Evolution of Scientific and Popular Ideas on the Nutritional Role of Vitamins and Minerals

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Nutrition is the science of food and its relation to health. Its evolution began even before the dawn of scientific medicine (1). In the 4th century BC, Hippocrates concluded that food provided heat and energy. In the 16th century AD, by weighing himself throughout the day, Sanctorius became aware that body substance decreased during fasting and was restored by food. It is clear from the subsequent history of nutrition that the roots of nutritional science are embedded in both medicine and chemistry and are still unfolding. It is also clear that nutrition science is a field and not a discipline, to which many scientists and physicians have made important contributions (2). I shall review some of these contributions in the sections that follow.

EARLY HISTORY OF NUTRITION KNOWLEDGE

Popular ideas about vitamins and minerals followed the scientific discoveries that disputed the prevalent view in the 19th century that all diseases were caused by harmful agents, i.e., bacteria, poisons, and trauma. Deficiency diseases were not recognized as entities until the latter half of the 19th century despite the earlier knowledge that both lack of oxygen (anoxia) and lack of food (starvation) could cause disease. When it became clear from scientific discoveries that not only food as a whole but also specific components of food—such as vitamins and minerals—could prevent and even cure deficiency diseases, it seemed to many that vitamin and mineral supplements could be a panacea for numerous health problems. To some, these discoveries provided new hope beyond the scientific facts for a new era of health. It seemed to them that the road to Shangri-La and even to the Fountain of Youth was paved with vitamins (3).

First I would like to review the role of physicians and chemists in the early discoveries of nutrition science.
The Role of Physicians

It was recognized by Hippocrates that food was a source of body energy and heat. In his mini-textbook of medicine, Hippocrates gives 25 injunctions about diet and nutrition that reflect in many ways the dietary guidelines that are in place today. Twelve of them are presented in Table 1 (4).

The classical vitamin deficiency diseases in man, namely, scurvy, rickets, pellagra, beriberi and xerophthalmia, were all described first by physicians as diseases of unknown etiology. Scurvy was observed during the crusades and on voyages to the New World. The recovery of British sailors from scurvy upon reaching tropical ports led to the view that the cure was dietary, possibly due to a lack of a component in citrus fruits. In 1747, James Lind, a British naval medical officer aboard the frigate Salisbury, carried out the first controlled clinical investigation in which he showed that citrus fruit could cure scurvy whereas other supplements could not (5). In 1907, scurvy was induced experimentally in guinea pigs by Holst and Frolich, but vitamin C was not isolated until 1920, independently by Albert Szent-Gyorgyi in Hungary and Charles Glenn King in the United States.

Beriberi was described in Oriental medical writings about the time of Christ. A Dutch physician reported the disease in persons in Java (Indonesia) in 1642, and in 1890 the Dutch government, alarmed by the prevalence of the disease in its Far East

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**TABLE 1. Aphorisms of Hippocrates relevant to nutrition**

1. A slender and restricted diet is generally more dangerous than one a little more liberal.
2. A diet brought to the extreme point of attenuation is dangerous; and repletion, when in the extreme, is also dangerous.
3. Old persons endure fasting most easily; next, adults; young persons not nearly so well; and most especially infants, and of them such as are of a particularly lively spirit.
4. Growing bodies have the most innate heat; they therefore require the most food, for otherwise their bodies are wasted. In old persons the heat is feeble, and therefore they require little fuel, as it were, to the flame, for it would be extinguished by much.
5. Neither repletion, nor fasting, nor anything else, is good when more than natural.
6. Diseases which arise from repletion are cured by depletion; and those that arise from depletion are cured by repletion.
7. We must consider, also, in which cases food is to be given once or twice a day, and in greater or smaller quantities, and at intervals. Something must be conceded to habit, to season, to country, and to age.
8. When more food than is proper has been taken, it occasions disease; this is shown by the treatment.
9. Old people, on the whole, have fewer complaints than young; but those chronic diseases which do befall them generally never leave them.
10. Persons who are naturally very fat are apt to die earlier than those who are slender.
11. Persons in good health quickly lose their strength by taking purgative medicines, or using bad food.
12. Those bodies which have been slowly emaciated should be slowly recruited; and those which have been quickly emaciated should be quickly recruited.
colony, dispatched a commission from Holland to Java, headed by Christian Eijkman MD. Eijkman not only described beriberi in great detail but also demonstrated in chickens that polished rice produced a polyneuritis that resembled beriberi and that rice bran would cure the disease in both chickens and humans.

