. It is possible that choline deficiency could be associated with this abnormal fat accumulation, and the failure of fat accumulation to dissipate could be due to 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 mobilization [277].

The role of choline deficiency in malnutrition awaits further work. In the meantime, it is recommended that the IOM RNI be followed (220 mg/1,000 kcal).

Tolerable upper limits of nutrients for the malnourished

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

For moderately malnourished children who have abnormalities of intestinal, liver, and renal function that 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 tolerable upper limit recommendations took into account. The upper limits were set for 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. For the moderately malnourished, a similar argument of particular sensitivity of the malnourished child has been advanced in this paper for restricting sodium and iron in the diets and, indeed, for setting tolerable upper limits for these two nutrients, in particular, that are more stringent than those for the normal, 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 consumed to excess without increments in the interacting nutrient. For example, the upper limit for zinc is set to avoid induction of copper deficiency if copper intake is marginal; similarly, the upper limit for folate is set to avoid neurological damage if vitamin B_{12} intake has been deficient. Such considerations do not obtain when a food that aims to include all essential nutrients in sufficient amounts with the correct balance to avoid such interactions is formulated and given as a complete diet or as a part of a diet that 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 consumed, all of the interacting nutrients are then consumed in appropriate ratios. This argument does not apply to a food-based approach, where the chosen diet may not contain enough 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, essential amino acid, copper:zinc, and calcium:phosphorus ratios. However, there are many other important balances that should be considered, such as potassium:sodium:nitrogen:phosphorus:zinc, iron:manganese, iron:selenium, and copper:molybdenum:sulfur ratios. 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 [435]; the report (sections 3.1.2 and 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 in terms of both absolute amounts and nutrient densities.

The recommendations for malnourished children 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, malnourished children are also likely to consume 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 consumed by the children they are less likely to reach the tolerable upper limit.

Magnesium

The tolerable upper limit for magnesium 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 WHO/FAO report [435] states that "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 of magnesium for skeletal growth;
- The lack of any osmotic diarrhea 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/day);
- The lack of any data from children showing an adverse effect of magnesium;
- 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 applies only 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 tolerable upper limit for supplemental magnesium.

Zinc

The largest discrepancy between the recommendations for malnourished children and the tolerable upper limits recommended by the IOM 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 WHO/FAO report [435] 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 consumed by normal, healthy individuals.

No reports were found of adverse effects of intakes of zinc naturally occurring in food that exceeded the upper limit.

The cited adverse effects of zinc are suppression of the immune response, changes in high-density lipoprotein (HDL) cholesterol, interference with iron

TABLE 44. Tolerable upper limits of nutrients in absolute amounts and amounts per 1,000 kcal, in relation to the recommendations for children with moderate acute malnutrition (MAM)

		IOM tolerable upper limits			MAM (food based)			MAM (complement based)			IOM tolerable upper limits				MAM (food based)	MAM (complement based)
		Absolute amount									Amount of nutrient/1,000 kcal					
Nutrient	Unit	7–12 mo	1–3 yr	4–8 yr	7–12 mo	1–2 yr	3–5 yr	7–12 mo	1–2 yr	3–5 yr	7–12 mo	1–3 yr	4–8 yr	Lowest	All	All
Protein	g	—	—	—	16	23	30	17	25	32	—	—	—	—	24	26
Minerals																
Sodium	mg	—	1,500	1,900	370	530	680	370	530	680		1,470	1,370	1,370	550	550
Potassium	mg	—	—	—	950	1,350	1,750	1,050	1,550	2,000	—	—	—	—	1,400	1,600
Magnesium	mg	—	65[a]	110[a]	**135**	**190**	**250**	**200**	**290**	**370**	—	65[a]	80[a]	65[a]	**200**	**300**
Phosphorus	mg	—	—	3,000	400	570	750	600	860	1,120	—	—	2,160	2,160	600	900
Sulfur	mg	—	—	—	0	0	0	135	190	250	—	—	—	—	0	200
Zinc	mg	5	7	12	**9**	**12**	**16**	**13**	**19**	**25**	7	7	9	7	**13**	**20**
Calcium	mg	—	2,500	2,500	400	570	740	560	800	1,050	—	2,445	1,800	1,800	600	840
Copper	µg	—	1,000	3,000	450	650	850	600	850	1,100	—	980	2,160	980	680	890
Iron	mg	40	40	40	6	9	11	12	17	22	60	40	30	30	9	18
Iodine	µg	—	200	300	135	190	250	135	190	250	—	200	215	200	200	200
Selenium	µg	60	90	150	20	30	35	35	55	70	90	90	110	90	30	55
Manganese	mg	—	—	2	0.8	1.1	1.5	0.8	1.1	1.5	—	—	1.4	1.4	1.2	1.2
Chromium	µg	—	—	—	7	11	14	7	11	14	—	—	—	—	11	11
Molybdenum	µg	—	—	300	10	15	20	10	15	20	—	—	215	215	16	16
Vitamins, water soluble																
Thiamine (vitamin B_1)	µg	—	—	—	400	575	750	670	950	1,250	—	—	—	—	600	1,000
Riboflavin (vitamin B_2)	µg	—	—	—	540	770	990	1,200	1,700	2,250	—	—	—	—	800	1,800
Pyridoxine (vitamin B_6)	µg	—	—	30,000	540	770	990	1,200	1,700	2,250	—	—	21,000	21,000	800	1,800
Cobalamin (vitamin B_{12})	ng	—	—	—	675	960	1,240	1,750	2,500	3,200	—	—	—	—	1,000	2,600
Folate	µg	—	300	400	150	210	270	240	330	**430**	—	—	290	290	220	350
Niacin	mg	—	—	10,000	6	8	11	12	17	22	—	—	7,200	7,200	8.5	18

Ascorbate (vitamin C)	mg	—	400	650	50	70	90	60	90	120	—	390	470	390	75	100
Pantothenic acid	mg	—	—	—	2.0	3.0	3.5	2.0	3.0	3.5	—	—	—	—	2.7	3
Biotin	µg	—	—	—	6.5	9.5	12.5	8.5	12.5	16.0	—	—	—	—	10	13
Vitamins, fat soluble																
Retinol (vitamin A)	µg	600	600	900	**650**	**920**	**1,190**	**1,280**	**1,820**	**2,360**	890	590	650	590	**960**	1,900
Cholecalciferol (vitamin D)	µg	25	50	50	5	7	9	7	11	15	—	50	35	35	7.4	11
Tocopherol (vitamin E)	mg	—	200	300	8	11	14	15	20	25	—	195	215	195	11.5	22
Phytomenadione (vitamin K)	µg	—	—	—	13	20	25	25	40	50	—	—	—	—	20	40

IOM, Institute of Medicine

a. The upper limit for magnesium applies only to supplemental magnesium and not to food magnesium.

The values that exceed the tolerable Upper Limits set by the Institute of Medicine, USA, are shown in bold.

absorption, and reduction of copper status. Immune suppression only occurred when massive doses of zinc were given for prolonged periods, and the cholesterol changes were inconsistent and were ignored by the IOM committee.

The effect of zinc on iron absorption was only observed when the zinc:iron ratio exceeded 3:1 and the two metals were given together in water. When they were given with a meal, no effect of the zinc on iron absorption was observed [436]. When the zinc:iron ratio was increased to 5:1, there was 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. Since it is proposed that zinc and iron should always be 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 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 [437], who added 4 mg/L zinc to a breastmilk substitute, resulting in a total daily intake of 5.8 mg. This supplement was given to 34 infants from just after birth for 6 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 their requirements for copper until 6 months of age; therefore, this study may not be appropriate to make any judgment about the effect of zinc on copper status in the infant. Second, this study, correctly, did not attempt to give additional copper to these infants. This study has been used to determine the level at which there is no observed adverse effect of zinc supplementation and to set the tolerable upper limit of zinc 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 were found of children over the age of 6 months who either had higher doses of zinc for prolonged periods or had their copper status assessed.

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

F100 supplies about 20 mg of zinc/1,000 kcal and has been given to severely malnourished children for up to

2 months without any adverse effect on copper status, although copper has routinely also been added to the diet at a zinc:copper ratio of 10:1 in order to obviate the known interaction of zinc and copper.

In none of the studies examined by the IOM committee that reported 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 medication 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 United States was applied to diets designed for the malnourished.

Folic acid

The present recommendations for folate intake exceeds the IOM tolerable upper limit for the older child by only 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 B_{12} deficiency. The level has been set at a deliberately conservative amount because vitamin B_{12} deficiency is commonly found in the elderly in developed countries. This is important. This consideration also applies to populations subsisting on largely vegetarian diets, such as the moderately malnourished. Marginal vitamin B_{12} status appears to be widespread in these populations. However, the need for such a conservative tolerable upper limit is obviated if vitamin B_{12} is given in adequate doses along with the folic acid. In principle, if a diet is being fortified with folate, particularly if the amount of folic acid approaches or exceeds the tolerable upper limit, then vitamin B_{12} 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 B_{12} to all medications and diets that are fortified with folic acid and given to populations at risk for vitamin B_{12} deficiency.

Vitamin A

Vitamin A toxicity in children causes increased intracranial pressure and bone changes. These effects occur when children are given vitamin A in excess of 5,500 μg per day for prolonged periods [438].

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 et al. [438] for children, although they described only five cases of intoxication.

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

In view of the high prevalence of vitamin A deficiency in moderately malnourished children and the increased mortality among vitamin A–deficient children in the developing world, it is important to have sufficient vitamin A in the diet. The question does arise about the possible danger to children who receive large doses of vitamin A from multiple sources. The RNI should take into account the presence of capsule distribution in the area of distribution.

Acknowledgments

I am grateful to Drs. André Briend, Kay Dewey, and Lindsay Allen for their detailed review and criticism of the drafts of this article. The article would not have been possible without discussion over many years with my colleagues and students while looking after and studying malnourished children; in particular Professors John Waterlow, David Picou, Alan Jackson, and Vernon Young and Dr. Yvonne Grellety. The immense amount of work done by the members of the IOM and FAO/WHO committees and the others upon whose work I have drawn forms the bedrock upon which the present recommendations are founded.

Appendix 1. Nutrient densities for normal healthy children

TABLE 45. Nutrient densities for normal, healthy children (RNIs and AIs) 6 months to 5 years of age according to age group, expressed as amount of nutrient/1,000 kcal, using the FAO mean female energy requirement as the denominator for the particular age range quoted by each authority[a]

Variable	Unit	Authority	Age group 1	Age group 2	Age group 3	Age group 4
Age range	—	FAO	—	7–12 mo	1–2 yr	3–5 yr
Age range	—	IOM	—	7–12 mo	1–3 yr	4–8 yr
Age range	—	UK	7–9 mo	10–12 mo	1–3 yr	4–6 yr
Age range	—	WHO/FAO/IAEA	—	7–12 mo	1–2 yr	3–5 yr
Energy	kcal/day	FAO	—	673	956	1,242
Energy	kcal/day	IOM	—	673	1,023	1,388
Energy	kcal/day	UK	641	703	1,023	1,333
All values below are expressed per 1,000 kcal female energy requirement						
Protein						
Protein	g	FAO/WHO 2007	—	10.1	11.1	14.5
Protein	g	FAO 1985	22.3	20.1	15.2	14.6
Protein	g	IOM	—	16.4	12.7	13.7
Protein	g	UK	21.4	21.2	15.2	14.8
Protein	%kcal	FAO	8.9	8.0	6.1	5.8
Protein	%kcal	IOM	—	6.5	5.1	5.5
Protein	%kcal	UK	8.6	8.5	6.1	5.9
Minerals						
Sodium	mg	IOM	—	550	978	864
Sodium (min)	mg	UK	503	491	529	518
Potassium	mg	IOM	—	1,041	2,934	2,737
Potassium (min)	mg	UK	1,099	1,001	818	821
Chlorine	mg	IOM	—	847	1,467	1,369
Chlorine (min)	mg	UK	776	757	817	799
Magnesium	mg	FAO	—	79	63	59
Magnesium	mg	IOM	—	112	78	94
Magnesium	mg	UK	121	114	89	88
Phosphorus	mg	IOM	—	409	450	360
Phosphorus	mg	UK	634	578	285	263
Calcium	mg	FAO	—	595	523	483
Calcium	mg	IOM	—	401	489	576
Calcium	mg	UK	820	747	369	340
Zinc (high)	mg	FAO (high)	—	3.7	2.5	2.5
Zinc (moderate)	mg	FAO (moderate)	—	6.1	4.3	4.1
Zinc (low)	mg	FAO (low)	—	12.5	10.8	9.1
Zinc	mg	IOM	—	4.5	2.9	3.6
Zinc	mg	UK	7.7	7.0	5.1	4.9
Zinc (high)	mg	WHO (high)	—	4.9	3.5	3.1
Zinc (moderate)	mg	WHO (moderate)	—	8.3	5.8	5.2
Zinc (low)	mg	WHO (low)	—	16.5	11.5	10.4
Copper	μg	IOM	—	327	332	317
Copper	μg	UK	496	452	399	429
Copper	μg	WHO	—	892	586	459
Iron (15%)	mg	FAO	—	5.9	4.2	4.8
Iron (12%)	mg	FAO	—	7.4	5.2	5.6
Iron (10%)	mg	FAO	—	8.9	6.3	7.2
Iron (5%)	mg	FAO	—	17.8	13.6	14.5
Iron	mg	IOM	—	16.4	6.8	7.2

continued

TABLE 45. Nutrient densities for normal, healthy children (RNIs and AIs) 6 months to 5 years of age according to age group, expressed as amount of nutrient/1,000 kcal, using the FAO mean female energy requirement as the denominator for the particular age range quoted by each authority[a] *(continued)*

