Malnutrition and Fat/Water-Soluble Vitamin Metabolism

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The unraveling of functional mechanisms for single nutrients has been a necessary stage in the research strategy of human nutrition. Nevertheless, it has become fashionable to say that in human populations, single nutrient deficiencies seldom if ever arise. Thus, complex interactions are part of the natural order and must be analyzed. The aim of this chapter is to examine some of the functional aspects of nutritional deficiencies, which possess a link with both vitamins and protein-energy malnutrition (PEM) and to attempt to highlight some important areas of ignorance, where further research is needed.

From the point of view of the malnourished child, the provision of a balanced diet, adequate in all known micronutrient requirements, may provide adequate therapy. Constrained by limited financial resources and presented with a wide variety of possible intervention options, it is essential from the public health point of view to understand the complexities of these processes in order to predict the outcome of a particular intervention at the population level and to weigh potential advantages against cost and against possible adverse effects.

THE STAGES OF NUTRIENT UTILIZATION AT WHICH PEM MAY INTERACT WITH VITAMINS

Table 1 gives a brief summary of the known functions of the individual vitamins, highlighting those aspects that may be of particular relevance to PEM. Table 2 summarizes currently available information concerning the metabolism and turnover of vitamins and their cofactor derivatives, and indicates the many gaps in our knowledge. Investigations of these processes in humans will soon be facilitated by the development of stable isotope-labeled vitamins. This should provide new information about the estimation of daily requirements and about specific nutrient interactions.

Since, of all vitamin deficiencies, that of vitamin A causes the most serious damage to quality of life and life expectancy, especially of children in Asia today, and since vitamin A deficiency interacts with PEM in a characteristic manner, a major topic to be reviewed will be the interaction of these two insults.
### TABLE 1. Functions of individual vitamins

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Functions with a clear relevance to PEM</th>
<th>Other functions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Well-established</td>
</tr>
<tr>
<td><strong>Fat-soluble</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Cell differentiation; protection against infection</td>
<td>Retinal pigment cycles</td>
</tr>
<tr>
<td>D</td>
<td></td>
<td>Calcium homeostasis; bone mineralization</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td>Membrane lipid protection</td>
</tr>
<tr>
<td>K</td>
<td></td>
<td>Hemostasis</td>
</tr>
<tr>
<td><strong>Water-soluble</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiamine (B₁)</td>
<td>Catabolism of carbohydrates; keto acid metabolism</td>
<td>Glutathione reduction; B₃ activation; iron mobilization; other redox processes</td>
</tr>
<tr>
<td>Riboflavin (B₂)</td>
<td>Electron transport; fatty acid oxidation</td>
<td></td>
</tr>
<tr>
<td>Vitamin B₆</td>
<td>Group transfers, especially in amino acid metabolism; protection against infection</td>
<td></td>
</tr>
<tr>
<td>Niacin</td>
<td>Energy release via pyridine nucleotide coenzymes</td>
<td></td>
</tr>
<tr>
<td>Folacin</td>
<td>DNA synthesis; methionine synthesis</td>
<td></td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
<td>Folacin activation/enablement</td>
<td></td>
</tr>
<tr>
<td>Biotin</td>
<td>Fatty acid biosynthesis (carboxylation)</td>
<td></td>
</tr>
<tr>
<td>Pantothenate</td>
<td>Fatty acid utilization</td>
<td></td>
</tr>
<tr>
<td>Carnitine*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Collagen biosynthesis</td>
<td>Catecholamine and carnitine synthesis; tyrosine catabolism; iron absorption</td>
</tr>
</tbody>
</table>