Rickets was first described by Frances Glisson, an English physician in London, in 1650, and cod liver oil was used empirically by John Darby at the Manchester Infirmary in 1789. Pellagra was first described by Gaspar Casal, physician to Phillip V of Spain, in 1735, and xerophthalmia by David Livingstone, a Scottish medical missionary in Africa in 1850. Experimental models for these diseases were developed many decades later.

The Role of Chemists

In parallel with these developments, during the 18th century Lavoisier and Laplace (6) showed that animal respiration was a chemical process that resulted in the consumption of oxygen and the production of carbon dioxide. These discoveries laid the foundation for the measurement of energy requirements and the determination of the energy value of foods. Direct calorimetry was pioneered by Liebig in 1824 and in turn his students (Voit, Atwater, and Benedict) applied these principles of direct calorimetry to measure the energy content of individual foods and the energy exchange in whole animals including humans (1). In fact, Lavoisier was the progenitor of many generations of nutrition scientists who extended his discoveries about energy exchange to all aspects of biochemistry and nutrition, as shown in Fig. 1.

Because of the dominance of Pasteur and the bacteriologists in the 19th century, it was difficult for early investigators of deficiency diseases to draw the conclusion that they had discovered a disease caused by lack of a protective chemical rather that the presence of a toxic chemical. Nonetheless, it was Frederick Hopkins at the University of Cambridge in England who, in 1906, first demonstrated a deficiency disease in animals (7). He purified all the macronutrients of milk—butterfat, casein, lactose, and the ash—and showed that weanling rats could not grow on such a ration. When a small supplement of whole milk, equivalent to less than 3% of energy intake, was added to such purified diets, the rats grew at a miraculous rate, as shown in Fig. 2. He concluded that “no animal can live upon a mixture of pure protein, fat and carbohydrate and even when the necessary inorganic material is carefully supplied the animal cannot flourish. The animal body is adjusted to live either upon plant tissues or tissues of other animals, and these tissues contain countless substances other than protein, carbohydrate and fat.” He called the factors active in promoting growth from milk “accessory food factors.” In 1912, Casimir Funk at the Lister Institute in London, who isolated nicotinic acid when he was looking for thiamine, coined the term vitamine—life giving amines—for these accessory food factors.

After Hopkins, biochemists in many parts of the world were able, in a space of
FIG. 1. The main line of the scientific progeny of Lavoisier included Berthollet, Gay-Lussac, and Leibig. Leibig had many students, the most notable of whom were Wohler (why synthesized urea), Voit (who investigated energy expenditure), and Kekule (who proposed the correct structure for benzene). Each of these three sublines of scholars produced outstanding nutritionists as well as enzymologists. Warburg was the mentor for Theorell, Krebs, and Meyerhoff. All of the more recent scientific giants had, in turn, many students. The figure illustrates the importance of scientific environment in shaping the talents of students (2).

25 years, to identify, isolate, characterize, and for the most part, synthesize the 13 vitamins we recognize today as essential for humans. This was the time when nutrition science was the principal concern of biochemists. By developing methods of isolating these trace organic compounds and testing them in deficiency microorganisms or animals for biological activity, they made rapid progress in characterizing the vitamins.