Variable	Unit	Authority	Age group 1	Age group 2	Age group 3	Age group 4
Iron	mg	UK	12.2	11.1	7.0	4.6
Iodine	μg	FAO	—	201	78	89
Iodine	μg	IOM	—	193	88	65
Iodine	μg	UK	94	85	73	75
Iodine	μg	WHO	—	74	94	72
Selenium	μg	FAO	—	14.9	17.8	16.9
Selenium	μg	IOM	—	29.7	19.6	21.6
Selenium	μg	UK	15.6	14.2	15.7	15.0
Selenium	μg	WHO	—	17.8	20.9	19.3
Fluorine	mg	IOM	—	0.74	0.68	0.72
Manganese	mg	IOM	—	0.89	1.17	1.08
Chromium	μg	IOM	—	8.18	10.76	10.80
Molybdenum	μg	IOM	—	4.46	16.62	15.85
Vitamins, water soluble						
Thiamine (vitamin B_1)	μg	FAO	—	446	523	483
Thiamine (vitamin B_1)	μg	IOM	—	446	489	432
Thiamine (vitamin B_1)	μg	UK	312	427	523	525
Riboflavin (vitamin B_2)	μg	FAO	—	595	523	483
Riboflavin (vitamin B_2)	μg	IOM	—	595	489	432
Riboflavin (vitamin B_2)	μg	UK	625	569	628	600
Pyridoxine (vitamin B_6)	μg	FAO	—	595	523	483
Pyridoxine (vitamin B_6)	μg	IOM	—	446	489	432
Pyridoxine (vitamin B_6)	μg	UK	468	569	732	675
Cobalamin (vitamin B_{12})	ng	FAO	—	743	941	966
Cobalamin (vitamin B_{12})	ng	IOM	—	743	880	864
Cobalamin (vitamin B_{12})	ng	UK	625	569	523	600
Folic acid	μg	FAO	—	119	167	161
Folic acid	μg	IOM	—	119	147	144
Folic acid	μg	UK	78	71	73	75
Niacin	μg	FAO	—	5,947	6,276	6,439
Niacin	μg	IOM	—	5,947	5,867	5,763
Niacin	μg	UK	6,245	7,112	8,368	8,252
Ascorbate (vitamin C)	mg	FAO	—	44.6	31.4	24.1
Ascorbate (vitamin C)	mg	IOM	—	74.3	14.7	18.0
Ascorbate (vitamin C)	mg	UK	39.0	35.6	31.4	22.5
Pantothenic acid	mg	FAO	—	2.68	2.09	2.41
Pantothenic acid	mg	IOM	—	2.68	1.96	2.16
Biotin	μg	FAO	—	8.92	8.37	9.66
Biotin	μg	IOM	—	8.92	8.37	9.66
Choline		IOM	—	223	196	180
Vitamins, fat soluble						
Vitamin A	μg	FAO	—	595	418	362
Vitamin A	μg	IOM	—	743	293	288
Vitamin A	μg	UK	546	498	418	375
Vitamin D	μg	FAO	—	7.43	5.23	4.02
Vitamin D	μg	IOM	—	7.43	4.89	3.60
Vitamin D	μg	UK	10.93	9.96	7.32	0.00
Vitamin E	mg	FAO	—	4.01	5.23	4.02
Vitamin E	mg	IOM	—	8.92	5.87	5.04

continued

TABLE 45. Nutrient densities for normal, healthy children (RNIs and AIs) 6 months to 5 years of age according to age group, expressed as amount of nutrient/1,000 kcal, using the FAO mean female energy requirement as the denominator for the particular age range quoted by each authority[a] *(continued)*

Variable	Unit	Authority	Age group 1	Age group 2	Age group 3	Age group 4
Vitamin K	μg	FAO	—	14.87	15.69	16.10
Vitamin K	μg	IOM	—	3.72	29.34	39.62
Amino acids						
His	mg	IOM	—	428	267	254
Ile	mg	IOM	—	575	356	349
Leu	mg	IOM	—	1,244	801	777
Lys	mg	IOM	—	1,191	750	729
Met + Cys	mg	IOM	—	575	356	349
Phe + Tyr	mg	IOM	—	1,124	686	650
Thr	mg	IOM	—	656	407	380
Try	mg	IOM	—	174	102	95
Val	mg	IOM	—	776	470	444
His	mg/g protein	IOM	—	26	21	19
Ile	mg/g protein	IOM	—	35	28	25
Leu	mg/g protein	IOM	—	76	63	57
Lys	mg/g protein	IOM	—	73	59	53
Met + Cys	mg/g protein	IOM	—	35	28	25
Phe + Tyr	mg/g protein	IOM	—	69	54	47
Thr	mg/g protein	IOM	—	40	32	28
Try	mg/g protein	IOM	—	11	8	7
Val	mg/g protein	IOM	—	47	37	32

AI, Adequate Intake; FAO, Food and Agriculture Organization; IAEA, International Atomic Energy Agency; IOM, Institute of Medicine; RNI, Recommended Nutrient Intake; UK, United Kingdom; WHO, World Health Organization

a. High, moderate, and low (Zinc) and percentages (Iron) refer to the bioavailability of these metals from diets of differing quality

Appendix 2: Proposed nutrient intakes for the moderately malnourished expressed in absolute units.

TABLE 46. Proposed nutrient intakes for children with moderate acute malnutrition (MAM) expressed as absolute amounts for comparison with the standard FAO/WHO RNIs and AIs for normal, healthy children

Nutrient (absolute amounts)		FAO/WHO RNIs			MAM (food based)			MAM (complement based)		
Age range	Unit	7–12 mo	1–2 yr	3–5 yr	7–12 mo	1–2 yr	3–5 yr	7–12 mo	1–2 yr	3–5 yr
Energy used as divisor	*kcal*	*673*	*956*	*1,242*	*673*	*956*	*1,242*	*673*	*956*	*1,242*
Protein	g	10.1	11.1	14.5	16	23	30	17	25	32
Nitrogen	g	1.6	1.8	2.3	2.6	3.7	4.8	2.8	4.0	5.2
Minerals										
Sodium	mg	—	—	—	370	530	680	370	530	680
Potassium	mg	—	—	—	950	1,350	1,750	1,050	1,550	2,000
Magnesium	mg	53	60	73	135	190	250	200	290	370
Phosphorus	mg	300	430	560	400	570	750	600	860	1,120
Sulfur	mg	0	0	0	0	0	0	135	190	250
Zinc (high)	mg	2.5	2.4	3.1	—	—	—	—	—	—
Zinc (moderate)	mg	4.1	4.1	5.1	—	—	—	—	—	—
Zinc (low)	mg	8.3	8.4	10.3	9	12	16	13	19	25
Calcium	mg	400	500	600	400	570	740	560	800	1,050
Copper	µg	—	—	—	450	650	850	600	850	1,100
Iron (15%)	mg	6	4	4	—	—	—	—	—	—
Iron (12%)	mg	8	5	5	—	—	—	—	—	—
Iron (10%)	mg	9	6	6	—	—	—	—	—	—
Iron (5%)	mg	19	12	13	6	9	11	12	17	22
Iodine	µg	135	75	110	135	190	250	135	190	250
Selenium	µg	10	17	21	20	30	35	35	55	70
Manganese	mg	—	—	—	0.8	1.1	1.5	0.8	1.1	1.5
Chromium	µg	—	—	—	7	11	14	7	11	14
Molybdenum	µg	—	—	—	10	15	20	10	15	20
Vitamins, water soluble										
Thiamine (vitamin B_1)	µg	300	500	600	400	575	750	670	950	1,250
Riboflavin (vitamin B_2)	µg	400	500	600	540	770	990	1,200	1,700	2,250
Pyridoxine (vitamin B_6)	µg	300	500	600	540	770	990	1,200	1,700	2,250
Cobalamin (vitamin B_{12})	ng	500	900	1,200	675	960	1,240	1,750	2,500	3,200
Folate	µg	80	160	200	150	210	270	240	330	430
Niacin	mg	4	6	8	6	8	11	12	17	22
Ascorbate (vitamin C)	mg	30	30	30	50	70	90	60	90	120
Pantothenic acid	mg	1.8	2	3	2.0	3.0	3.5	2.0	3.0	3.5
Biotin	µg	6	8	12	6.5	9.5	12.5	8.5	12.5	16.0
Vitamins, fat soluble										
Retinol (vitamin A)	µg	400	400	450	650	920	1,190	1,280	1,820	2,360
Cholecalciferol (vitamin D)	µg	5	5	5	5	7	9	7	11	15
Tocopherol (vitamin E)	mg	2.7	5	5	8	11	14	15	20	25
Phytomenadione (vitamin K)	µg	10	15	20	13	20	25	25	40	50

AI, Adequate Intake; FAO, Food and Agriculture Organization ; RNI, Recommended Nutrient Intake; WHO, World Health Organization

a. The values recommended, expressed in nutrient:energy densities, have been back-converted from the recommendations derived to absolute amounts using the average energy requirement for female children within the age range quoted, and rounded.