*Not regularly included in the current lists of vitamins in human nutrition, but included here because of its PEM-related functions. Other "borderline" vitamins include the bioflavonoids and biopterin, which can become limiting in special circumstances, but these and substances that do not feature as vitamins in human nutrition (e.g., choline, inositol, etc.) have been excluded. Certain carotenoids may have the characteristics of vitamins, independently of their conversion to vitamin A, but this needs further investigation.
<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Known metabolic pathways</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat-soluble</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Biosynthesis from carotenoids</td>
<td>Carotene dioxygenase (intestinal mucosa) is depressed by protein deficiency in rats</td>
</tr>
<tr>
<td></td>
<td>? Catabolism of retinol, probably via retinoic acid, to inactive products</td>
<td>Little known about metabolic control of turnover</td>
</tr>
<tr>
<td>D</td>
<td>Biosynthesis of cholecalciferol in the skin</td>
<td>Requires sunlight or equivalent light exposure</td>
</tr>
<tr>
<td></td>
<td>Activation by conversion to 25-hydroxy and 1,25-dihydroxy forms in liver and kidney, respectively</td>
<td>Conversion to 25-hydroxy form depends mainly on availability of the parent vitamin D, but the 1-hydroxylation is strictly limited and controlled by functional requirement</td>
</tr>
<tr>
<td></td>
<td>Catabolism/inactivation: poorly characterized</td>
<td>Recent evidence for increased vitamin D turnover when dietary calcium is limiting</td>
</tr>
<tr>
<td>E</td>
<td>Redox function involves interconversion of reduced and oxidized forms; this may involve vitamin C for regeneration</td>
<td>Little known about ultimate control of turnover</td>
</tr>
<tr>
<td>K</td>
<td>Redox cycle with epoxidation</td>
<td>Little known about turnover</td>
</tr>
<tr>
<td>Water-soluble</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Activation requires conversion to thiamine pyrophosphate</td>
<td>Little known about control of activation or turnover. &quot;Thiaminase&quot; enzymes in some biological material cause irreversible inactivation</td>
</tr>
<tr>
<td>B&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Activation requires conversion to flavin mononucleotide (FMN), flavin adenine dinucleotide (FAD), or covalent binding to enzyme protein. Thyroid hormone involvement</td>
<td>Little known about turnover; some inactive urinary products described</td>
</tr>
<tr>
<td>B&lt;sub&gt;6&lt;/sub&gt;</td>
<td>Activation requires oxidation (B&lt;sub&gt;6&lt;/sub&gt;-dependent) and phosphorylation</td>
<td>Impaired by B&lt;sub&gt;2&lt;/sub&gt; deficiency. Inactivation involves oxidation, mainly to pyridoxic acid. Little known about control</td>
</tr>
<tr>
<td>Niacin</td>
<td>Synthesis from tryptophan (B&lt;sub&gt;3&lt;/sub&gt;-dependent); preformed niacin is poorly available in some foods</td>
<td>Turnover yields urinary N'-methyl nicotinamide and N'-methyl 2-pyridone 5-carboxamide, in relatively large amounts. Increased in burned patients</td>
</tr>
<tr>
<td>Folacin</td>
<td>Complex cycles of interconversions of different forms, including redox changes, C&lt;sub&gt;7&lt;/sub&gt;-substitutions, and polyglutamate side-chain alterations, some of which are B&lt;sub&gt;12&lt;/sub&gt;-dependent</td>
<td>Little known about turnover, but recent evidence suggests an increased rate during pregnancy (rats)</td>
</tr>
<tr>
<td>B&lt;sub&gt;12&lt;/sub&gt;</td>
<td>Several interconvertible forms</td>
<td>Turnover extremely slow and poorly understood</td>
</tr>
<tr>
<td>Biotin</td>
<td>Generally synthesized by intestinal microflora in sufficient amounts</td>
<td>Turnover little studied</td>
</tr>
<tr>
<td>Carnitine</td>
<td>Usually, but not always, sufficiently supplied in diet; de novo synthesis requires lysine and vitamins C and B&lt;sub&gt;6&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Redox function involves interversion of reduced form with two partially oxidized forms (semi-dehydroascorbate and dehydroascorbate). Some sulfation. Degradation via oxalic acid</td>
<td>Rate of turnover in humans fairly constant at ~3% body pool/day. Control not understood</td>
</tr>
</tbody>
</table>
It is necessary first to consider the relationship of vitamin deficiencies to growth of the organism and the different stages of development and maturation during which deficiencies usually become evident. Second, one must examine the successive stages of utilization during which vitamin deficiencies may affect, or be affected by, PEM.

**VITAMIN REQUIREMENTS IN RELATION TO GROWTH**

Several micronutrients, if withheld from the diet of a weanling, rapidly growing rat, will cause a drastic reduction in, or even a cessation of, growth. Only at a much later stage, after prolonged and severe deprivation, do pathologic signs of deficiency appear. Clearly, such a reduction in growth rate is a protective, homeostatic mechanism, designed to relieve the demand on limited micronutrient resources needed for tissue accretion and growth. A similar response occurs during protein or zinc deprivation.

Although this homeostatic response is a common phenomenon in the major part of the animal (and plant) kingdoms, it occurs to only a very limited extent in humans and in higher primates. With a few possible exceptions [e.g., (1)], stunting and wasting are not characteristic results of specific vitamin deficiencies in children, whereas pathologic deficiency signs are. Rapidly growing children become especially vulnerable to nutritional insults, whether they be PEM, vitamin deficiencies, or a mixture. By the same token, male children are likely to be more vulnerable to nutrient deficiencies than females, because of their relatively higher growth rates.

**VITAMIN REQUIREMENTS IN RELATION TO STAGE OF MATURITY**

For several reasons (which include the variable size of body vitamin stores at birth; the variable contribution from mothers' milk and other sources; and the variability in rates of demand, accretion, and turnover during development and aging), each vitamin differs with respect to the peak age for association with deficiency signs and symptoms. A brief summary of this is provided in Table 3.

A few examples may be selected: Vitamin K is perhaps the prime example of a nutrient for which the peak vulnerability to deficiency occurs at birth (2). The problem then disappears almost entirely after the first few weeks of life. Requirements for vitamin E may also peak very early in postnatal life, particularly for preterm infants when exposed to high oxygen tensions when lung function is inadequate (3).

For vitamin A, peak vulnerability to deficiency occurs in the preschool child, probably due to the very low content of vitamin A and its precursors in Third World weaning foods (4). The coincidence of the vitamin A deficiency and PEM peaks, together with peak susceptibility to childhood infections such as measles in Africa and gastrointestinal and respiratory diseases elsewhere, results in a potentially lethal combination of insults.