FIG. 2. Growth of weanling rats on various diets. The lower curve (up to 18th day) shows growth of eight rats on purified diet. Upper curve shows growth in eight rats on purified diet taking 3 ml of milk per day. On the 18th day, marked by vertical dotted line, the milk supplement was transferred from one set of rats to the other. Weight in grams is shown in ordinate; time in days on the abscissa (7).
The Advent of Enzymology

The advent of enzymology hastened understanding of the function of vitamins and trace minerals. Enzymology became an integral part of biology in 1835 with the discoveries of the Swedish chemist Berzelius, who recognized that a number of biological extracts including saliva, gastric juice, and malt extract could break down carbohydrates and proteins to their component parts (8). Berzelius further suggested that far from being a vital force, these substances might be catalysts for the digestion of macronutrients. By 1874 it was recognized by Kuhne that these ferments—which he called enzymes—could direct chemical reactions along particular paths and hence accelerate reaction rates. Although it was discovered that heating the biological extracts would destroy enzyme activity, the conclusion that the enzymes were in fact proteins was not accepted until Sumner isolated urease from jack beans in 1926 and showed that it was a crystalline protein (9). Since then, hundreds of enzymes have been isolated and many crystallized. Each enzyme proved to be a distinct and unique protein.

In 1932 Warburg and Christian identified the vitamin riboflavin as part of the coenzyme flavin mononucleotide, which in turn was required for the activity of the enzyme glucose-6-phosphate dehydrogenase (10). This discovery created a new linkage between nutrition and enzymology, and led to the identification of all the vitamins of the B complex as precursors of coenzymes in animal and plant tissues. In contrast, the fat-soluble vitamins were identified as catalysts for synthesis or modification of proteins in highly differentiated organisms (11). The development of enzymology in the first half of this century gave a great impetus to nutrition science as investigators began to study enzyme activity as a function of nutritional status.

It became obvious from these studies that not only do vitamins play a role in controlling enzyme activity, but the trace minerals do also. Iron, zinc, copper, manganese, molybdenum, and selenium were soon found to be required for the biological activity of selected proteins (12). Iodine was found to be a component of thyroxin. Iron was shown to be an essential component of hemoglobin, myoglobin, and a variety of cytochromes. Zinc was found to be a component of many dehydrogenases, carbonic anhydrase, and an array of digestive enzymes. Copper is a component of cytochrome oxidase, lysyl oxidase, ceruloplasmin, superoxide dismutase, tyrosinase, and dopamine-β-hydroxylase. Selenium was found to be an intrinsic part of the enzymes glutathione peroxidase, glycine reductase, and formate dehydrogenase.

MOLECULAR BIOLOGY AND ITS IMPACT ON NUTRITIONAL SCIENCE

At the present time molecular biologists dominate the field of biochemistry and are providing new technologies for application of molecular biology to nutrition science. Beginning with the discovery of the structure of DNA by Watson and Crick in 1953 (13) and the elucidation of the genetic code, advances in our understanding of gene structure and regulation of gene expression have led to an explosion of new
knowledge about biochemical genetics. Through the use of restriction enzymes discovered by Nathans and Smith at Johns Hopkins University (14), it has been possible to introduce genetic material into plasmids of bacteria, which amplify the gene number and make possible the production of novel mammalian products in bacterial systems such as hormones, cytokines, and coagulation proteins. Cloning genes has now become a routine procedure in biochemical laboratories. This new knowledge has already produced many spectacular results and led to the hope that genetic engineering can be applied to human subjects to correct genetic disorders.

It is clear that the application of molecular biology to nutritional problems will cast new light on the function of nutrients and the regulation of metabolism. Molecular biology already has made important contributions to nutrition science. For example, it was shown by Goodridge (15) that nutrients in the diet can affect the gene expression of a series of enzymes concerned with fatty acid synthesis and oxidation. The pathway from nutrient to genome is not clear, but it is now certain that many nutrients can affect gene expression. This is well illustrated by the recent finding that the receptors for active vitamin A (retinoic acid) (16) and active vitamin D (1,25-dihydroxycholecalciferol) (17) belong to the superfamily of steroid and thyroid hormone receptors that interact directly with the genome to affect gene expression (18). The structures of these two receptors plus those for glucocorticoids and the thyroid hormones are shown in Fig. 3.