References

1. Wellcome Working Party (Editorial). Classification of infantile malnutrition. Lancet 1970;2:302–3.
2. Michaelsen KF, Hoppe C, Roos N, Kæstel P, Stougaard M, Lauritzen L, Mølgaard C, Girma T, Friis H. Choice of foods and ingredients for moderately malnourished children 6 months to 5 years of age. Food Nutr Bull 2009;30:S344-405.
3. Golden MH, Briend A, Grellety Y. Supplementary feeding programmes with particular reference to refugee populations. Eur J Clin Nutr 1995;49:137–45.
4. Golden MH. Derivation of the Proposed Nutritional Composition of an Emergency Relief food for Refugees and Displaced Persons. 2001. U.S Agency for International Development, Washington DC. Ref Type: Report
5. IOM. High-Energy, Nutrient-Dense Emergency Relief Food Product. Washington DC: National Academy Press, 2002.
6. WHO. Trace Elements in Human Nutrition and Health. Geneva: World Health Organisation, 1996.
7. Human Vitamin and Mineral Requirements: Report of a joint FAO/WHO expert consultation. Bangkok, Thailand. Rome: Food and Agriculture Organisation, 2001.
8. FAO. Human energy requirements: Report of a Joint FAO/WHO/UNU Expert Consultation. Rome: Food and Agriculture Organisation, 2004.
9. IOM. Dietary reference intakes: calcium, phosphorus, magnesium, vitamin D and fluoride. Washington DC: National Academy Press, 1997.
10. IOM. Dietary reference intakes: thiamine, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin and choline. Washington DC: National Academy Press, 2000.
11. IOM. Dietary reference intakes: vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium and zinc. Washington DC: National Academy Press, 2002.
12. IOM. Dietary reference values: water, potassium, sodium, chloride and sulfate. 2004. Washington DC, National Academies Press. Ref type: Report
13. IOM. Dietary reference intakes: energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. Washington DC: National Academies Press, 2005.
14. IOM. Dietary reference intakes: vitamin C, vitamin E, selenium and carotenoids. 2000. Washington DC, National Academies Press.
15. Yates AA. National nutrition and public health policies: issues related to bioavailability of nutrients when developing dietary reference intakes. J Nutr 2001;131:1331S–4S.
16. Russell RM. Setting dietary intake levels: problems and pitfalls. Novartis Found Symp 2007;282:29–36.
17. Anonymous. The Sphere Project: Humanitarian Charter and Minimum Standards in Disaster Response. Geneva, Switzerland: The Sphere Project, 2004.
18. Golden MH, Golden BE, Harland PSEG, Jackson AA. Zinc and immunocompetence in protein-energy malnutrition. Lancet 1978;1:1226–8.
19. Golden MH, Jackson AA, Golden BE. Effect of zinc on thymus of recently malnourished children. Lancet 1977;ii:1057–9.
20. Patrick J, Golden BE, Golden MH. Leucocyte sodium transport and dietary zinc in protein energy malnutrition. Am J Clin Nutr 1980;33:617–20.
21. Hadden DR. Glucose, free fatty acid, and insulin interrelations in kwashiorkor and marasmus. Lancet 1967;ii:589–93.
22. Klahr S, Alleyne GAO. Nutrition and the kidney. In: Suki WN, Eknoyan G, eds. The kidney in systemic disease. New York: John Wiley & Sons 1981:307–46.
23. Hansen-Smith FM, Picou DIM, Golden MH. Growth of muscle fibres during recovery from severe malnutrition. Br J Nutr 1979;41:275–82.
24. MacLean WC, Graham GG. The effect of energy intake on nitrogen content of weight gained by recovering malnourished infants. Am J Clin Nutr 1980;33:903–9.
25. Cheek DB, Hill DE, Cordano A, Graham GG. Malnutrition in infancy: changes in muscle and adipose tissue before and after rehabilitation. Pediatr Res 1970; 4:135–44.
26. Brooke OG, Wheeler EF. High energy feeding in protein-energy malnutrition. Arch Dis Child 1976;51:968–71.
27. Wheeler EF. Changes in anthropometric measurements of children recovering from protein-energy malnutrition. Proc Nutr Soc 1975;34:35A–6A.
28. Golden BE, Golden MH. effect of zinc supplementation on the composition of newly synthesised tissue in children recovering from malnutrition. Proc Nutr Soc. 1985;44:110.
29. Golden BE, Golden MH. Plasma zinc, rate of weight gain, and the energy cost of tissue deposition in children recovering from severe malnutrition on a cow's milk or soya protein based diet. Am J Clin Nutr. 1981;34:892–9.
30. Golden MH, Golden BE. Effect of zinc supplementation on the dietary intake, rate of weight gain, and energy cost of tissue deposition in children recovering from severe malnutrition. Am J Clin Nutr 1981;34:900–8.
31. Golden BE, Golden MH. Effect of zinc on lean tissue synthesis during recovery from malnutrition. Eur J Clin Nutr 1992;46:697–706.
32. Morris A, Golden MH, Ramdath DD. A new recovery diet for use in the treatment of malnutrition. West Indian Med J 1989;38(Suppl.1):64.
33. Ramdath DD, Golden MH. Comparison of antioxidant status during recovery from malnutrition on a corn oil or coconut oil based diet. West Indian Med J 1993;42 (suppl 1):23.
34. Malcolm LA. Growth retardation in a New Guinea boarding school and its response to supplementary feeding. Am J Clin Nutr 1970;24:297–305.
35. Popkin BM, Richards MK, Montiero CA. Stunting is associated with overweight in children of four nations that are undergoing the nutrition transition. J Nutr 1996;126:3009–16.
36. Trowbridge FL. Prevalence of growth stunting and obesity: Pediatric nutrition surveillance system, 1982. MMWR CDC Surveill Summ 1983;32:23SS–6SS.
37. Golden MH. Severe malnutrition. In: Weatherall DJ, Ledington JGG, Warrell DA, eds. Oxford textbook of medicine. Oxford: Oxford University Press 1996:1278–96.
38. Golden MH, Briend A. Treatment of malnutrition in

refugee camps. Lancet 1993;342:360.
39. Briend A, Golden MH. Treatment of severe child malnutrition in refugee camps. Eur J Clin Nutr 1993;47:750–4.
40. World Health Organization. Management of severe malnutrition: a manual for physicians and senior health workers. Geneva: World Health Organization, 1999.
41. Briend A, Lacsala R, Prudhon C, Mounier B, Grellety Y, Golden MH. Ready-to-use therapeutic food for treatment of marasmus. Lancet 1999;353:1767–8.
42. WHO. WHO child growth standards: Methods and development: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age. Geneva: World Health Organization, 2006.
43. Patrick J, Reeds PJ, Jackson AA, Seakins A, Picou DIM. Total body water in malnutrition: the possible role of energy intake. Br J Nutr 1978;39:417–24.
44. Jackson AA, Picou DIM, Reeds PJ. The energy cost of repleting tissue deficits during recovery from protein-energy malnutrition. Am J Clin Nutr 1977;30:1514–7.
45. Ashworth A. Growth rates children recovering from protein-calorie malnutrition. Br J Nutr 1969;23:835.
46. Kerr DS, Ashworth A, Picou DIM, Poulter N, Seakins A, Spady D, Wheeler EF. Accelerated recovery from infant malnutrition with high calorie feeding. In: Gardner L, Amacher P, eds. Endocrine aspects of malnutrition. Santa Ynez, California: Kroc Foundation 1973:467–86.
47. Whitehead RG. The protein needs of malnourished children. In: Porter JW, Rolls BA, eds. Proteins in Human Nutrition. New York: Academic Press 1980:103–115.
48. Spady DW, Payne PR, Picou DIM, Waterlow JC. Energy balance during recovery from malnutrition. Am J Clin Nutr 1976;29:1073–88.
49. Waterlow JC. The rate of recovery of malnourished infants in relation to the protein and calorie levels of the diet. J Trop Pediatr 1961;7:16–22.
50. Golden BE, Golden MH. Relationships among dietary quality, children's appetites, growth stunting and efficiency of growth in poor populations. Food Nutr Bull 1991;13:105–9.
51. Fomon SJ, Thomas LN, Filer LJ Jr., Ziegler EE, Leonard MT. Food consumption and growth of normal infants fed milk-based formulas. Acta Paediatr Scand Suppl 1971;223:1–36.
52. Payne PR, Waterlow JC. Relative energy requirements for maintenance, growth, and physical activity. Lancet 1971;2:210–1.
53. Fletcher PDL, Grantham-McGregor SM. Indicators of childhood malnutrition. In: Sinclair SA, Patterson AW, Campbell V, Rainford K, eds. Regional conferance on health, nutrition and population in the Caribbean. Kingston, Jamaica: Caribbean Food and Nutrition Institute/PAHO 1988:30–6.
54. Roberts SB, Young VR. Energy costs of fat and protein deposition in the human infant. Am J Clin Nutr 1988;48:951–5.
55. Golden MH. Is complete catch-up possible for stunted malnourished children? Eur J Clin Nutr 1994;48:S58–S71.
56. Brown KH, Black RE, Becker S. Seasonal changes in nutritional status and the prevalence of malnutrition in a longitudinal study of young children in rural Bangladesh. Am J Clin Nutr 1982;36:303–13.
57. Martorell R, Khan LK, Schroeder DG. Reversibility of stunting: epidemiological findings in children from developing countries. Eur J Clin Nutr 1994;48 Suppl 1:S45–S57.
58. Martorell R, Schroeder DG, Rivera JA, Kaplowitz HJ. Patterns of linear growth in rural Guatemalan adolescents and children. J Nutr 1995;125:1060S–7S.
59. Golden MH. The role of individual nutrient deficiencies in growth retardation of children as exemplified by zinc and protein. In: Waterlow JC, ed. Linear growth retardation in less developed countries. New york: Raven press 1988:143–63.
60. Karlberg J. On the construction of the infancy-childhood-puberty growth standard. Acta Paediatr Scand 1989;356:26–37.
61. Prader A, Tanner JM, von Harnack GA. Catch-up growth following illness or starvation. An example of developmental canalization in man. J Pediatr 1963;62:646–59.
62. Tanner JM. Catch up growth in man. Br Med Bull 1981; 37:233–8.
63. Prader A. Catch up growth. Postgrad Med J 1981;54 (suppl):133–43.
64. Cooper ES, Bundy DAP, MacDonald TT, Golden MH. Growth suppression in the trichuris dysentry syndrome. Eur J Clin Nutr 1990;44:285–91.
65. Kabir I, Malek MA, Mazumder RN, Rahman MM, Mahalanabis D. Rapid catch-up growth of children fed a high-protein diet during convalescence from shigellosis. Am J Clin Nutr 1993;57:441–5.
66. Walker SP, Golden MH. Growth in length of children recovering from severe malnutrition. Eur J Clin Nutr 1988;42:395–404.
67. Valverde V, Delgado H, Martorell R, Belizan JM, Mejia-Pivaral V, Klein RE. Seasonality and nutritional status. A review of findings from developed and developing countries. Arch Latinoam Nutr 1982;32:521–40.
68. Van den Brande JL. A personal view on the early history of the insulin-like growth factors. Horm Res 1999;51 Suppl 3:149–75.
69. Daughaday WH, Hall K, Raben MS, Salmon WD Jr., Van den Brande JL, van Wyk JJ. Somatomedin: proposed designation for sulphation factor. Nature 1972;235:107.
70. Grant DB, Hambley J, Becker D, Pimstone BL. Reduced sulphation factor in undernourished children. Arch Dis Child 1973;48:596–600.
71. McCance RA. The effect of calorie deficiencies and protein deficiencies on final weight and stature. In: McCance RA, Widdowson EM, eds. Calorie deficiencies and protein deficiencies. London: Churchill 1968:319–26.
72. Hammond J, Mason IL, Robinson TJ. Hammond's farm animals. London: Edward Arnold, 1971.
73. Golden MH. The nature of nutritional deficiency in relation to growth failure and poverty. Acta Paediatr Scand 1991;374:95–110.
74. Krebs NF, Hambidge KM, Walravens PA. Increased food intake of young children receiving a zinc supplement. Am J Dis Child 1984;138:270–3.
75. Rudman D, Millikan WJ, Richardson TJ, Bixler II TJ, Stackhouse WJ, McGarrity WC. Elemental balances during intravenous hyperalimentation of underweight adult subjects. J Clin Invest 1975;55:94–104.
76. Bigot A, Chauvin P, Moren A. Epidemic of nutritional neuropathy in Afghanistan. 1994. Paris, Epicentre.
77. Isanaka S, Nombela N, Djibo A, Poupard M, Van BD, Gaboulaud V, Guerin PJ, Grais RF. Effect of preventive