Vitamin D deficiency appears as rickets in children, and in adults as osteomala-
### TABLE 3. Prevalence of overt nutrient deficiency syndromes related to age and development

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Population groups exhibiting highest prevalence of overt deficiency</th>
<th>Name/description of deficiency states or responsive syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein-energy</td>
<td>Preschool children</td>
<td>Marasmus, kwashiorkor, marasmic-kwashiorkor</td>
</tr>
<tr>
<td>A</td>
<td>Preschool children (Pregnant women)*</td>
<td>Keratomalacia and other morbidity (Nightblindness)</td>
</tr>
<tr>
<td>D</td>
<td>Schoolchildren</td>
<td>Rickets</td>
</tr>
<tr>
<td>E</td>
<td>Elderly</td>
<td>Osteomalacia</td>
</tr>
<tr>
<td>K</td>
<td>(Preterm infants)</td>
<td>(E-responsive anemia, intracranial bleeding, retinopathy, lung disease)</td>
</tr>
<tr>
<td>Water-soluble vitamins</td>
<td>Newborn infants</td>
<td>Hemorrhagic disease of the newborn</td>
</tr>
<tr>
<td>B₁</td>
<td>Infant; preschool children</td>
<td>&quot;Wet&quot; beriberi²</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>&quot;Dry&quot; beriberi², Wernicke's (alcoholic) encephalopathy</td>
</tr>
<tr>
<td>B₂</td>
<td>Pregnant women</td>
<td>Mucocutaneous lesions</td>
</tr>
<tr>
<td></td>
<td>(Formula-fed infants)</td>
<td>(B₂-responsive seizures)</td>
</tr>
<tr>
<td>Niacin</td>
<td>Adults and schoolchildren</td>
<td>Pellagra²</td>
</tr>
<tr>
<td>Folacin</td>
<td>Young infants</td>
<td>Growth retardation</td>
</tr>
<tr>
<td></td>
<td>Pregnant women</td>
<td>Megaloblastic bone marrow/anemia</td>
</tr>
<tr>
<td>B₁₂</td>
<td>(Young infants)</td>
<td>(Failure to thrive)</td>
</tr>
<tr>
<td></td>
<td>All ages</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>Biotin</td>
<td>(Infants)</td>
<td>(Seborrheic dermatitis and other biotin-responsive inborn errors)</td>
</tr>
<tr>
<td>Pantothenate</td>
<td>Rarely encountered</td>
<td>(Carnitine-responsive inborn errors)</td>
</tr>
<tr>
<td>Carnitine</td>
<td>(Infants)</td>
<td>(Carnitine-responsive inborn errors)</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Infants</td>
<td>Infantile scurvy</td>
</tr>
<tr>
<td></td>
<td>Adults and elderly</td>
<td>Scurvy</td>
</tr>
</tbody>
</table>

The items in parentheses either are relatively uncommon, are controversial, or are insufficiently investigated to rank as well-established deficiency diseases.

Current controversies about the attribution of beriberi and pellagra to thiamine and niacin deficiencies (7–9) should be noted.

The most common occurrence of vitamin B₁₂ deficiency is that of pernicious anemia, due to lack of intrinsic factor secreted by the stomach, leading to impaired intestinal absorption. Therefore, it ranks as a metabolic error (comparable to other instances of inborn errors of vitamin metabolism), not as a dietary deficiency.

Lack of exposure to sunlight is a major factor, exacerbated by calcium deficiency (5). Under ideal conditions of light exposure, vitamin D would not be needed as a component of the diet at all. Like carnitine, it is required in the diet only when the alternative (biosynthetic) pathway is overstretched.

Folate deficiency is particularly common during pregnancy, and a major increment in its intake is needed to avoid bone marrow megaloblastosis (6). During pregnancy, most micro- and macronutrient requirements are increased, and severe maternal deficiencies often result in fetal resorption, but during moderate deficiency, the fetus takes precedence over maternal tissues, and the consequent nutri-
ent drain into the fetus can result in overt maternal deficiency. Recent evidence suggests that folate turnover may be enhanced during pregnancy (7).

There are major geographic variations in the prevalence of certain vitamin deficiency signs or associations; thus, Bitot’s spots are frequently observed in some vitamin-A-deficient populations but not in others. A close association between vitamin A deficiency and measles is encountered in certain parts of Africa, but not to the same degree elsewhere (3). These observations highlight the fact that the clinical manifestation of diseases that are primarily nutritional in origin has a strongly regional aspect, either through interactions with the particular environment and with other exacerbating disease processes or perhaps through genetic variations in response or susceptibility. Clearly, these variations need further study.

Clinical signs may be very age-dependent; thus, although scurvy has been observed in all age groups, from young infants to elderly people, the characteristic signs of scurvy in a young infant are quite different from those of an adult, and likewise the signs and symptoms of vitamin D deficiency differ radically between a growing child and an elderly person. The nature of the links between metabolic function and clinical deficiency signs are not well understood, especially for the water-soluble vitamins. Many B-vitamin deficiencies affect epithelial surfaces in ways that are not easily explicable in terms of their known biochemical functions. Although ingenious suggestions have been made about possibly convergent pathways (8), it would be premature to claim that we have a clear picture of the links between the biochemistry and the pathology of deficiency, either for PEM or for deficiencies of other micronutrients. Pellagra and beriberi are examples of human diseases that are frequently portrayed as representing simple, well-understood deficiencies of certain specific vitamins, but the evidence remains conflicting and controversial (9–11). They may present with different clinical signs in different age groups, and their appearance in, or disappearance from, specific populations cannot be satisfactorily explained by known changes in dietary patterns. Likewise, there remain many uncertainties about the ways in which functional variables such as physical work capacity (12,13) or brain function (14) can be affected by PEM or by micronutrient status.