**FIG. 3.** Structures of human genomic receptors for glucocorticoids (hGR), retinoic acid (hRR), thyroid hormones (hT₃R₈), and 1,25(OH)_2 vitamin D₃ (hvDR). The amino acid content of each receptor is shown by numbers at the right of each bar. The receptors are aligned to show the constances of the highly conserved DNA binding domain. The enhancer domain which provides immunologic specific and maximum activity, is at the N-terminal portion of the receptor and is highly variable. The hormone or vitamin binding domain averages about 250 amino acids in length and is at the C-terminal end of the receptor. When the hormone or vitamin combines with the receptor it alters its conformation, promotes DNA binding, and affects gene expression (18).
VITAMINS AND MINERALS IN MEDICINE

Vitamin and trace mineral preparations are used extensively in the practice of medicine and are valuable when used properly (19). It is important that a clear distinction be made between vitamins and/or minerals as dietary supplements and as therapeutic agents. A vitamin and/or mineral supplement is defined as one containing 50% to 150% of the Recommended Dietary Allowance (RDA) whereas therapeutic preparations contain 5 to 10 times the RDA. It is also important for the practitioner to understand the usefulness and the limitations of given nutrient preparations in given clinical situations.

Vitamins are essential organic substances, the usual source of which is food. They are required by man in amounts ranging from micrograms to milligrams per day. There are four fat-soluble vitamins (A, D, E, and K) and nine water-soluble vitamins (thiamine, riboflavin, niacin, pantothenic acid, folic acid, biotin, and vitamins B-6, B-12, and C). All are essential for the normal growth, development, and maintenance of the human organism. The trace minerals are essential inorganic substances that are required by man in amounts that also range from micrograms to milligrams per day. They include iron, zinc, copper, manganese, fluoride, chromium, molybdenum, selenium, and iodine.

Vitamins and Minerals as Dietary Supplements

Healthy adult men and healthy adult nonpregnant, nonlactating women consuming a usual varied diet do not need vitamin or mineral supplements. This assumes that foods are derived from a variety of sources—dairy foods, meats and/or legumes, cereals and bread, and fruits and vegetables. Infants may need dietary supplements at given times, as may pregnant and lactating women. Occasionally, vitamin supplements may be useful for people with unusual life-styles or modified diets, including certain weight reduction regimens and strict vegetarians diets—i.e., one that excludes all foods of animal origin.

Infants and Children

The normal breast-fed infant of a well nourished mother receives sufficient quantities of all vitamins except vitamins K and D. Concerning vitamin K, newborns have sterile intestines, and cannot initially synthesize menaquinones. Because human milk contains only 1–2 μg/liter of phyloquinone, as compared to 10–15 μg/liter in cow’s milk—which meets the estimated daily allowances (20)—it is recommended that all newborns receive a single intramuscular dose of 0.5 to 1.0 mg of phyloquinone as prophylaxis against hemorrhagic disease of the newborn (21). Low birthweight infants may require a second injection at about one week of age. Because the vitamin D content of human milk is extremely low (about 22 IU/liter), breast-fed infants may
need supplemental vitamin D (400 IU/d) if they have limited exposure to sunlight. Breast-fed infants whose mothers are strict vegetarians require supplemental vitamin B-12, and infants on cows’ milk formulas require iron supplementation for the first three months (22).

Adults

Healthy nonsmoking, nonalcoholic adults receiving adequate diets should have no need for supplementary vitamins or minerals. In some instances, however, poverty may limit the amount and quality of foods consumed, which may necessitate supplemental vitamins. In young women, excessive menstruation may require iron supplementation. Before deciding whether a vitamin supplement should be recommended to an adult, however, a history regarding the adequacy of dietary intake, usual dietary practices, and specific issues of life-style—such as the extent of smoking and drinking—and life situation must be carefully evaluated. If the individual appears not to be meeting his or her recommended intake of vitamins and minerals in the diet, an attempt to correct the situation by improving the selection of foods and the pattern of eating should be made before recommending a supplement.

As regards the elderly, neither the Food and Nutrition Board of the National Academy of Sciences/National Research Council (20) nor the World Health Organization recognizes any need for increasing the vitamin and mineral allowances for healthy elderly individuals above those recommended for healthy young adults. In fact, the Food and Nutrition Board recommends a slightly decreased daily allowance for men over the age of 51 years for niacin, riboflavin, and thiamine. This reduction is related to an overall decrease in energy exchange by the elderly.