supplementation with ready-to-use therapeutic food on the nutritional status, mortality, and morbidity of children aged 6 to 60 months in Niger: a cluster randomized trial. JAMA 2009;301:277–85.
78. Pelletier DL, Frongillo EA Jr., Schroeder DG, Habicht JP. The effects of malnutrition on child mortality in developing countries. Bull WHO 1995;73:443–8.
79. Stuart HC, Stevenson SS. Textbook of pediatrics. In: Nelson WE, ed. Textbook of pediatrics. Philadelphia: Saunders 1959:50–1.
80. Diop el HI, Dossou NI, Ndour MM, Briend A, Wade S. Comparison of the efficacy of a solid ready-to-use food and a liquid, milk-based diet for the rehabilitation of severely malnourished children: a randomized trial. Am J Clin Nutr 2003;78:302–7.
81. Alleyne GAO. The effect of severe protein calorie malnutrition on the renal function of Jamaican children. Pediatrics 1967;39:400–11.
82. Alleyne GAO. Cardiac function in severely malnourished Jamaican children. Clin Sci 1966;30:553–62.
83. Waterlow JC. The nature and significance of nutritional adaptation. Eur J Clin Nutr 1999;53 Suppl 1:S2–S5.
84. Jackson AA, Golden MH. The human rumen. Lancet 1978;2:764–8.
85. Porter TK. Growth, health and physical work capacity of adolescents in refugee and non-refugee communities in Tanzania. PhD Thesis. University of Oxford; 2001.
86. World Health Organization. Preparation and use of food-based dietary guidelines: Annex three—The scientific basis for diet, nutrition and health relationships (WHO/NUT/96.6). 1996. Geneva, WHO.
87. IOM. Dietary Reference Intakes: Applications in dietary planning. Washington DC: National Academies Press, 2003.
88. Walker SP, Powell CA, Grantham-McGregor SM. Dietary intakes and activity levels of stunted and non-stunted children in Kingston, Jamaica. Part 1: Dietary intakes. Eur J Clin Nutr 1990;in press.
89. Golden MH, Waterlow JC, Picou D. Protein turnover, synthesis and breakdown before and after recovery from protein-energy malnutrition. Clin Sci Mol Med 1977; 53:473–7.
90. Protein and amino acid requirements in human nutrition. Report of a joint WHO/FAO/UNU expert consultation. Geneva: World Health Organization, 2007.
91. Energy and protein requirements. Report of a Joint FAO/WHO/UNU Expert Consultation. Geneva: World Health Organization 1985.
92. Committee on Medical Aspects of Food Policy. Dietary reference values for food energy and nutrients for the United Kingdom. London: HMSO, 1991.
93. Energy and protein requirements. Proceedings of an IDECG workshop. London, United Kingdom, 31 October–4 November 1994. Eur J Clin Nutr 1996;50 Suppl 1:S1–197.
94. Smythe PM. Changes in intestinal bacterial flora and role of infection in kwashiorkor. Lancet 1958;2:724–7.
95. Dale DC, Mata LJ. Studies of diarrheal disease in Central America. 11. Intestinal bacterial flora in malnourished children. Am J Trop Med Hyg 1968;17:397–403.
96. James WPT. Effects of protein-calorie malnutrition on intestinal absorption. Ann NY Acad Sci 1971;176:244–61.
97. Gorbach SL, Banwell JG, Chatterjee BD, Jacobs B, Sack RB. Acute undifferentiated diarrhea in the tropics: 1. Alterations in intestinal microflora. J Clin Invest 1971;50:881–9.
98. James WPT, Drasar BS, Miller C. Physiological mechanism and pathogenesis of weanling diarrhea. Am J Clin Nutr 1972;25:564–71.
99. Mata LJ, Jimenez F, Cordon M, Rosales R, Prera E, Schneider RE, Viteri FE. Gastrointestinal flora of children with protein–calorie malnutrition. Am J Clin Nutr 1972; 25:118–26.
100. Gorbach SL. Microflora of the gastrointestinal tract in tropical enteritis: a current appraisal. Am J Clin Nutr 1972;25:1127–30.
101. Rowland MG, Cole TJ, McCollum JPK. Waenling diarrhoea in the Gambia: implications of a jejunal intubation study. Trans R Soc Trop Med Hyg 1981;75:215–8.
102. Tabaqchali S. Abnormal intestinal flora: metabolic and clinical consequences. Gastroenterol Jpn 1984;19:351–62.
103. McPherson L. Lectins in the etiology of protein–energy malnutrition. J R Soc Health 1989;109:66–8.
104. Cleghorn GJ, Erlich J, Bowling FG, Forrest Y, Greer R, Holt TL, Shepherd RW. Exocrine pancreatic dysfunction in malnourished Australian aboriginal children. Med J Aust 1991;154:45–8.
105. Sauniere JF, Sarles H. Exocrine pancreatic function and protein-calorie malnutrition in Dakar and Abidjan (West Africa): silent pancreatic insufficiency. Am J Clin Nutr 1988;48:1233–8.
106. Gilman RH, Partanen R, Brown KH, Spira WM, Khanum S, Greenberg B, Bloom SR, Ali A. Decreased gastric acid secretion and bacterial colonization of the stomach in severely malnourished Bangladeshi children. Gastro 1988;94:1308–14.
107. Schwela D. Cooking smoke: a silent killer. People Planet 1997;6:24–5.
108. Chen BH, Hong CJ, Pandey MR, Smith KR. Indoor air pollution in developing countries. World Health Stat Q 1990;43:127–38.
109. Wafula EM, Onyango FE, Thairu H, Boleij JS, Hoek F, Ruigewaard P, Kagwanja S, De KH, Pio A, Kimani E. Indoor air pollution in a Kenyan village. East Afr Med J 1990;67:24–32.
110. Mishra V, Retherford RD. Does biofuel smoke contribute to anaemia and stunting in early childhood? Int J Epidemiol 2007;36:117–29.
111. Jackson AA, Golden MH, Byfield R, Jahoor PF, Royes J, Soutter L. Nitrogen balance and whole body nitrogen flux in children consuming dietary energy and protein around maintenance requirements. In: Rand WM, Uauy R, Scrimshaw NS, eds. Protein-energy-requirement studies in developing countries: Results of International Research. Tokyo: United Nations University 1984:240–6.
112. Ashworth A, Bell R, James WPT, Waterlow JC. Calorie requirements of children recovering from protein-calorie malnutrition. Lancet 1968;2:600–3.
113. Chan HC, Waterlow JC. The protein requirement of infants at the age of about 1 year. Br J Nutr 1966;20:775–82.
114. Golden MH, Golden BE. Albumin and nutritional oedema. Lancet 1980;i:114–6.
115. Cheek DB, Graystone JE, Read MS. Cellular growth, nutrition and development. Pediatrics 1970;45:315–34.
116. Golden MH, Waterlow JC, Picou DIM. Protein turnover,

synthesis and breakdown before and after recovery from protein-energy malnutrition. Clin Sci Mol Med 1977;53:473–77.
117. Michaelsen KF, Clausen T. Inadequate supplies of potassium and magnesium in relief food: implications and countermeasures. Lancet 1987;1:1421–3.
118. Golden MH. Protein-energy interactions in the management of severe malnutrition. Clin Nutr 1997;16 (Supplement 1):19–23.
119. Waterlow JC. Oxidative phosphorylation in the livers of normal and malnourished human infants. Proc R Soc (B) 1961;155:96–114.
120. Guder WG, Haussinger D, Gerok W. Renal and hepatic nitrogen metabolism in systemic acid base regulation. J Clin Chem Clin Biochem 1987;25:457–66.
121. Wiklund L. Carbon dioxide formation and elimination in man. Recent theories and possible consequences. Ups J Med Sci 1996;101:35–67.
122. Stephen JML, Waterlow JC. Effect of malnutrition on activity of two enzymes concerned with aminoacid metabolism in human liver. Lancet 1968;1:118–9.
123. Waterlow JC. Enzyme changes in malnutrition. J Clin Pathol 1970;4:75–9.
124. Whitehead RG, Arnstein HRV. Imidazole acrylic acid excretion in kwashiorkor. Nature 1961;190:1105–6 .
125. Whitehead RG, Milburn TR. Metabolites of phenylalanine in the urine of children with kwashiorkor. Nature 1962;196:580–1.
126. Whitehead RG. An unidentified compound in the serum of children with kwashiorkor (protein-calorie malnutrition). Nature 1964;204:389.
127. Burt JC. Water requirements of malnourished children in extreme hot and dry environments. MsC thesis. University of Aberdeen; 1999.
128. Ramdath DD, Golden MH. Urinary mercapturic acid outputs of severely malnourished children. Proc Nutr Soc 1988;47:7A.
129. Simmons WK. Variation in urinary inorganic sulphur and urea nitrogen excretion in children on a rural African diet. Arch Latinoam Nutr 1972;22:403–16.
130. Michie CA. Urinary sulphates in children recovering from severe malnutrition. Proc Nutr Soc 1989;2.
131. Ittyerah TR. Urinary excretion of sulfate in kwashiorkor. Clin Chim Acta 1969;25:365–9.
132. Amadi B, Fagbemi AO, Kelly P, Mwiya M, Torrente F, Salvestrini C, Day R, Golden MH, Eklund EA, Freeze HH, Murch SH. Reduced production of sulfated glycosaminoglycans occurs in Zambian children with kwashiorkor but not marasmus. Am J Clin Nutr 2009;89:592–600.
133. Chandrasekaran EV, Mukherjee KL, Bachhawat BK. Isolation and characterization of glycosaminoglycans from brain of children with protein-calorie malnutrition. J Neurochem 1971;18:1913–20.
134. Golden MH. Oedematous malnutrition. Br Med Bull 1998;54:433–44.
135. Baba M, Snoeck R, Pauwels R, De Clercq E. Sulfated polysaccharides are potent and selective inhibitors of various enveloped viruses, including herpes simplex virus, cytomegalovirus, vesicular stomatitis virus, and human immunodeficiency virus. Antimicrob Agents Chemother 1988;32:1742–5.
136. Schmidt RE, MacDermott RP, Bartley G, Bertovich M, Amato DA, Austen KF, Schlossman SF, Stevens RL, Ritz J. Specific release of proteoglycans from human natural killer cells during target lysis. Nature 1985;318:289–91.
137. Hansen JDL, Brock JF. Potassium deficiency in the pathogenesis of nutritional oedema in infants. Lancet 1954;2:477.
138. Thompson MD. Potassium deficiency and kwashiorkor. Lancet 1955;i:1181.
139. Metcoff J, Frenk S, Gordillo G, Gomez F, Ramos-Galvan R, Cravioto J, Janeway CA, Gamble JL. Intracellular composition homeostatic mechanisms in severe chronic infantile malnutrition. 4. Development and repair of the biochemical lesion. Pediatrics 1957;20:317–35.
140. Smith R, Waterlow JC. Total exchangeable potassium in infantile malnutrition. Lancet 1960;1:147–9.
141. Garrow JS. Total body potassium in kwashiorkor and marasmus. Lancet 1965;2:455–8.
142. Garrow JS. Loss of brain potassium in kwashiorkor. Lancet 1967;2:643–5.
143. Alleyne GAO. Studies on total body potassium in infantile malnutrition: the relation to body fluid spaces and urinary creatinine. Clin Sci 1968;34:199–209.
144. Nichols BL, Alleyne GAO, Barnes DJ, Hazlewood CF. Relationship between muscle potassium and total body potassium in infants with malnutrition. J Pediatr 1969;74:49–57.
145. Alleyne GAO, Viteri FE, Alvarado J. Indices of body composition in infantile malnutrition: total body potassium and urinary creatinine. Am J Clin Nutr 1970; 23:875–8.
146. Alleyne GAO, Milward DJ, Scullard GH. Total body potassium muscle electrolytes and glycogen in malnourished children. J Pediatr 1970;76:75–81.
147. Manary MJ, Brewster DR. Potassium supplementation in kwashiorkor. J Pediatr Gastroenterol Nutr 1997;24:194–201.
148. Subcommittee on the Tenth Edition of the RDAs. Recommended Dietary Allowances. Washington, DC: National Academy Press, 1989.
149. Alleyne GAO. Studies on total body potassium in malnourished infants. Factors affecting potassium repletion. Br J Nutr 1970;24:205–12.
150. Alleyne GAO. The excretion of water and solute by malnourished children. West Indian Med J 1966;15:150–4.
151. Klahr S, Davis TA. Changes in renal function with chronic protein-calorie malnutrition. In: Mitch WE, Klahr S, eds. Nutrition and the kidney. Boston: Toronto: Little, Brown & Co. 1988:59–79.
152. Klahr S, Alleyne GAO. Effects of chronic protein-calorie malnutrition on the kidney. Kidney Int 1973;3:129–41.
153. Klahr S, Tripathy K. Evaluation of renal function in malnutrition. Arch Intern Med 1966;118:322–5.
154. Klahr S, Tripathy K, Garcia FT, Mayoral LG, Ghitis J, Bolanos O. On the nature of the renal concentrating defect in malnutrition. Am J Med 1967;43:84–96.
155. Squires RD, Huth EJ. Experimental potassium depletion in normal human subjects. I. Relation of ionic intakes to the renal conservation of potassium. J Clin Invest 1959; 38:1134–48.
156. Huth EJ, Squires RD, Elkinton JR. Experimental potassium depletion in normal human subjects. II. Renal and hormonal factors in the development of extracellular alkalosis during depletion. J Clin Invest