POTENTIAL SITES OF INTERACTION BETWEEN PEM AND VITAMINS

Intestinal Absorption

It is well known that there are many nutritional insults that affect the integrity and competence of the intestinal mucosa. Because of the rapid turnover of nutrients at this site, they are highly vulnerable, responding very rapidly to a wide variety of insults. An example of this phenomenon is the induction of localized malabsorption of folacin and vitamin B₁₂ in tropical sprue, a situation that is temporarily ameliorated by vitamin supplements even when the causative infective agent is still present.
Likewise, fat-soluble vitamin malabsorption can arise through steatorrhea or diarrhea, and PEM can interfere with vitamin A or carotenoid absorption in a variety of ways (17). In extreme cases of intestinal damage, for example, after extensive surgical removal or in the case of patients with inborn abnormalities of intestinal function or with developmental immaturity such as that of preterm infants, parenteral nutrition may become necessary in order to break the cycle of poor nutrient absorption, which leads to further gut deterioration and hence to extensive loss of absorptive capacity. Further work clearly is needed to determine the balance of advantages of enteral versus parenteral nutrition in subjects who are generally malnourished and who therefore cannot absorb nutrients efficiently. An objective index of intestinal function would facilitate the choice of rehabilitation schedules.

Transport Between Organs and Tissues

At this level, general malnutrition or PEM may also affect specific vitamin transport or utilization. An obvious example is the failure of hepatic synthesis of retinol-binding protein in conditions of protein deficiency, with reduced transport of retinol from the liver and hence peripheral tissue deficiency, even when the central store is adequate (17–19). There are numerous instances in the literature of children with kwashiorkor having low circulating levels of retinol with consequent ocular effects, despite adequate vitamin stores in the liver.

Another example of an adverse effect of PEM on vitamin status is that of starvation and hence muscle wasting on riboflavin status. Even short periods of fasting or starvation result in the liberation of riboflavin into the circulation and an overflow into the urine (20), thus resulting in a "false" picture of riboflavin sufficiency by conventional status tests, whereas in reality, the body is losing part of its normal complement of riboflavin cofactors. Naturally, when the tissue is later replaced during refeeding, these losses must be replaced. While it appears obvious that the rebuilding of wasted tissue requires all the essential micronutrient components, as well as macronutrient building blocks, this fact has often been forgotten during the checkered history of rehabilitation and parenteral feeding. It is certainly inefficient, and probably dangerous, to provide an imbalanced supplement during the rehabilitation of malnourished subjects.

Chemical Activation and Cofactor Synthesis

All the B-vitamins and some others require chemical transformation before they become effective in their metabolic tasks. These activation processes may be vulnerable to general malnutrition. Activation of riboflavin provides an example. Its conversion to the flavin mononucleotide (FMN) and flavin adenine nucleotide (FAD) enzyme cofactors requires high-energy phosphate in the form of adenosine triphosphate (ATP), which may be in short supply during PEM, in addition to which the activation steps are also adversely affected by hypothyroidism, a condition that
may well arise as a secondary result of PEM (21). Here again, a vicious circle is encountered, which must be broken by appropriate supplementation. As long as the tissue demand is minimized by the inhibitory effects of PEM on metabolic pathways, equilibrium between supply and demand may be maintained. However, during rehabilitation the increased demand may fail to be met, and latent vitamin deficiencies may become overt.

A somewhat different relationship between protein and vitamins is illustrated by the specific utilization of tryptophan for niacin synthesis. Niacin status is protected by a generous dietary supply of tryptophan-containing proteins (22). On the other hand, requirements for vitamin B$_6$, which is a key cofactor in the transformation of all amino acids into energy substrates, are increased by a high intake of protein (23).

**ORGAN-SPECIFIC ROLES OF VITAMINS**

As a prelude to the consideration of interactions between PEM and vitamins in individual organs and tissues in the body, it is necessary to consider the organ specificity of vitamin action, which is clearly a major and complex subject. It is well known that some vitamins have sites of action that are clearly localized and confined to one or a small number of target organs or tissues. This is true for the special actions of vitamin D in the intestine and in bone, controlling calcium transport, and for those actions of vitamin K at the sites of blood clotting and bone formation. The actions of vitamin A are of particular significance in the eye and the gonads, but a major function of vitamin A, which crosses many organ boundaries, is the maintenance of epithelia, wherever these occur. Vitamin E has an even more widespread sphere of activity, being required at all sites where polyunsaturated fats come into contact with oxygen and its free radical derivatives.

The B-vitamins are required in all metabolically active tissues. However, by focusing on each in turn, we find a considerable complexity of distribution patterns and a gradation of susceptibility to the effects of dietary deficiency between different organs and tissues. Our own studies on riboflavin deficiency in rats (24) have illustrated this: It was found, for instance, that the extent of depletion of the riboflavin-derived cofactor, FAD, from the enzyme glutathione reductase, during dietary riboflavin deficiency, differed very markedly between red blood cells, liver, kidney, intestine, and skin. The same was also true for two other flavoproteins: succinate dehydrogenase and NADH dehydrogenase. Similar interorgan differences have been reported for several other B-vitamin-dependent enzymes.

The reasons for these interorgan differences in avidity for limited vitamin supplies are not clear, nor are the mechanisms by which they are achieved. It may be assumed that they represent a gradation of requirements at different sites and that they are achieved by the differences in potency of specific transport or activation processes between different tissues. It is clear that the different vitamin-dependent enzymes within a tissue have different priority ratings for limited supplies of cofactors. For some enzymes and within some tissues, the cofactor-depleted apoenzyme
may be stable for long periods in vivo and can be reactivated when supplies of the vitamin are restored. An example of this is the riboflavin-dependent enzyme glutathione reductase in erythrocytes. For others, however (e.g., hepatic NADH dehydrogenase), the loss of the coenzyme is paralleled by loss of activatable apoenzyme, and new apoenzyme must be synthesized when the vitamin supply is restored (24). Clearly, this is of potential relevance during rehabilitation: Whereas the resaturation of some enzyme functions is very rapid after refeeding, that of others is slower and perhaps out of synchrony with the restoration of growth. Vitamin B₆, in particular, shows a high degree of mobility between tissue and enzyme compartments, and there is a characteristic pattern under hormonal control, which is altered during pregnancy and during oral contraceptive use (25). The altered ratio of free pyridoxal to pyridoxal phosphate in the plasma of women during pregnancy (26), for instance, may have important implications for the use of pyridoxal phosphate as an index of B₆ status.