Although requirements for vitamins are not increased by age, socioeconomic conditions, reduced physical activity, and illness among the elderly may lead to a curtailment in total food intake. Under such restrictive conditions (19), the use of a vitamin preparation in the prevention of deficiency may be indicated. When such is the case, the doses of vitamins (50% to 150% of the US RDA) recommended elsewhere in this report as effective in the prevention and treatment of specific deficiency states or multiple deficiency states in most adults are adequate for use in the elderly population (19).

A specific instance in which supplemental vitamins and minerals are very often indicated is for the pregnant or lactating woman (24). The physiologic need for vitamins during pregnancy is increased over usual requirements. Even though appetite and dietary recommendations for pregnant and lactating women encourage a greater intake of food, the recommended increases in vitamin intake above basal requirements may not be achieved. For this reason, vitamin and mineral supplements—particularly calcium, iron, and folic acid—are often prescribed for pregnant and lactating women. Surveys among less privileged segments of the US population reveal larger deficits in vitamin intakes relative to requirements during pregnancy and lactation (19,20,24).
Vegetarians

Vegetarianism has provoked concern among nutritionists about vitamin adequacy, particularly for strict vegetarian diets that exclude all foods of animal origin and may result in deficiencies of vitamins B-12, D, and riboflavin (25). Intake of these vitamins will be adequate if appropriately fortified soy formula or fortified soybean milk drink is used. Inadequate intake is not a problem for persons who consume lactovegetarian diets, which include milk or milk products, or lacto-ovo-vegetarian diets, which include dairy products and eggs.

Weight Reduction

Certain weight reduction diets may lead to inadequate vitamin intakes. Even with a sound approach to slimming, it may be difficult to meet recommended vitamin intakes at an energy level of 800 to 1,000 kcal/d (3360 to 4200 kJ/d), and hence a modest supplement may be recommended. The addition of a supplemental vitamin preparation to a very low energy weight reduction program, however, will not necessarily make the diet safe. Crash diets supplying 400–800 kcal/d have been found to be useless for achieving a sustained weight loss. The overall metabolic status of persons consuming a low energy diet should be periodically evaluated by a physician.

Behavioral Disorders

Emotional disturbances can also alter dietary patterns and energy intake. Depression is associated with a variety of eating disturbances. Patients with anorexia nervosa and the binge-purge syndrome (bulimia) usually have very low net energy intakes. Vitamin intakes may be insufficient, but, once again, the clinical situation requires a more comprehensive analysis and solution than the addition of a vitamin supplement to an insufficient diet.

Vitamins and Minerals as Therapeutic Agents

Vitamins in therapeutic amounts are indicated only for the treatment of deficiency states or pathologic conditions in which absorption and utilization of vitamins are reduced or requirements increased, and for vitamin-dependent genetic diseases that require larger doses of vitamins to attain physiological adequacy (19). The dosage range is 5 to 10 times the dose required for the prevention of deficiency diseases indicated in Table 2. The decision to employ vitamin preparations in therapeutic amounts clearly rests with the physician, and the importance of medical supervision when such amounts are given is emphasized. Therapeutic vitamin mixtures should be so labeled and should not be used as dietary supplements. The quantities of vitamins included in mixtures intended for therapeutic use should not exceed ten
times the US RDA, depending on the vitamin. Trace mineral supplements should be used in therapeutic doses only to treat bona fide deficiencies (e.g., iron, copper, and zinc).

**Misuse of Vitamins and Minerals**

The FDA has estimated that 40% of the adult population in the USA use vitamin and mineral supplements on a daily basis. Ascorbic acid (vitamin C), either alone or in combination with other nutrients, was the most widely consumed nutrient (90.6%) among supplement users. Even among 2,000 registered nurses surveyed, 38% were taking multiple vitamin supplements daily; 23% were using high dosages of ascorbic acid, the most common being 500 mg daily; 15% took 400 IU of vitamin E daily; and 4% took 10,000 IU of vitamin A daily (26).