1959;38:1149–65.
157. Golden BE, Golden MH. Zinc, sodium and potassium losses in the diarrhoeas of malnutrition and zinc deficiency. In: Mills CF, Bremner I, Chesters JK, eds. Trace element metabolism in man and animals—5. Aberdeen: Commonwealth Agricultural Bureau 1985:228–32.
158. Darrow DC. Physiological basis of potassium therapy. J Am Med Assoc 1956;162:1310–5.
159. Darrow DC, Pratt EL. Fluid therapy; relation to tissue composition and the expenditure of water and electrolyte. J Am Med Assoc 1950;143:432–9.
160. Ruz M, Solomons NW. Mineral excretion during acute, dehydrating diarrhea treated with oral rehydration therapy. Pediatr Res 1990;27:170–5.
161. Garrow JS, Smith R, Ward EE. Electrolyte metabolism in severe infantile malnutrition. Oxford: Pergamon Press, 1968.
162. Patrick J. Relationship between intracellular and extracellular potassium in normal and malnourished subjects as studied in leucocytes. Pediatr Res 1978;12:767–70.
163. Patrick J. Interrelations between the physiology of sodium, potassium and water, and nutrition. J Hum Nutr 1978;32:405–18.
164. Caddell JL. Magnesium in the therapy of protein-calorie malnutrition of childhood. J Pediatr 1965;66:392–413.
165. Caddell JL. Studies in protein-calorie malnutrition. 2. A double-blind trial to assess magnesium therapy. N Engl J Med 1967;276:535–40.
166. Caddell JL. Magnesium in the therapy of orofacial lesion of severe protein-calorie malnutrition. Br J Surg 1969;56:826–8.
167. Caddell JL, Goddard DR. Studies in protein-calorie malnutrition. 1. Chemical evidence for magnesium deficiency. N Engl J Med 1967;276:533–5.
168. Montgomery RD. Magnesium metabolism in infantile protein malnutrition. Lancet 1960;2:74–6.
169. Montgomery RD. Magnesium balance studies in marasmic kwashiorkor. J Pediatr 1961;59:119–23.
170. Pretorius PJ, Wehmeyer AS, Theron JJ. Magnesium balance studies in South African Bantu children with kwashiorkor. Am J Clin Nutr 1963;13:331–9.
171. Branca F, Robins SP, Ferro-Luzzi A, Golden MH. Bone turnover in malnourished children. Lancet 1992;340:1493–6.
172. Suh SM, Tashjian AH Jr., Matsuo N, Parkinson DK, Fraser D. Pathogenesis of hypocalcemia in primary hypomagnesemia: normal end-organ responsiveness to parathyroid hormone, impaired parathyroid gland function. J Clin Invest 1973;52:153–60.
173. Ralston S, Boyle IT, Cowan RA, Crean GP, Jenkins A, Thomson WS. PTH and vitamin D responses during treatment of hypomagnesaemic hypoparathyroidism. Acta Endocrinol (Copenh) 1983;103:535–8.
174. Nanji AA. Symptomatic hypercalcaemia precipitated by magnesium therapy. Postgrad Med J 1985;61:47–8.
175. Dorup I, Skajaa K, Thybo NK. Oral magnesium supplementation restores the concentrations of magnesium, potassium and sodium-potassium pumps in skeletal muscle of patients receiving diuretic treatment. Journal of Internal Medicine 1993;233:117–23.
176. Dorup I, Clausen T. Correlation between magnesium and potassium contents in muscle: role of Na(+)–K+ pump. Am J Physiol 1993;264:C457–C463.
177. Dyckner T, Ek B, Nyhlin H, Wester PO. Aggravation of thiamine deficiency by magnesium depletion. A case report. Acta Med Scand 1985;218:129–31.
178. Tantibhedhyangkul P, Hashim SA. Medium-chain triglyceride feeding in premature infants: effects on calcium and magnesium absorption. Pediatrics 1978;61:537–45.
179. Linder GC, Hansen JDL, Karabus CD. The metabolism of magnesium and other inorganic cations and of nitrogen in acute kwashiorkor. Pediatrics 1963;31:552–68.
180. Nichols BL, Alvarado J, Hazlewood CF, Viteri FE. Magnesium supplementation in protein-calorie malnutrition. Am J Clin Nutr 1978;31:176–88.
181. Hessov I. Magnesium deficiency in Crohn's disease. Clin Nutr 1990;9:297–8.
182. Nyhlin H, Dyckner T, Ek B, Wester PO. Magnesium in Crohn's disease. Acta Med Scand Suppl 1982;661:21–5.
183. Petersen VP. Metabolic studies in clinical magnesium deficiency. Acta Med Scand 1963;173:285–98.
184. Reichman P, Stein H. Radiological features on plain radiographs in malnutrition in African children. Br J Radiol 1968;41:296–9.
185. Adams P, Berridge FR. Effects of kwashiorkor on cortical and trabecular bone. Arch Dis Child 1969;44:705–9.
186. Dickerson JW, John PM. The effect of protein-calorie malnutrition on the composition of the human femur. Br J Nutr 1969;23:917–24.
187. Schuette SA, Lashner BA, Janghorbani M. Bioavailability of magnesium diglycinate vs magnesium oxide in patients with ileal resection. J Parenter Enteral Nutr 1994;18:430–5.
188. Adesola AO. The influence of severe protein deficiency (kwashiorkor) on gastric acid secretion in Nigerian children. Br J Surg 1968;55:866.
189. Bhattacharyya AK, Chaudhuri RN. Kwashiorkor and marasmus: study of gastric acidity. Bull Calcutta Sch Trop Med 1962;10:55–6.
190. Guha Mazumdar DN, Mitra RC, Mitra N, Sen NN, Chatterjee BD. Gastric secretory study in protein calorie malnutrition (PCM) in adults and correlation with gastric mucosal structure, small bowel microflora and absorption. J Indian Med Assoc 1978;71:25–30.
191. Maffei HV, Nobrega FJ. Gastric pH and microflora of normal and diarrhoeic infants. Gut 1975;16:719–26.
192. Hay RW, Whitehead RG. The therapy of the severely malnourished child: a practical manual. Kampala: National Food and Nutrition Council of Uganda, 1973.
193. Lindberg JS, Zobitz MM, Poindexter JR, Pak CY. Magnesium bioavailability from magnesium citrate and magnesium oxide. J Am Coll Nutr 1990;9:48–55.
194. Walker AF, Marakis G, Christie S, Byng M. Mg citrate found more bioavailable than other Mg preparations in a randomised, double-blind study. Magnes Res 2003; 16:183–91.
195. Coudray C, Rambeau M, Feillet-Coudray C, Gueux E, Tressol JC, Mazur A, Rayssiguier Y. Study of magnesium bioavailability from ten organic and inorganic Mg salts in Mg-depleted rats using a stable isotope approach. Magnes Res 2005;18:215–23.
196. Golden MH, Mesrobian AL. magnesium chloride induced acidosis in malnutrition. West Indian Med.J. 1983;32 (Suppl. 1):28–9 .
197. Morris ME, LeRoy S, Sutton SC. Absorption of magnesium from orally administered magnesium sulfate in

man. J Toxicol Clin Toxicol 1987;25:371–82.
198. Foldes J, Balena R, Ho A, Parfitt AM, Kleerekoper M. Hypophosphatemic rickets with hypocalciuria following long-term treatment with aluminum-containing antacid. Bone 1991;12:67–71.
199. Pattaragarn A, Alon US. Antacid-induced rickets in infancy. Clin Pediatr (Phila) 2001;40:389–93.
200. Worley G, Claerhout SJ, Combs SP. Hypophosphatemia in malnourished children during refeeding. Clin Pediatr (Phila.) 1998;37:347–52.
201. Waterlow JC, Golden MH. Serum inorganic-phosphate in protein-energy malnutrition. Eur J Clin Nutr 1994; 48:503–6.
202. Camp MA, Allon M. Severe hypophosphatemia in hospitalized patients. Mineral & Electrolyte Metabolism 1990;16:365–8.
203. Manary MJ, Hart CA, Whyte MP. Severe hypophosphatemia in children with kwashiorkor is associated with increased mortality. J Pediatr 1998;133:789–91.
204. Dickerson JWT, Widdowson EM. Chemical changes in skeletal muscle during development. Biochem J 1960;74:247–57.
205. Lentner C. Geigy scientific tables. Volume 3. Basle: Ciba-Geigy Ltd., 1984.
206. Berner YN, Shike M. Consequences of phosphate imbalance. Annu Rev Nutr 1988;8:121–48.
207. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. Br Med J 2008;336:1495–8.
208. Stanga Z, Brunner A, Leuenberger M, Grimble RF, Shenkin A, Allison SP, Lobo DN. Nutrition in clinical practice—the refeeding syndrome: illustrative cases and guidelines for prevention and treatment. Eur J Clin Nutr 2008;62:687–94.
209. Korbonits M, Blaine D, Elia M, Powell-Tuck J. Metabolic and hormonal changes during the refeeding period of prolonged fasting. Eur J Endocrinol 2007;157:157–66.
210. Marinella MA. Refeeding syndrome and hypophosphatemia. J Intensive Care Med 2005;20:155–9.
211. Holemans K, Lambrechts A. Calcium and phosphorus metabolism in malnutrition and in kwashiorkor. J Trop Pediatr 1959;4:129–32.
212. Metcoff J, Frenk S, Yoshida T, Pinedo RT, Kaiser E, Hansen JD. Cell composition and metabolism in Kwashiorkor. (Severe protein-calorie malnutrition in children). Medicine (Baltimore) 1966;45:365–90.
213. Thompson A, Damyanovich A, Madapallimattam A, Mikalus D, Allard J, Jeejeebhoy KN. 31P-nuclear magnetic resonance studies of bioenergetic changes in skeletal muscle in malnourished human adults. Am J Clin Nutr 1998;67:39–43.
214. Schneider RE, Viteri FE. Luminal events of lipid absorption in protein-calorie malnourished children; relationship with nutritional recovery and diarrhea. 2. Alterations in bile acid content of duodenal aspirates. Am J Clin Nutr 1974;27:788–95.
215. Shaw JC. Technical problems in parenteral nutrition of the premature infant. Acta Chir Scand Suppl 1981; 507:258–68.
216. Golden MH, Golden BE. Trace elements: potential importance in human nutrition with particular reference to zinc and vanadium. Br Med Bull 1981;37:31–6.
217. Walravens PA, Krebs NF, Hambidge KM. Linear growth of low income preschool children receiving a zinc supplement. Am J Clin Nutr 1983;38:195–201.
218. Patrick J, Michael J, Golden MH, Golden BE, Hilton PJ. Effect of zinc on leucocyte sodium transport in-vitro. Clin Sci 1978;54:585–7.
219. Golden MH, Golden BE, Harland PSEG., Jackson AA. Zinc and immunocompetence in PEM. Lancet 1978;i:1226–7.
220. Fitzgerald SL, Gibson RS, Quan de SJ, Portocarrero L, Vasquez A, de ZE, Lopez-Palacios CY, Thompson LU, Stephen AM, Solomons NW. Trace element intakes and dietary phytate/Zn and Ca x phytate/Zn millimolar ratios of periurban Guatemalan women during the third trimester of pregnancy. Am J Clin Nutr 1993; 57:195–201.
221. Gibson RS, Smit Vanderkooy PD, Thompson L. Dietary phytate x calcium/zinc millimolar ratios and zinc nutriture in some Ontario preschool children. Biol Trace Elem Res 1991;30:87–94.
222. Hurley LS, Tao SH. Alleviation of teratogenic effects of zinc deficiency by simultaneous lack of calcium. Am J Physiol 1972;222:322–5.
223. Fell GS, Fleck A, Cuthbertson DP, Queen K, Morrison C, Bessent RG, Husain SL. Urinary zinc levels as an indication of muscle catabolism. Lancet 1973;1:280–2.
224. Williams RB, Mills CF. The experimental production of zinc deficiency in the rat. Br J Nutr 1970;24:989–1003.
225. Mills CF, Dalgarno AC, Williams RB, Quarterman J. Zinc deficiency and the zinc requirements of calves and lambs. Br J Nutr 1967;21:751–68.
226. Castillo-Duran C, Vial P, Uauy R. Trace mineral balance during acute diarrhea in infants. J Pediatr 1988; 113:452–7.
227. Dagnelie PC, van Staveren WA, Hautvast JG. Stunting and nutrient deficiencies in children on alternative diets. Acta Paediatr Scand Suppl 1991;374:111–8.
228. Doherty CP, Sarkar MA, Shakur MS, Ling SC, Elton RA, Cutting WA. Zinc and rehabilitation from severe protein-energy malnutrition: higher-dose regimens are associated with increased mortality. Am J Clin Nutr 1998;68:742–8.
229. Selle PH, Ravindran V, Caldwell A, Bryden WL. Phytate and phytase: consequences for protein utilisation. Nutr Res Rev 2000;13:255–78.
230. Troesch B, Egli I, Zeder C, Hurrell RF, de PS, Zimmermann MB. Optimization of a phytase-containing micronutrient powder with low amounts of highly bioavailable iron for in-home fortification of complementary foods. Am J Clin Nutr 2009;89:539–44.
231. Hotz C, Gibson RS, Temple L. A home-based method to reduce phytate content and increase zinc bioavailability in maize-based complementary diets. Int J Food Sci Nutr 2001;52:133–42.
232. Kuhnlein HV, Calloway DH, Harland BF. Composition of traditional Hopi foods. J Am Diet Assoc 1979;75:37–41.
233. McCance RA. Experimental human salt deficiency. Lancet 1936;1:823–30.
234. Kerr DN, Robson A, Ashcroft R. Diet in chronic renal failure. Proc R Soc Med 1967;60:115–6.
235. Darrow DC. Body-fluid physiology: the role of potassium in clinical disturbances of body water and electrolyte. N Engl J Med 1950;242:1014–8.
236. Darrow DC, Pratt EL. Disturbances of water and