Vitamin C shows a unique and unexpected distribution pattern between tissues and organs, with high concentrations occurring in adrenals, pituitary, leukocytes, and ocular tissues, and relatively low concentrations in plasma, skin, and muscle (27). These tissue gradients are maintained by tissue-specific active transport systems. The requirement for adrenal hormone synthesis, and the characteristic changes in adrenal ascorbate concentration that occur in response to stress, may well give us clues as to the reasons for the particularly high concentrations of ascorbate that occur in the adrenal glands.

**RESPONSE TO STRESS**

It seems reasonable to suggest that the body’s response to stress, whether due to infections, noxious or toxic chemicals, or trauma, is an important aspect of the maintenance of homeostasis in the face of malnutrition. A better understanding of the normal armament of defenses against stress will clearly enhance our understanding of the deterioration that results from malnutrition. Clues may be obtained from the pattern of localization and relocation of vitamins at particular sites, particularly in response to stressful situations [e.g., the homing of vitamin C into areas of tissue damage (28)].

**Protection Against Infection**

The immune system is sensitive to nutrient deficiencies in a wide variety of ways and is influenced differently by various nutrient deficiencies (29,30). Cell-mediated immunity probably heads the list of nutrient-sensitive immune systems. Recent advances in recognizing the complexity of its component parts have shown that there is a great deal still to be learned about the nature of responses of individual components to particular nutrient deficiencies. Delayed hypersensitivity, secretory immu-
malnourished, and the complement system all respond in characteristic ways to nutrient deprivation, whereas humoral immunity seems somewhat less sensitive. In certain cases where the host and parasite are differently affected by nutrient deficiencies, paradoxic effects may arise; thus, malarial parasitemia may in some circumstances be reduced by marginal nutrient depletion of the host (31,33).

Clearly, immunocompetence is affected both by PEM and by specific nutrient deficiencies. Overall immune status reflects the sum of several different nutritional inputs. It also seems likely that the development and maturation of immune functions may be especially sensitive to nutrient deprivation, with important consequences for young children. However, this field is totally unexplored.

Protection Against Free-Radical Damage

Dietary components have an important influence on the tissue balance between oxidative stress and antioxidative protective mechanisms (34). It has recently been proposed that uncontrolled oxidative damage to tissue components by oxygen-derived free radicals may be an important factor in the etiology of kwashiorkor and that certain vitamins, particularly carotenoids and vitamins E and C, may play a protective role (35). The next few years will undoubtedly see a clarification of free-radical nutrient and tissue interactions, and may help to put the concept on a sounder footing.

VITAMIN A

In considering the subject of vitamin deficiency and PEM, particularly when these are placed in the context of Indonesia, it seems essential to put special emphasis on the important relation of PEM to vitamin A deficiency.

Mode of Action of Vitamin A

Despite a great deal of research, several of the functions of vitamin A at the molecular level are very poorly understood. It has a fairly well-characterized function in the retina, involving the translation of light energy to nerve impulses in the optic nerve, mediated by the cis–trans conversion of retinaldehyde, in rhodopsin. This represents, however, only one of a diverse array of actions of vitamin A (36). It is not responsible for the life-threatening morbidity associated with vitamin A deficiency. Cell differentiation is undoubtedly the principal area of current interest, e.g., the significance of retinoic acid for morphogenesis (37). The visual pigments, the germinal epithelia, spermatogenesis and testosterone synthesis, and placental and fetal development all require a reduced form of vitamin A (retinol or retinaldehyde), whereas the oxidized form, retinoic acid, can support the other somatic functions, including oogenesis, fertilization, and implantation in the female (36). These
observations clearly are germane to the question of the mode of action of vitamin A. However, a unifying theory has yet to emerge.

Evidence for a Link Between Vitamin A Deficiency and PEM

An association between vitamin A deficiency and kwashiorkor has been recognized in many diverse populations (4,38,39), although the two do not invariably occur together (40). In Indonesia, the severity of corneal lesions due to vitamin A deficiency was closely correlated with serum albumin and transferrin levels. Nevertheless, it is unlikely that protein malnutrition in the absence of vitamin A deficiency can result in xerophthalmia (53). It is of interest that anorexia nervosa, a form of PEM that is increasing in Western society, is frequently accompanied by deranged vitamin A metabolism (41).

There are several probable sites of interaction between PEM and vitamin A biochemistry and physiology. These will be discussed briefly in the following sections.

Absorption of Retinol from Dietary Esters and Utilization of Carotenoids

In a classic study (42), South American children suffering from PEM (mainly kwashiorkor) showed virtually no serum response to a 75,000-μg oral dose of retinyl ester until milk therapy had restored their protein-energy status: Impaired absorption was therefore inferred. Reduced or delayed absorption of vitamin A was also observed in Indian children with PEM (4). Two possible reasons for the deleterious effects of PEM on vitamin A absorption are a decreased secretion of conjugated bile acids, which are required for the actions of retinyl ester hydrolase and synthetase (43–45), and reduced synthesis of these enzymes.