With such widespread use of vitamins by the American public, there is ample opportunity for misuse. Misuse of vitamins is considered to be the ingestion of a vitamin in a dose that is inappropriate or for a purpose that has no basis in established scientific practice. The rationales of users are often based on myths, beliefs, or distortions of experimental studies in laboratory animals. Some vitamins, such as A, D, E, C, and B-6, are abused more commonly than others. Some persons have taken large doses of multivitamins in the belief that vitamins combat the chronic
degenerative diseases or extend life. No objective benefits, however, have been demonstrated (27).

Some of the most frequently encountered examples of vitamin misuse include the following: vitamin E has been taken in large quantities in pursuit of rejuvenation, increased libido, and improved sexual performance; under the rubric of "orthomolecular psychiatry," large doses of niacin have been given for the treatment of a variety of mental disorders without measurable effect (27). Furthermore, at high doses (> 2,000 mg/d) niacin is frequently a hepatotoxin. Large doses of vitamin B-6 have been promoted for the treatment of carpal tunnel syndrome, premenstrual tension, and mental disorders, without established benefit. In fact, a serious toxic effect of vitamin B-6 when given in doses of 1–2 g/day is a sensory ataxia which results from the destruction of dorsal roots in the spinal cord (28), and ascorbic acid remains one of the most widely misused vitamins; there is still no reliable evidence that large doses of ascorbic acid prevent colds or cancer.

Several vitamins have been heralded as anticancer agents, supposedly preventing the development of many types of malignancies. Although epidemiological studies have suggested that certain types of cancer are associated with a low intake of yellow and green vegetables and low plasma vitamin A and carotene levels (29), there is no evidence yet that taking large doses of vitamin A or carotene will prevent cancer in man. Vitamins with antioxidant properties, such as ascorbic acid and vitamin E are recommended in studies to prevent cancer, but no results are yet available (29). Moreover, two randomized double-blind trials demonstrated the failure of large doses of ascorbic acid to alter the death rate in patients with terminal cancer (30).

Other substances claimed to be vitamins have been misused for both their supposed nutrient effects and therapeutic effects. No essential nutrient function has been reported for laetrile (wrongly referred to as vitamin B-17), pangamic acid (wrongly referred to as vitamin B-15), or the bioflavinoids, rutin and hesperidin (the so-called vitamin P factors). No evidence has been presented indicating that these substances are effective for any disorder (27). Choline, inositol, and p-aminobenzoic acid have been listed as vitamins for some species in the past. They are not required by man and have no established vitamin function in man although they are nutrients and can be metabolized in the human body. Toxicity can result from megadoses of vitamins, as discussed below.

Toxicity of the Fat-Soluble Vitamins

As a general rule, when ingested in excess, fat-soluble vitamins tend to cause toxic reactions at lower multiples of the RDA than do water-soluble vitamins. This is because fat-soluble vitamins tend to be stored in the body rather than excreted. Some fat-soluble vitamins in molar excess of the concentration of their carrier proteins are taken up by membranes, with pathologic results (31). The ratios of safe doses of vitamins to the Recommended Dietary Allowance are shown in Table 3.

The prolonged used of vitamin A in excessive doses can cause a variety of
symptoms, including dry, coarse, scaly skin; angular stomatitis; pain and tenderness of the bone; hyperostosis; hypercalcemia; disease syndrome of pseudotumor cerebri, which may produce increased intracranial pressure with headache, papilledema, and diplopia; hepatosplenomegaly; and disturbed blood clotting with hemorrhage (24). In children, anorexia, pruritus, and failure to gain weight are followed by irritability, bone pain, and the limitation of joint motion. Large daily doses of vitamin A (> 50,000 IU) and its derivatives, furthermore, are teratogenic (32).

Vitamin D is the most likely of all vitamins to cause overt toxic reactions in small multiples of the US RDA (24,31). An epidemic of “idiopathic hypercalcemia” in infants, with anorexia, vomiting, hypertension, renal insufficiency, and failure to thrive, occurred in England in the 1950s. It was traced to an intake of vitamin D between 2,000 and 3,000 IU/d (31). In adults, dosages of 10,000 IU/d for several months have resulted in marked disturbances in calcium metabolism with hypercalcemia, hyperphosphatemia, hypertension, anorexia, nausea, vomiting, weakness, polyuria, polydypsia, azotemia, nephrolithiasis, ectopic calcification, renal failure, and, in some cases, death.