electrolytes in infantile diarrhea. Pediatrics 1949;3: 129–56.
237. Patrick J, Golden MH. Leukocyte electrolytes and sodium transport in protein energy malnutrition. Am J Clin Nutr 1977;30:1478–81.
238. Willis JS, Golden MH. Active and passive transport of sodium and potassium ions in erythrocytes of severely malnourished Jamaican children. Eur J Clin Nutr 1988;42:635–45.
239. Patrick J. Death during recovery from severe malnutrition and its possible relationship to sodium pump activity in the leucocyte. Br Med J 1977;1:1051–4.
240. Nichols BL, Alvarado MJ, Hazlewood CF, Viteri FE. Clinical significance of muscle potassium in protein-calorie malnutrition. J Pediatr 1972;80:319–30.
241. Vis H, Dubois R, Vanderborght H, De Maeyer E. [Study of electrolyte disorders accompanying marastic kwashiorkor]. Rev Fr Etud Clin Biol 1965;10:729–41.
242. Metcoff J, Frenk S, Yoshida T, Pinedo RT, Kaiser E, Hansen JDL. Cell composition and metabolism in kwashiorkor (severe protein-calorie malnutrition in children). Medicine 1966;45:365–90.
243. Frenk S, Metcoff J, Gomez F, Ramos-Galvan R, Cravioto J, Antonowicz I. Intracellular composition and homeostatic mechanisms in severe chronic infantile malnutrition. 2. Composition of tissues. Pediatrics 1957;20:105–20.
244. Fomon SJ. Infant nutrition. Philadelphia: Saunders, 1974.
245. Fomon SJ. Potential renal solute load: considerations relating to complementary feedings of breastfed infants. Pediatrics 2000;106:1284.
246. Ziegler EE. Milks and formulas for older infants. J Pediatr 1990;117:S76–S79.
247. Ziegler EE, Fomon SJ. Potential renal solute load of infant formulas. J Nutr 1989;119:1785–8.
248. Shaw JC, Jones A, Gunther M. Mineral content of brands of milk for infant feeding. Br Med J 1973;2:12–5.
249. Wharton BA. An approach to setting maxima in infant formulas. J Nutr 1989;119:1768–72.
250. Young VR, Pelletier VA. Adaptation to high protein intakes, with particular reference to formula feeding and the healthy, term infant. J Nutr 1989;119:1799–809.
251. Ziegler EE. Adverse effects of cow's milk in infants. Nestle Nutr Workshop Ser Pediatr Program 2007;60:185–96.
252. Zoppi G, Zamboni G. Mechanism of diet-induced uraemia and acidosis in infants. Eur J Pediatr 1977;125:197–204.
253. Garn SM, Rohmann CG, Behar M, Viteri FE, Guzman MA. Compact bone deficiency in protein-calorie malnutrition. Science 1964;145:1444–5.
254. Prentice A, Laskey MA, Shaw J, Cole TJ, Fraser DR. Bone mineral content of Gambian and British children aged 0–36 months. Bone Miner 1990;10:211–24.
255. Pettifor JM. Nutritional rickets: deficiency of vitamin D, calcium, or both? Am J Clin Nutr 2004;80:1725S–9S.
256. Pettifor JM, Ross FP. Low dietary calcium intake and its role in the pathogenesis of rickets. S Afr Med J 1983;63:179.
257. Sly MR, Van der Walt WH, du Bruyn DB, Pettifor JM, Marie PJ. Exacerbation of rickets and osteomalacia by maize: a study of bone histomorphometry and composition in young baboons. Calcif Tissue Int 1984;36:370–9.
258. Weaver CM, Proulx WR, Heaney R. Choices for achieving adequate dietary calcium with a vegetarian diet. Am J Clin Nutr 1999;70:543S–8S.
259. Heaney RP, Weaver CM. Oxalate: effect on calcium absorbability. Am J Clin Nutr 1989;50:830–2.
260. Sheikh MS, Santa Ana CA, Nicar MJ, Schiller LR, Fordtran JS. Gastrointestinal absorption of calcium from milk and calcium salts. N Engl J Med 1987;317:532–6.
261. Lopriore C, Guidoum Y, Briend A, Branca F. Spread fortified with vitamins and minerals induces catch-up growth and eradicates severe anemia in stunted refugee children aged 3–6 y. Am J Clin Nutr 2004;80:973–81.
262. Powers HJ, Bates CJ, Prentice AM, Lamb WH, Jepson M, Bowman H. The relative effectiveness of iron and iron with riboflavin in correcting a microcytic anaemia in men and children in rural Gambia. Hum Nutr Clin Nutr 1983;37:413–25.
263. Powers HJ, Bates CJ. Micronutrient deficiencies in the aetiology of anaemia in a rural area in The Gambia. Trans R Soc Trop Med Hyg 1987;81:421–5.
264. Powers HJ. Riboflavin (vitamin B-2) and health. Am J Clin Nutr 2003;77:1352–60.
265. Borelli P, Blatt S, Pereira J, de Maurino BB, Tsujita M, de Souza AC, Xavier JG, Fock RA. Reduction of erythroid progenitors in protein-energy malnutrition. Br J Nutr 2007;97:307–14.
266. Fondu P, Haga P, Halvorsen S. The regulation of erythropoiesis in protein-energy-malnutrition. Br J Haematol 1978;38:29–36.
267. Srikantia SG, Gopalan C. Role of ferritin in nutritional oedema. J Appl Physiol 1959;14:829–33.
268. Miles J, Golden MH, Ramdath DD, Golden BE. Hepatic trace elements in kwashiorkor. In: Hurley LS, Keen CL, Lonnerdal B, Rucker RB, eds. Trace element metabolism in man and animals—6. New York: Plenum Press 1988:497–8.
269. Dempster WS, Sive AA, Rosseau S, Malan H, Heese HV. Misplaced iron in kwashiorkor. Eur J Clin Nutr 1995;49:208–10.
270. Golden MH, Golden BE, Bennett FI. High ferritin values in malnourished children. In: Mills CF, Bremner I, Chesters JK, eds. Trace element metabolism in man and animals—5. Aberdeen: Commonwealth Agricultural Bureau 1985:775–9.
271. Ramdath DD, Golden MH. Non-haematological aspects of iron nutrition. Nutr Res Rev 1989;2:29–49.
272. Ramdath DD, Golden MH, Golden BE, Howell R. plasma iron, transferrin and transferrin saturation of severely malnourished jamaican children. West Indian Med J 1990;39 (Suppl. 1):42.
273. Ramdath DD, Morris AJ, Howell R, Golden BE, Golden MH. Iron status during recovery from malnutrition. West Indian Med J 1993;42 (suppl 1):23–4.
274. Golden MH, Ramdath DD, Hudson MA. Urinary iron excretion following desferrioxamine in malnourished children. IP 1994.
275. Sive AA, Dempster WS, Rosseau S, Kelly M, Malan H, Heese HD. Bone marrow and chelatable iron in patients with protein energy malnutrition. S Afr Med J 1996;86:1410–3.
276. Sive AA, Dempster WS, Malan H, Rosseau S, Heese HD. Plasma free iron: a possible cause of oedema in kwashiorkor. Arch Dis Child 1997;76:54–6.
277. Waterlow JC. Fatty liver disease in infants in the British West Indies. Medical Research Council Special Report Series. No 263. London: His Majesty's Stationary Office 1948:5–84.

278. Golden MH, Ramdath DD. Free radicals in the pathogenesis of kwashiorkor. Proc Nutr Soc 1987;46:53–68.
279. Smith IF, Taiwo O, Golden MH. Plant protein rehabilitation diets and iron supplementation of the protein-energy malnourished child. Eur J Clin Nutr 1989;43:763–8.
280. van Rheenen PF, Gruschke S, Brabin BJ. Delayed umbilical cord clamping for reducing anaemia in low birthweight infants: implications for developing countries. Ann Trop Paediatr 2006;26:157–67.
281. Chaparro CM, Neufeld LM, Tena AG, Eguia-Liz CR, Dewey KG. Effect of timing of umbilical cord clamping on iron status in Mexican infants: a randomised controlled trial. Lancet 2006;367:1997–2004.
282. Committee on International Nutrition—Vitamin C in Food Aid. Vitamin C fortification of food aid commodities. Washington, DC: Institute of Medicine, 2009.
283. Sazawal S, Black RE, Ramsan M, Chwaya HM, Stoltzfus RJ, Dutta A, Dhingra U, Kabole I, Deb S, Othman MK, Kabole FM. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. Lancet 2006;367:133–43.
284. Oppenheimer SJ. Iron and its relation to immunity and infectious disease. J Nutr 2001;131:616S–33S.
285. Gillman J, Gillman T. Perspectives in human nutrition. New York: Grune and Stratton, 1951.
286. National Reseach Council. Selenium. Washington DC: National Academy of Sciences, 1976.
287. Bennett FI, Golden MH, Ramdath DD, Golden BE. Use of red cell peroxide dismutase activity to measure copper status in severe malnutrition. West Indian Med.J. 1984;33(Suppl. 1):46.
288. Graham GG, Cordano A. Copper depletion and deficiency in the malnourished infant. Johns Hopkins Med J 1969;124:139–50.
289. Castillo-Duran C, Fisberg M, Valenzuela A, Egana JI, Uauy R. Controlled trial of copper supplementation during the recovery from marasmus. Am J Clin Nutr 1983;37:898–903.
290. O'Neill NC, Tanner MS. Uptake of copper from brass vessels by bovine milk and its relevance to Indian childhood cirrhosis. J Pediatr Gastroenterol Nutr 1989;9:167–72.
291. Tanner MS. Role of copper in Indian childhood cirrhosis. Am J Clin Nutr 1998;67:1074S–81S.
292. Gibbs K, Walshe JM. Liver copper concentration in Wilson's disease: effect of treatment with 'anti-copper' agents. J Gastroenterol Hepatol 1990;5:420–4.
293. Mason J, Cardin CJ, Dennehy A. The role of sulphide and sulphide oxidation in the copper molybdenum antagonism in rats and guinea pigs. Res Vet Sci 1978;24:104–8.
294. Howell R, Golden BE, Robotham H, Golden MH. The use of eggs in the assessment of selenuim status of a community. West Indian Med.J. 1989;38(Suppl.1):66–7.
295. Majaj AS, Hopkins LL. Selenium and kwashiorkor. Lancet 1966;1:592–3.
296. Levine RJ, Olsen RE. Blood selenium in Thai children with protein-calorie malnutrition. Proc Soc Exp Biol Med 1970;134:1030–4.
297. Fondu P, Hariga Muller C, Mozes N, Neve J, Van Steirteghem A, Mandelbaum IM. Protein-energy malnutrition and anemia in Kivu. Am J Clin Nutr 1978;31:46–56.
298. Golden MH, Golden BE. Trace elements in malnourished populations. In: Hurley LS, Keen CL, Lonnerdal B, Rucker RB, eds. Trace element metabolism in man and animals—6. New York: Plenum Press 1988:197–201.
299. Markoska V. Antioxidant capacity of breast-milk taken by patients with kwashiorkor. MsC thesis. University of Aberdeen; 2000.
300. Golden MH, Ramdath DD, Golden BE. Free radicals and malnutrition. In: Dreosti IE, ed. Trace elements, micronutrients and free radicals. Totowa, New Jersey: Humana Press 1991:199–222.
301. Ciliberto H, Ciliberto M, Briend A, Ashorn P, Bier D, Manary M. Antioxidant supplementation for the prevention of kwashiorkor in Malawian children: randomised, double blind, placebo controlled trial. Br Med J 2005;330:1109–14.
302. Sun QA, Su D, Novoselov SV, Carlson BA, Hatfield DL, Gladyshev VN. Reaction mechanism and regulation of mammalian thioredoxin/glutathione reductase. Biochem 2005;44:14528–37.
303. Zheng Y, Zhong L, Shen X. Effect of selenium-supplement on the calcium signaling in human endothelial cells. J Cell Physiol 2005;205:97–106.
304. Kalantari P, Narayan V, Natarajan SK, Muralidhar K, Gandhi UH, Vunta H, Henderson AJ, Prabhu KS. Thioredoxin reductase-1 negatively regulates HIV-1 transactivating protein Tat-dependent transcription in human macrophages. J Biol Chem 2008;283:33183–90.
305. Arthur JR, Beckett GJ. Thyroid function. Br Med Bull 1999;55:658–68.
306. Levander OA. The selenium–coxsackie virus connection: chronicle of a collaboration. J Nutr 2000;130:485S–8S.
307. Levander OA, Beck MA. Selenium and viral virulence. Br Med Bull 1999;55:528–33.
308. Shor-Posner G, Miguez MJ, Pineda LM, Rodriguez A, Ruiz P, Castillo G, Burbano X, Lecusay R, Baum M. Impact of selenium status on the pathogenesis of mycobacterial disease in HIV-1-infected drug users during the era of highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2002;29:169–73.
309. Foster HD. Coxsackie B virus and myocardial infarction. Lancet 2002;359:804.
310. Xu XM, Carlson BA, Grimm TA, Kutza J, Berry MJ, Arreola R, Fields KH, Shanmugam I, Jeang KT, Oroszlan S, Combs GF, Jr., Marx PA, Gladyshev VN, Clouse KA, Hatfield DL. Rhesus monkey simian immunodeficiency virus infection as a model for assessing the role of selenium in AIDS. J Acquir Immune Defic Syndr 2002;31:453–63.
311. Foster HD. Why HIV-1 has diffused so much more rapidly in Sub-Saharan Africa than in North America. Med Hypotheses 2003;60:611–4.
312. Beck MA, Levander OA, Handy J. Selenium deficiency and viral infection. J Nutr 2003;133:1463S–7S.
313. Beck MA, Handy J, Levander OA. Host nutritional status: the neglected virulence factor. Trends Microbiol 2004;12:417–23.
314. Kupka R, Msamanga GI, Spiegelman D, Morris S, Mugusi F, Hunter DJ, Fawzi WW. Selenium status is associated with accelerated HIV disease progression among HIV-1-infected pregnant women in Tanzania. J Nutr 2004;134:2556–60.