The utilization of carotenoids for vitamin A synthesis is also vulnerable, partly because the rate-limiting step in the conversion, intestinal carotene dioxygenase, is depressed by protein deficiency (46–48). Vitamin A deficiency, on the other hand, enhances the activity of this enzyme, at least in the rat (49). Dietary fat can assist carotenoid utilization (50). Several types of parasitic infestations that predispose to PEM also appear to increase the risk of vitamin A deficiency (51–53), and impaired absorption presumably contributes to this (54–56).

Effect of PEM on Metabolism and Transport of Vitamin A

Plasma retinol binding protein and thyroxine binding prealbumin, both of which are required for the transport of vitamin A from liver stores to peripheral tissues, are sensitive to the effects of PEM, since they have high turnover rates and small pool sizes (17–19,57,58).

Children with severe kwashiorkor nearly always have diminished plasma retinol levels. However, a proportion have sufficient hepatic vitamin A stores to permit mo-
bilization of vitamin A with restoration of dietary protein alone (59). Studies have been made of the time course and characteristics of repletion by combinations of protein, energy, and vitamin A in children with PEM (60,61). The first few weeks of treatment are accompanied by a considerable increase in plasma retinol and retinol-binding protein (RBP) levels. However, these are then followed by a paradoxical fall, suggesting some delayed compensatory changes (60). The holo-RBP response to massive-dose vitamin A therapy is directly related to the level of protein nutrition (61).

Another possibly relevant effect of protein deficiency observed in weanling rats is a reduction in hepatic retinyl palmitate hydrolase activity (62).

Zinc deficiency has similar effects to those of protein deficiency on plasma transport of vitamin A. Zinc supplementation may prove effective in mobilizing liver retinol stores in refractory cases (63).

**Effects of Vitamin A Deficiency on Immunocompetence**

Of all the micronutrient deficiencies reviewed by Scrimshaw (64), that of vitamin A stood out as being associated most clearly with frequent and severe bouts of infection in children. In vitamin-A-deficient animals and children, the numbers of circulating T-lymphocytes and the bacteriocidal activity of the macrophages are reduced. Conversely, episodes of infection depress circulating levels of retinol and retinol-binding protein by decreasing absorption of vitamin A (65,66) and by increasing the rate of vitamin A turnover (67,68), thus depleting body stores. Measles and acute hepatitis have major effects on vitamin A status. The coincidence of measles epidemics with signs of vitamin A deficiency makes it appear practically certain that either insult lowers the body’s defenses against the other (53,69,70). Studies of Indonesian children by Sommer’s group (71) have demonstrated clear associations between mild xerophthalmia (vitamin A deficiency) and systemic infections, especially those associated with diarrhea and respiratory disease. They showed that it is possible to reduce childhood mortality very significantly by vitamin A supplementation alone in this population.

Various infective agents (viral, bacterial, and eukaryotic) have all been shown to act more virulently in vitamin-A-deficient than in vitamin-A-replete animals. Atrophy of the thymus, bursa, spleen, and other lymphoid tissues occurs in vitamin-A-deficient rats (72). Gnotobiotic rats can be maintained for much longer periods than conventional ones without vitamin A in their diet (73).

Thus, both animal and human studies exist to support the contention that vitamin A deficiency has a profound influence on immunocompetence and resistance to infection, acting synergistically with PEM in increasing morbidity and mortality, especially in preschool children.

**LITERATURE REVIEW**

During the past 3 decades, several studies of specific vitamin deficiencies in protein-energy-malnourished human subjects have been reported (Table 4). Not sur-
TABLE 4. Changes in vitamin status reported in association with PEM

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Country (ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiamine</td>
<td>Thailand (89,91), Dominica (90), Ghana (92)</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>India (85), Guatemala (86)*, Sicily (87), Kenyan (88), Thailand (89,91), Dominica (90)</td>
</tr>
<tr>
<td>Niacin</td>
<td>S. Africa (93,94)</td>
</tr>
<tr>
<td>Vitamin B₆</td>
<td>S. Africa (95), Egypt (96)</td>
</tr>
<tr>
<td>Folic acid</td>
<td>India (74,121), Colombia (75), Egypt (76,77,123), Sudan (78), S. Africa (79,122), Nigeria (80), France (81), Thailand (89)</td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
<td>Guatemala (82), Israel (83), Zaire (84), Egypt (123), India (121)</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Guatemala (97)</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Jordan (37,38,112), Guatemala (41,58), India (16,18,39,85,100,102, 104,119,120), Thailand (67,91,101,107), Sumatra (60), Senegal (68), Sri Lanka (103), Egypt (56,98,99)</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Nigeria (105), Egypt (106), Thailand (107), Israel (83), Brazil (108)</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Jamaica (34), Lebanon (116), Uganda (109,117), Jordan (110,112,115), Zaire (118), Thailand (113), India (114), Egypt (111)</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>S. Africa (124)</td>
</tr>
<tr>
<td>Review articles</td>
<td>(3,63,125,126)</td>
</tr>
</tbody>
</table>

*Paradoxically increase reported.

Surprisingly, the countries of origin have mainly been developing countries, and nearly all the known vitamins have, at some time, been reported to be either nutritionally deficient or both, in various protein-energy-deficient groups. Clearly, such associations are strongly influenced by the particular characteristics of the diet of different regions and of human groups, and in PEM, it is possible to observe single or multiple associated micronutrient deficiencies or occasionally none. The essential challenge for future studies will now be to determine how the different nutrient deficiencies interact metabolically with one another and what practical lessons can thereby be learned about prevention and cure of those diseases that have important nutritional components.