Relatively large amounts of vitamin E—in the range of 400–800 IU/d—have been taken for months or years without causing any apparent harm. Occasionally, muscle weakness, fatigue, nausea, and diarrhea have been reported in persons taking 800–3,200 IU/d. The most significant toxic effect of vitamin E at dosages exceeding 1,000 IU/d is the antagonism to vitamin K action and the enhancement of the effect of oral coumarin anticoagulant drugs, with overt hemorrhage (19,24).

Toxicity of the Trace Minerals

As regards minerals, iron, copper, zinc, selenium, and iodine can also be toxic if taken in megadoses (24). Iron overload with hepatic toxicity can occur in persons heterozygous for the hemochromatosis gene, in chronic liver disease, and in other hereditary defects in iron absorption. The toxicity of zinc is principally due to its competition with copper for absorption. Hypocupremia induced by zinc therapy has been observed in adults receiving high doses of zinc for sickle cell anemia. These

### TABLE 3. Ratio of safe doses of vitamins to recommended dietary allowances (RDA)*

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<th>Vitamin</th>
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<tr>
<td>Thiamine</td>
<td>+ ++ +</td>
<td>Vitamin B-12</td>
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<td>Riboflavin</td>
<td>+ + + +</td>
<td>Vitamin C</td>
<td>+ +</td>
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<td>Pyridoxine</td>
<td>+ +</td>
<td>Vitamin A</td>
<td>+</td>
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<td>Niacin</td>
<td>+ + +</td>
<td>Vitamin D</td>
<td>+</td>
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<tr>
<td>Pantothenate</td>
<td>+ + + +</td>
<td>Vitamin E</td>
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<tr>
<td>Folate</td>
<td>+</td>
<td>Vitamin K</td>
<td>+ + + +</td>
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<tr>
<td>Biotin</td>
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* (+) up to ten times; (+ +) 11–50 times; (+ + +) 51–100 times; (+ + + +) ≥ 100 times
individuals receive as much as 220 mg zinc sulfate three times a day (equivalent to 150 mg elemental zinc/day), or ten times the RDA. Associated with the hypopoeumia was neutropenia and microcytic anemia, which are classical signs of copper deficiency. Copper at doses above 250 mg of copper sulfate is an emetic and also can cause liver disease. Selenium in doses of 2–5 mg/day can cause loss of hair and nails, as well as central nervous system symptoms.

FOOD FADDISM: A CAUSE FOR THE MISUSE OF VITAMINS AND MINERALS

Food faddism, despite its economic wastefulness, its unscientific approach to nutrition, and the harmfulness to its practitioners, persists and grows. This unfortunate activity is the result of a distortion of the emotional value of food and its symbolic value for health, cultural identification, and social acceptance in the minds of many consumers (33).

Food faddism is of two kinds: individual and collective. The former generally stems from acute or chronic psychological aberration, including psychosis. The latter comes about through acceptance of stereotyped dietary practices designed to improve health or cure disease. The latter may be cultural or may be stimulated for profit by a smooth-talking, pseudo-sophisticated, high-pressure salesman with a minimum of training in nutrition and a maximum of purported professional associations and degrees, most from unaccredited institutions. Much of the misuse of vitamins and minerals are promoted by health food hucksters and regrettable by some physicians.

EVOLUTION OF IDEAS ON THE USE OF VITAMINS AND MINERALS

The science of nutrition will continue to evolve as new discoveries are made in the 21st century. Most new knowledge will deal with the mode of activity of the fat-soluble vitamins and the trace minerals. New links will be forged between nutrition and genetics.

Whether new scientific advances will influence the beliefs of consumers about vitamins and minerals is questionable. Because the beliefs of cultists are rarely changed by facts, it is likely that the health food fallacies and the misuse of vitamins will continue.