315. van LM, West CE, van der Meer JW, Wieringa FT, Semba RD. Low plasma selenium concentrations, high plasma human immunodeficiency virus load and high interleukin-6 concentrations are risk factors associated with anemia in adults presenting with pulmonary tuberculosis in Zomba district, Malawi. Eur J Clin Nutr 2005;59:526–32.
316. Kupka R, Garland M, Msamanga G, Spiegelman D, Hunter D, Fawzi W. Selenium status, pregnancy outcomes, and mother-to-child transmission of HIV-1. J Acquir Immune Defic Syndr 2005;39:203–10.
317. Hurwitz BE, Klaus JR, Llabre MM, Gonzalez A, Lawrence PJ, Maher KJ, Greeson JM, Baum MK, Shor-Posner G, Skyler JS, Schneiderman N. Suppression of human immunodeficiency virus type 1 viral load with selenium supplementation: a randomized controlled trial. Arch Intern Med 2007;167:148–54.
318. Beck MA. Selenium and vitamin E status: impact on viral pathogenicity. J Nutr 2007;137:1338–40.
319. Jaspers I, Zhang W, Brighton LE, Carson JL, Styblo M, Beck MA. Selenium deficiency alters epithelial cell morphology and responses to influenza. Free Radic Biol Med 2007;42:1826–37.
320. Broome CS, McArdle F, Kyle JA, Andrews F, Lowe NM, Hart CA, Arthur JR, Jackson MJ. An increase in selenium intake improves immune function and poliovirus handling in adults with marginal selenium status. Am J Clin Nutr 2004;80:154–62.
321. Frost DV. Selenium and poultry. An exercise in nutrition toxicology which involves arsenic. Worlds Poult Sci J 1965;21:139–56.
322. Levander OA, Baumann CA. Selenium metabolism. VI. Effect of arsenic on the excretion of selenium in the bile. Toxicol Appl Pharmacol 1966;9:106–15.
323. Levander OA, Argrett LC. Effects of arsenic, mercury, thallium, and lead on selenium metabolism in rats. Toxicol Appl Pharmacol 1969;14:308–14.
324. Muth OH, Whanger PD, Weswig PH, Oldfield JE. Occurrence of myopathy in lambs of ewes fed added arsenic in a selenium-deficient ration. Am J Vet Res 1971; 32:1621–3.
325. Arnold RL, Olson OE, Carlson CW. Dietary selenium and arsenic additions and their effects on tissue and egg selenium. Poult Sci 1973;52:847–54.
326. Levander OA. Metabolic interrelationships between arsenic and selenium. Environ Health Perspect 1977;19:159–64.
327. Sweins A. Protective effect of selenium against arsenic-induced chromosomal damage in cultured human lymphocytes. Hereditas 1983;98:249–52.
328. Golden MH. Arsenic, selenium and African trypanosomiasis. Lancet 1992;339:1413.
329. Waterlow JC, Garrow JS, Millward DJ. The turnover of [75Se]selenomethionine in infants and rats measured in a whole body counter. Clin Sci 1969;36:489–504.
330. McGready R, Simpson JA, Cho T, Dubowitz L, Changbumrung S, Bohm V, Munger RG, Sauberlich HE, White NJ, Nosten F. Postpartum thiamine deficiency in a Karen displaced population. Am J Clin Nutr 2001;74:808–13.
331. Vimokesant SL, Hilker DM, Nakornchai S, Rungruangsak K, Dhanamitta S. Effects of betel nut and fermented fish on the thiamin status of northeastern Thais. Am J Clin Nutr 1975;28:1458–63.
332. Golden BE, Ramdath DD, Appleby J, Charley L, Golden MH. Erythrocyte glutathione reductase activity and riboflavine status in severely malnourished children. West Indian Med J 1987;36 (Suppl):31.
333. Williams EA, Powers HJ, Rumsey RD. Morphological changes in the rat small intestine in response to riboflavin depletion. Br J Nutr 1995;73:141–6.
334. Powers HJ, Wright AJ, Fairweather-Tait SJ. The effect of riboflavin deficiency in rats on the absorption and distribution of iron. Br J Nutr 1988;59:381–7.
335. Blanck HM, Bowman BA, Serdula MK, Khan LK, Kohn W, Woodruff BA. Angular stomatitis and riboflavin status among adolescent Bhutanese refugees living in southeastern Nepal. Am J Clin Nutr 2002;76:430–5.
336. Malnutrition and micronutrient deficiencies among Bhutanese refugee children—Nepal, 2007. MMWR Morb Mortal Wkly Rep 2008;57:370–3.
337. Horwitt MK, Harvey CC, Hills OW, Liebert E. Correlation of urinary excretion of riboflavin with dietary intake and symptoms of ariboflavinosis. J Nutr 1950;41:247–64.
338. Horwitt MK, Hills OW. Effects of dietary depletion of riboflavin. J Nutr 1949;39:357–73.
339. Ermolieff S, Grosshans E. [Pellagra: a disease resurging in Zaire. A study of 231 cases (author's transl)]. Ann Dermatol Venereol 1979;106:591–5.
340. Jansen AA, Horelli HT. Pellagra in Kenya. Past and present. East Afr Med J 1984;61:220–6.
341. Seal AJ, Creeke PI, Dibari F, Cheung E, Kyroussis E, Semedo P, van den BT. Low and deficient niacin status and pellagra are endemic in postwar Angola. Am J Clin Nutr 2007;85:218–24.
342. Baquet S, Wuillaume F, Van EK, Ibanez F. Pellagra outbreak in Kuito, Angola. Lancet 2000;355:1829–30.
343. Moren A, Lemoult D, Brodel A. Pellagra in Mozambican refugees. Lancet 1990;335:1403–4.
344. Malfait P, Moren A, Dillon JC, Brodel A, Begkoyian G, Etchegorry MG, Malenga G, Hakewill P. An outbreak of pellagra related to changes in dietary niacin among Mozambican refugees in Malawi. Int J Epidemiol 1993;22:504–11.
345. Carpenter KJ, Lewin WJ. A reexamination of the composition of diets associated with pellagra. J Nutr 1985;115:543–52.
346. Bender DA, Totoe L. Inhibition of tryptophan metabolism by oestrogens in the rat: a factor in the aetiology of pellagra. Br J Nutr 1984;51:219–24.
347. Shibata K, Toda S. Effects of sex hormones on the metabolism of tryptophan to niacin and to serotonin in male rats. Biosci Biotechnol Biochem 1997;61:1200–2.
348. Shibata K, Fukuwatari T, Murakami M, Sasaki R. Increase in conversion of tryptophan to niacin in pregnant rats. Adv Exp Med Biol 2003;527:435–41.
349. Gillman T, Gillman J. Hepatic damage in infantile pellagra and its response to vitamin, liver and dried stomach therapy as determined by repeated liver biopsies. JAMA 1945;129:12–13.
350. Reynolds RD, Acharya S, Leklem JE, Moser PB. Effects of low maternal dietary intake of calcium, selenium and vitamin B-6 upon breast milk composition in Nepal. In: Hamosh M, Goldman AS, eds. Human lactation 2. Maternal and environmental factors. New York: Plenum Press 1986:205–13.
351. Reynolds RD. Bioavailability of vitamin B-6 from plant foods. Am J Clin Nutr 1988;48:863–7.

352. McCullough AL, Kirksey A, Wachs TD, McCabe GP, Bassily NS, Bishry Z, Galal OM, Harrison GG, Jerome NW. Vitamin B-6 status of Egyptian mothers: relation to infant behavior and maternal-infant interactions. Am J Clin Nutr 1990;51:1067–74.
353. Adams EB, Scragg JN. Serum vitamin B12 concentrations in megaloblastic anemia associated with kwashiorkor and marasmus. J Pediatr 1962;60:580–5.
354. Satoskar RS, Kulkarni BS, Mehta BM, Sanzgiri RR, Bamji MS. Serum vitamin B12 and folic acid (PGA) levels in hypoproteinaemia and marasmus in Indian children. Arch Dis Child 1962;37:9–16.
355. Majaj AS. Vitamin E-responsive macrocytic anemia in protein-calorie malnutrition. Measurements of vitamin E, folic acid, vitamin C, vitamin B12 and iron. Am J Clin Nutr 1966;18:362–8.
356. Khalil M, Tanios A, Moghazy M, Aref MK, Mahmoud S, El-Lozy M. Serum and red cell folates, and serum vitamin B 12 in protein calorie malnutrition. Arch Dis Child 1973;48:366–9.
357. Lejeune-Lenain C, Fondu P. Serial measurements of vitamin B-12 and vitamin B-12-binding capacity in marasmic kwashiorkor. Clin Chim Acta 1975;59:81–6.
358. Mozes N. Transcobalamin II in protein-energy malnutrition among residents of the Kivu area. Clin Chim Acta 1982;124:157–62.
359. Grassmann R, Retief FP. Serum vitamin-B12-binding proteins in kwashiorkor. Br J Haematol 1969;17:237–43.
360. Albert MJ, Mathan VI, Baker SJ. Vitamin B12 synthesis by human small intestinal bacteria. Nature 1980;283:781–2.
361. Hill MJ. Intestinal flora and endogenous vitamin synthesis. Eur J Cancer Prev 1997;6 Suppl 1:S43–S45.
362. Giannella RA, Broitman SA, Zamcheck N. Vitamin B12 uptake by intestinal microorganisms: mechanism and relevance to syndromes of intestinal bacterial overgrowth. J Clin Invest 1971;50:1100–7.
363. Brandt LJ, Bernstein LH, Wagle A. Production of vitamin B-12 analogues in patients with small-bowel bacterial overgrowth. Ann Intern Med 1977;87:546–51.
364. Jones KM, Ramirez-Zea M, Zuleta C, Allen LH. Prevalent vitamin B-12 deficiency in twelve-month-old Guatemalan infants is predicted by maternal B-12 deficiency and infant diet. J Nutr 2007;137:1307–13.
365. Garrod MG, Green R, Allen LH, Mungas DM, Jagust WJ, Haan MN, Miller JW. Fraction of total plasma vitamin B12 bound to transcobalamin correlates with cognitive function in elderly Latinos with depressive symptoms. Clin Chem 2008;54:1210–7.
366. Ghitis J, Tripathi K, Mayoral G. Malabsorption in the tropics. 2. Tropical sprue versus primary protein malnutrition: vitamin B12 and folic acid studies. Am J Clin Nutr 1967;20:1206–11.
367. Fuld H. Effect of vitamin B12 on neuropathy in pernicious anaemia treated with folic acid. Br Med J 1950;2:147–8.
368. Murthy GL, Srinivasan VR, Kaul S, Gayathri K. Myelopathy during treatment of autoimmune hemolytic anaemia. J Assoc Physicians India 2002;50:1075–6.
369. Ross JF, Belding H, Paegel BL. The development and progression of subacute combined degeneration of the spinal cord in patients with pernicious anemia treated with synthetic pteroylglutamic (folic) acid. Blood 1948; 3:68–90.
370. Dickinson CJ. Does folic acid harm people with vitamin B12 deficiency? QJM 1995;88:357–64.
371. Scott JM, Weir DG. The methyl folate trap. A physiological response in man to prevent methyl group deficiency in kwashiorkor (methionine deficiency) and an explanation for folic-acid induced exacerbation of subacute combined degeneration in pernicious anaemia. Lancet 1981;2:337–40.
372. Waslien CI, Kamel K, El-Ramly Z, Carter JP, Mourad KA, Khattab AK, Darby WJ. Folate requirements of children. I. A formula diet low in folic acid for study of folate deficiency in protein-calorie malnutrition. Am J Clin Nutr 1972;25:147–51.
373. Wickramasinghe SN, Akinyanju OO, Grange A, Litwinczuk RA. Folate levels and deoxyuridine suppression tests in protein-energy malnutrition. Br J Haematol 1983;53:135–43.
374. Nkrumah FK, Nathoo KJ, Sanders DM. Iron, folate and vitamin B12 in severe protein-energy malnutrition. Cent Afr J Med 1988;34:39–43.
375. Tamura T, Shin YS, Buehring KU, Stokstad EL. The availability of folates in man: effect of orange juice supplement on intestinal conjugase. Br J Haematol 1976;32:123–33.
376. Bhandari SD, Gregory JF, III. Inhibition by selected food components of human and porcine intestinal pteroylpolyglutamate hydrolase activity. Am J Clin Nutr 1990;51:87–94.
377. Bachowski GJ, Thomas JP, Girotti AW. Ascorbate-enhanced lipid peroxidation in photooxidized cell membranes: cholesterol product analysis as a probe of reaction mechanism. Lipids 1988;23:580–6.
378. Fisher AE, Naughton DP. Vitamin C contributes to inflammation via radical generating mechanisms: a cautionary note. Med Hypotheses 2003;61:657–60.
379. Blaire MG, Holley HL. Vitamin C and rheumatoid arthritis. J Chronic Dis 1956;4:549–51.
380. Majaj AS, Dinning JS, Azzam SA, Darby WJ. Vitamin E responsive megaloblastic anemia in infants with protein-calorie malnutrition. Am J Clin Nutr 1963;12:374–9.
381. Marvin HN, Audu IS. A preliminary study of vitamin E and the anemia of kwashiorkor. West Afr Med J 1964;13:3–8.
382. Sandstead HH, Gabr MK, Azzam SA, Shuky AS, Weiler RJ, El-Din OM, Mokhtar N, Prasad AS, El-Hifney A, Darby WJ. Kwashiorkor in Egypt. 2. Hematologic aspects (the occurrence of a macrocytic anemia associated with low serum vitamin E and a wide range of serum vitamin B12 levels). Am J Clin Nutr 1965;17:27–35.
383. Whitaker JA, Fort EG, Vimokesant S, Dinning JS. Hematologic response to vitamin E in the anemia associated with protein-calorie malnutrition. Am J Clin Nutr 1967;20:783–9.
384. Darby WJ. Tocopherol-responsive anemias in man. Vitam Horm 1968;26:685–704.
385. Krishnamurthy S, Prasanna D. Serum vitamin E and lipid peroxides in malnutrition, hyper and hypothyroidism. Acta Vitaminol Enzymol 1984;6:17–21.
386. Charley L, Foreman JDM, Ramdath DD, Bennett FI, Golden BE, Golden MH. Vitamin e in malnutrition. West Indian Med.J. 1985;34 (Suppl. 1):62–3.
387. Ahmed HM, Laryea MD, el Karib AO, el Amin EO, Biggemann B, Leichsenring M, Mayatepek E, Bremer HJ. Vitamin E status in Sudanese children with protein-energy malnutrition. Z Ernahrungswiss 1990;29:47–53.