REFERENCES


DISCUSSION

**Dr. Karyadi:** What is the role of riboflavin in improving iron status in starved and/or malnourished children?

**Dr. Bates:** If starvation is sufficiently prolonged to result in muscle wasting, riboflavin will be released and riboflavin status of other tissues improves (1). The same could theoretically be true for iron. The body's response to starvation may complicate the picture, but it will not alter the fact that adequate riboflavin is essential for the efficient utilization of iron, either from stores or from the diet.

**Dr. Karyadi:** Does iron supplementation improve vitamin A status of malnourished children?

**Dr. Bates:** Whereas the correction of vitamin A deficiency may improve iron status (2), I am not aware of any mechanism by which iron supplementation or the correction of iron deficiency can improve vitamin A status, although any interventions that correct defects in the immune system might have an indirect beneficial effect on vitamin A status (3). The adult Gambian subjects we studied generally had acceptable vitamin A status, despite their very low intakes of vitamin A and its precursors. We are currently looking at the vitamin A status of young children there. The development of new and more sensitive techniques for the detection and confirmation of marginal vitamin A deficiency should facilitate the study of such interactions.

**Dr. Suskind:** While vitamin A status has been well studied in malnourished children, it is my impression that the metabolism of vitamin D and the water-soluble vitamins are areas that need further investigation.

**Dr. Bates:** I agree that the relationship of vitamin deficiencies to general malnutrition is, at present, poorly understood. In the case of vitamin D, we have observed deficiencies even in areas of abundant sunlight. Calcium is clearly an important factor, since there is now evidence that calcium deficiency may increase the turnover of vitamin D (4). There may also be the lack of exposure, even in countries where sunlight is plentiful. There is little information at the moment about the possibility that the metabolism of vitamin D to its active metabolites may be affected by other types of malnutrition.

Although we are at a very early stage in defining which nutrient deficiencies can occur in association with general malnutrition, I believe that a research priority should be to understand the pathophysiology involved at the tissue level. Second, we must try to understand the mechanisms and adaptive processes that permit some individuals and populations to withstand very low levels of certain micronutrients, while other populations are functionally suboptimal, even at higher intakes.

**Dr. Suskind:** In studying the vitamin B complex deficiency states, we look at various red cell enzymes. Would these be good markers in the child who is protein-energy-deficient, or are these enzymes affected by the protein-calorie status of the child as well as by the status of the vitamin B complex? If we were going to document the prevalence of deficiency states, which is the most effective method of assessment? What treatment would you recommend?
In Thailand, we developed a supplement, given to each child, which provided at least twice the RDA for each of the water- and fat-soluble vitamins.

**Dr. Bates:** One criterion for selecting status indicators, in animal models, is that they should be specific for the particular vitamin and not affected by inanition alone. This is not always easy to achieve. A good example is the problem of recognizing zinc deficiency, because suppression of growth dominates and overshadows the more specific responses.

With respect to supplementation programs, it is probably advisable to give a generous micronutrient supplement in the early stages of repletion, in order to prevent secondary deficiencies from developing as the requirement for the micronutrient increases. It is also important to avoid imbalanced supplements and to remember that some nutrients, such as iron, may be contraindicated if body stores are already high.

**Dr. Soriano:** Benton and Roberts (5), studying children with subclinical deficiencies, found that children supplemented with vitamins and minerals for 8 months showed a significant increase in nonverbal intelligence over controls. What might the implications be for Third World countries?

**Dr. Bates:** I believe it was essentially mineral, rather than vitamin, intake that was cited. I also believe more evidence is needed to substantiate the effects of supplementation on nonverbal intelligence. Vitamin B₆ is required for several reactions involved in the metabolism of neurotransmitters, but there is little evidence at present that a deficiency can affect intelligence in humans. Although some studies from India suggest that vitamin B₆ deficiency can accompany general malnutrition, the close link between B₆ requirements and protein intake usually prevents B₆ from becoming severely limiting in general malnutrition (6).

There are now reports of toxic effects of B₆ after prolonged daily doses of several hundred mg (7). One has to take account of the risk/benefit ratio, when vitamins above the normal dietary range are consumed.

**Dr. Durie:** Could you provide the evidence for malabsorption of fat and fat-soluble vitamins in malnutrition?

**Dr. Bates:** Except for vitamin A (8), uncomplicated protein-energy malnutrition (PEM) may well have little effect on fat-soluble vitamin absorption. Substances like carotenoids seem to be better absorbed and utilized if they are eaten with fatty foods. Diarrheal disease and other intestinal malfunction reduce absorption of fat-soluble vitamins, so that one may encounter a vicious circle in malnourished subjects with intestinal malfunction, especially in relation to vitamin A deficiency (2,9). There is need for further studies of these interactions.

**Dr. Guesry:** The Japanese report breast-fed babies' experiencing vitamin K deficiency and bleeding, even when the mother is well-nourished. Do you know anything about the relationship between the nutritional status of the mother, especially vitamin status, and the quantity of vitamin K in human milk?

**Dr. Bates:** It is paradoxical, but even in well-nourished communities, there is a proportion of newborns who have too little vitamin K for normal hemostasis, leading to intracranial bleeding and other problems during the first weeks of life (10). I know of no evidence that suggests much difference between well-nourished and malnourished populations.

The small amount of vitamin K normally found in human milk can be increased considerably by high-dose supplementation. The practice of supplementing all newborn babies, although only a small percentage need it, has greatly reduced the problem (11). However, having to intervene in an entire population is not an entirely satisfactory solution.