388. Morris AJ, Doherty JF, Golden BE, Ramdath DD, Golden MH. Vitamin E status in oedematous and non-oedematous malnourished children. West Indian Med J 1991;40 (Suppl. 1):18–9.
389. Kalra V, Grover J, Ahuja GK, Rathi S, Khurana DS. Vitamin E deficiency and associated neurological deficits in children with protein-energy malnutrition. J Trop Pediatr 1998;44:291–5.
390. Hassan H, Hashim SA, Van Itallie TB, Sebrell WH. Syndrome in premature infants associated with low plasma vitamin E levels and high polyunsaturated fatty acid diet. Am J Clin Nutr 1966;19:147–57.
391. Kanno C, Kobayashi H, Yamauchi K. Transfer of orally administered alpha-tocopherol into human milk. J Nutr Sci Vitaminol (Tokyo) 1989;35:649–53.
392. Orhon FS, Ulukol B, Kahya D, Cengiz B, Baskan S, Tezcan S. The influence of maternal smoking on maternal and newborn oxidant and antioxidant status. Eur J Pediatr 2009;168:975–81.
393. Barua S, Tarannum S, Nahar L, Mohiduzzaman M. Retinol and alpha-tocopherol content in breast milk of Bangladeshi mothers under low socio-economic status. Int J Food Sci Nutr 1997;48:13–8.
394. Sauerwein RW, Mulder JA, Mulder L, Lowe B, Peshu N, Demacker PN, van, der Meer JW, Marsh K. Inflammatory mediators in children with protein-energy malnutrition. Am J Clin Nutr 1997;65:1534–9.
395. Tatli MM, Vural H, Koc A, Kosecik M, Atas A. Altered anti-oxidant status and increased lipid peroxidation in marasmic children. Pediatr Int 2000;42:289–92.
396. Ashour MN, Salem SI, El Gadban HM, Elwan NM, Basu TK. Antioxidant status in children with protein-energy malnutrition (PEM) living in Cairo, Egypt. Eur J Clin Nutr 1999;53:669–73.
397. Manary MJ, Leeuwenburgh C, Heinecke JW. Increased oxidative stress in kwashiorkor. J Pediatr 2000;137:421–4.
398. Glasziou PP, Mackerras DE. Vitamin A supplementation in infectious diseases: a meta-analysis. Br Med J 1993;306:366–70.
399. Fawzi WW, Chalmers TC, Herrera MG, Mosteller F. Vitamin A supplementation and child mortality. A meta-analysis. JAMA 1993;269:898–903.
400. D'Souza RM, D'Souza R. Vitamin A for the treatment of children with measles—a systematic review. J Trop Pediatr 2002;48:323–7.
401. Potential interventions for the prevention of childhood pneumonia in developing countries: a meta-analysis of data from field trials to assess the impact of vitamin A supplementation on pneumonia morbidity and mortality. The Vitamin A and Pneumonia Working Group. Bull World Health Organ 1995;73:609–19.
402. Donnen P, Sylla A, Dramaix M, Sall G, Kuakuvi N, Hennart P. Effect of daily low dose of vitamin A compared with single high dose on morbidity and mortality of hospitalized mainly malnourished children in senegal: a randomized controlled clinical trial. Eur J Clin Nutr 2007;61:1393–9.
403. Donnen P, Dramaix M, Brasseur D, Bitwe R, Vertongen F, Hennart P. Randomized placebo-controlled clinical trial of the effect of a single high dose or daily low doses of vitamin A on the morbidity of hospitalized, malnourished children. Am J Clin Nutr 1998;68:1254–60.
404. Rothman KJ, Moore LL, Singer MR, Nguyen US, Mannino S, Milunsky A. Teratogenicity of high vitamin A intake. N Engl J Med 1995;333:1369–73.
405. Hollis BW, Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. Am J Clin Nutr 2004;80:1752S–8S.
406. Wagner CL, Hulsey TC, Fanning D, Ebeling M, Hollis BW. High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. Breastfeed Med 2006;1:59–70.
407. Saadi HF, Dawodu A, Afandi B, Zayed R, Benedict S, Nagelkerke N, Hollis BW. Effect of combined maternal and infant vitamin D supplementation on vitamin D status of exclusively breastfed infants. Matern Child Nutr 2009;5:25–32.
408. Nickkho-Amiry M, Prentice A, Ledi F, Laskey MA, Das G, Berry JL, Mughal MZ. Maternal vitamin D status and breast milk concentrations of calcium and phosphorus. Arch Dis Child 2008;93:179.
409. Heaton KW. Bile salts in health and disease. Edinburgh: Churchill Livingstone, 1972.
410. Bugel S. Vitamin K and bone health in adult humans. Vitam Horm 2008;78:393–416.
411. Douglas AS, Miller MH, Reid DM, Hutchison JD, Porter RW, Robins SP. Seasonal differences in biochemical parameters of bone remodelling. J Clin Pathol 1996;49:284–9.
412. New SA, Robins SP, Campbell MK, Martin JC, Garton MJ, Bolton-Smith C, Grubb DA, Lee SJ, Reid DM. Dietary influences on bone mass and bone metabolism: further evidence of a positive link between fruit and vegetable consumption and bone health? Am J Clin Nutr 2000;71:142–51.
413. Roth KS. Biotin in clinical medicine—a review. Am J Clin Nutr 1981;34:1967–74.
414. Velazquez A, Martin-del CC-C, Baez A, Zamudio S, Quiterio M, Aguilar JL, Perez-Ortiz B, Sanchez-Ardines M, Guzman-Hernandez J, Casanueva E. Biotin deficiency in protein-energy malnutrition. Eur J Clin Nutr 1989;43:169–73.
415. Velazquez A, Teran M, Baez A, Gutierrez J, Rodriguez R. Biotin supplementation affects lymphocyte carboxylases and plasma biotin in severe protein-energy malnutrition. Am J Clin Nutr 1995;61:385–91.
416. Velazquez A. Biotin deficiency in protein-energy malnutrition: implications for nutritional homeostasis and individuality. Nutrition 1997;13:991–2.
417. Wolff JA, Margolis S, Bujdoso Wolff K, Matusick E, MacLean WC. Plasma and red blood cell fatty acid composition in children with protein-calorie malnutrition. Pediatr Res 1984;18:162–7.
418. Decsi T, Koletzko B. Effects of protein-energy malnutrition and human immunodeficiency virus-1 infection on essential fatty acid metabolism in children. Nutrition 2000;16:447–53.
419. Marin MC, Rey GE, Pedersoli LC, Rodrigo MA, de Alaniz MJ. Dietary long-chain fatty acids and visual response in malnourished nursing infants. Prostaglandins Leukot Essent Fatty Acids 2000;63:385–90.
420. Franco VH, Hotta JK, Jorge SM, dos Santos JE. Plasma fatty acids in children with grade III protein-energy malnutrition in its different clinical forms: marasmus,

marasmic kwashiorkor, and kwashiorkor. J Trop Pediatr 1999;45:71–5.
421. Marin MC, De Tomas ME, Mercuri O, Fernandez A, de Serres CT. Interrelationship between protein-energy malnutrition and essential fatty acid deficiency in nursing infants. Am J Clin Nutr 1991;53:466–8.
422. Heymans HS, Van Den Heuvel CG, Smit W, Steendijk R. Catch-up growth following long-term administration of essential fatty acids in a girl with growth failure and essential fatty acid deficiency. Acta Paediatr Scand 1982;71:1037–9 .
423. Holman RT, Johnson SB, Mercuri O, Itarte HJ, Rodrigo MA, De Tomas ME. Essential fatty acid deficiency in malnourished children. Am J Clin Nutr 1981;34:1534–9.
424. Naismith DN. The role of the essential fatty acids in the aetiology of kwashiorkor. Proc Nutr Soc 1964;23:7.
425. Hansen AE, Wiese HF. Essential fatty acids and human nutrition. 2. serum level for unsaturated fatty acids in poorly-nourished infants and children. J Nutr 1954; 52:367–74.
426. Carl GF, Keen CL, Gallagher BB, Clegg MS, Littleton WH, Flannery DB, Hurley LS. Association of low blood manganese concentrations with epilepsy. Neurology 1986;36:1584–7.
427. Burger FJ, Hogewind ZA. Changes in trace elements in kwashiorkor. S Afr Med J 1974;48:502–4.
428. Garcia-Aranda JA, Meza-Camacho C, Pandzich-Arapov S. [Manganese determination in blood from malnourished children]. Bol Med Hosp Infant Mex 1990;47:247–50.
429. Warren PJ, Hansen JDL, Lehmann BH. The concentration of copper, zinc and manganese in the liver of African children with marasmus and kwashiorkor. Proc Nutr Soc 1969;28:6A–7A.
430. Gurson CT, Saner G. Effects of chromium supplementation on growth in marasmic protein–calorie malnutrition. Am J Clin Nutr 1973;26:988–91.
431. Gurson CT, Saner G. Effect of chromium on glucose utilization in marasmic protein-calorie malnutrition. Am J Clin Nutr 1971;24:1313–9.
432. Jeejeebhoy KN, Chu RC, Marliss EB, Greenberg GR, Bruce-Robertson A. Chromium deficiency, glucose intolerance, and neuropathy reversed by chromium supplementation, in a patient receiving long-term total parenteral nutrition. Am J Clin Nutr 1977;30:531–8.
433. Waterlow JC. Amount and rate of disappearance of liver fat in malnourished infants in Jamaica. Am J Clin Nutr 1975;28:1330–6.
434. Doherty JF, Adam EJ, Griffin GE, Golden MH. Ultrasonographic assessment of the extent of hepatic steatosis in severe malnutrition. Arch Dis Child 1992;67:1348–52.
435. World Health Organization. A model for establishing upper levels of intake for nutrients and related substances: report of a joint FAO/WHO technical workshop on nutrient risk assessment. 2006. Geneva, World Health Organization.
436. Davidsson L, Almgren A, Sandstrom B, Hurrell RF. Zinc absorption in adult humans: the effect of iron fortification. Br J Nutr 1995;74:417–25.
437. Walravens PA, Hambidge KM. Growth of infants fed a zinc supplemented formula. Am J Clin Nutr 1976;29:1114–21.
438. Persson B, Tunell R, Ekengren K. Chronic Vitamin A intoxication during the first half year of life. Acta Paediatr Scand 1965;54:49–60.