**Dr. Warrier:** Regarding infection as the possible starting point for most malnutrition, could you comment on the role of vitamin A and mucosal immunity in PEM?
Dr. Bates: Obviously, vitamin A has a very important role for epithelial surfaces in general, but there are effects on cell-mediated immunity as well.

Dr. Tanner: We have found that in malnourished rats with mucosal hypoplasia, the gut functioned normally with respect to absorption and recovered from an acute chemical insult exactly the same as the normally fed rats (12). Also, in the United Kingdom, we see vitamin D deficiency, not in the schoolchild, but in the toddler and in the adolescent. Except for preterm babies, the child with vitamin E deficiency, whether due to abetalipoproteinemia or prolonged cholestasis, presents with neurologic problems in later childhood.

Regarding vitamin A and collagen, it is known that in gross excess, vitamin A causes hepatic fibrosis. Vitamin A is, of course, stored in the Ito cell, which in situations of vitamin A excess, can secrete collagen and indeed become a fibroblast. Is it possible that in a situation of malnutrition in which the synthesis of retinol-binding protein is impaired, a more modest vitamin A excess might cause hepatic fibrosis?

Dr. Bates: One of the responses that a cell may make to damage or to metabolic insult is to become fibrotic, and this could theoretically happen in situations of periodic vitamin A dosing, although I do not know of any specific evidence for it. I doubt whether the impairment of retinol-binding-protein synthesis alone would produce such an effect, because in that case, vitamin A would presumably remain in the esterified form in the liver cells instead of being liberated into the circulation. I believe that the danger of toxicity arises mainly when vitamin A, and especially vitamin A as free retinol, is present in the lipid fraction of the blood instead of being transported as the complex with retinol-binding protein (RBP) (13). RBP is not, as far as I know, of particular importance in protecting liver cells against vitamin A overload, although there is one report of hepatotoxicity associated with liver accumulation of vitamin A in a protein-deficient subject (14). There are, however, gaps in our knowledge about the effects of malnutrition on the transport of vitamin A between different hepatic cells.

I agree that my description for the age distribution of fat-soluble vitamin deficiency states was somewhat simplified, and there are exceptions.

Dr. M. Mehta: I should like to question the supplementation of vitamin K for all newborns, and add that administering vitamin K to pregnant women has no effect on the potential of hemorrhagic disease in the baby.

Dr. Bates: In the United Kingdom, nearly all newborn babies receive vitamin K prophylactically, although only a small proportion would otherwise suffer from hemorrhagic disease. The potential is greater, of course, for premature infants, because transfer of vitamin K to the fetus occurs most rapidly at the end of gestation (15). Supplementation of the mother during pregnancy does not seem to be at all effective.

Dr. Truswell: Several studies show that vitamin A absorption in untreated PEM is impaired, although massive doses may produce some effect. Second, in attempting to determine vitamin E status, the plasma vitamin E level is measured. Since vitamin E is carried on low-density lipoproteins, and these lipoproteins are half-normal, it appears vitamin E is also deficient, although tissue levels may not be as low. I agree that we need a systematic reevaluation of these laboratory assessments. As another example, I understand that the amino transferase test for vitamin B₆ is not specific, and a better test would be to use plasma pyridoxal 5' phosphate or free pyridoxal. Another test that needs replacing is the one for niacin, where either measuring metabolites in the urine, which depends on the methylation process, or looking at tryptophan levels in the plasma is very difficult to interpret (16). To determine niacin activity accurately, a good test, like that used to determine thiamine status, the red blood cell (RBC) transketolase, and thiamine pyrophosphate (TPP) effect, is needed.
Dr. Suroto: We have studied 4,000 mothers from gestation through the first month after delivery. We found a positive correlation between arm circumference and low birth weight. We found no hemorrhagic disease in the newborns, even though there was no intervention. The nonexistence of hemorrhagic disease could be because 95% of our babies were breast-fed.

Dr. Haschke: Kries et al. (17) indicated that pharmacologic doses of vitamin K, between 0.5 and 3 mg of oral vitamin K\textsubscript{1}, produced substantial rises in breast milk vitamin K\textsubscript{1} with peak levels between 12 and 24 hr. Preliminary data from our study showed that daily vitamin K\textsubscript{1} supplements in the range of the recommended dietary intakes (RDI) of vitamin K did not influence vitamin K\textsubscript{1} concentrations in breast milk at 1 and 3 months of lactation (18).

Dr. Suskind: Our studies in Thailand found that vitamin E was not an important factor in the development of the anemia of PEM. In addition, we found that the production of vitamin-K-dependent coagulation factors was also dependent on protein intake. There are also several questions regarding vitamin D metabolism in PEM. If one were to postulate that PEM has a significant effect on liver and renal function, one might anticipate that there might be an effect of PEM on the hydroxylation of vitamin D, both in the liver and in the kidney. This is an area open for development, especially in reference to the population that consumes vitamins and minerals in amounts far above and below the RDA.

Dr. Bates: There are several potentially sensitive steps in the hydroxylation of vitamin D, such as the cytochrome P-450-dependent hydroxylation pathway (19). Dr. Truswell, could you comment on this?

Dr. Truswell: 25-Hydroxylation of vitamin D is little impaired in adults with alcoholic fatty liver, but I have not been able to track down a systematic study of vitamin D metabolism in PEM (20).

Dr. Soriano: In the Brazilian study (21), they determined 25-hydroxy-vitamin D\textsubscript{3} levels in malnourished children and found no abnormalities when there was exposure to sunlight.

REFERENCES