Nonetheless, better programs of nutrition education aimed at both the consumer and the health practitioner are essential for the appreciation of new discoveries in nutrition science. Because it is unlikely that the clamor for the public's attention by unscrupulous vendors and quacks marketing fallacious nutritional panaceas will diminish in the 21st century, it is imperative that industry, government, and academia forge an alliance dedicated to telling the “truth about nutrition” and actually contesting illicit claims in the market place.
REFERENCES

IDEAS ON VITAMINS AND MINERALS

DISCUSSION

Dr. Walker: Your emphasis has been on the developed world, where taking too many vitamins may be a problem. In the developing world, the problem will continue to be to ensure that everyone gets a balanced diet with enough minerals and vitamins. Good planning will be essential.

Dr. Olson: During my work in northern Thailand we studied many children with protein-energy malnutrition. Some of these had specific vitamin deficiencies, the most common being xerophthalmia. A few had deficiencies of thiamine and riboflavin. Their diet at home was mainly rice with small amounts of other foods. They required a diet containing adequate protein and energy for nutritional rehabilitation. Even apparently healthy schoolchildren were stunted and vitamin supplements alone did not change their nutritional status. Although vitamins are of course essential, the main problem in this population is lack of macronutrients.

Dr. Vis: It is not justified to claim that in most situations the problem of malnutrition will be solved merely by increasing the food intake. One has to take into account the quality of the food. In black Africa malnutrition is usually the result of an insufficient intake of protein of good quality. The problem will not be solved by increasing the energy intake but only by changing the quality of the food. Vitamins and trace elements are very important in this context.

Dr. Olson: I agree. All essential nutrients are needed in a palatable diet.

Dr. Hulse: When making recommendations about daily nutrient requirements, should we not be sensitive to the implications for developing nations? In Canada we sometimes wonder whether recommendations for ascorbic acid made by our neighbor to the south may not in some degree be influenced by the size of the citrus crop.

Dr. Olson: Remember that the RDA are the amounts of essential nutrients that will supply the requirements of practically all healthy persons. Because requirements vary, the RDA is usually 2 SD above the mean requirement. The lower the percentage of the RDA taken by an individual the higher the probability that it will not be enough. In the case of vitamin C the experts in the United Kingdom set the RDA of 30 mg on the basis of the mean requirement to prevent scurvy, which is lower than the mean requirement to maintain a pool size of ascorbic acid of around 1,500 mg in the adult male. The 1985 RDA Committee in the USA recommended a reduction in the RDA for ascorbate from 60 mg to 40 mg for adult males, but this was rejected by the Food and Nutrition Board.

Dr. Grütte: Was Linus Pauling wrong to recommend megadoses of vitamin C?

Dr. Olson: Yes, I should say he was 100% wrong! A tremendous amount of research was generated by his assertions and none of his claims has been validated.

Dr. Mauron: Could there be a danger of habituation to megadoses of vitamins such that deficiency might occur if they were discontinued suddenly?

Dr. Olson: There are several case reports that megadoses—3–10 g of vitamin C—may cause an unusual dependency which can lead to scurvy when the dose is withdrawn. At these doses vitamin C is treated like a xenobiotic and the body oxidizes it. Because ascorbic acid is not normally oxidized in man, an intake of 60 mg per day will not be enough during the period of withdrawal from megadoses.

Dr. Walker: In relation to possible toxic effects of megadoses it is important to remember that vitamin A may have teratogenic effects. We need to be very careful of recommending supplementation, particularly with vitamin A, to pregnant women.

Dr. Olson: Women who become pregnant while on high doses of retinoic acid for acne are indeed at risk of teratogenic effects. Women contemplating pregnancy should not take megadoses of retinoic acid or derivatives.
Dr. Harper: One must be careful about maintaining a scientific attitude on this subject. It is possible that megadoses of nutrients may exert a pharmacological effect, so claims should always be tested. It takes time and money to resolve these matters but it is important to have scientific evidence to separate myth from reality.

Dr. Olson: All legitimate scientifically rational claims for the actions of nutrients at high doses should be investigated. An example of dietary pharmacology is the case of linoleic acid which will supply the EFA requirement at 1.5% of energy intake, while at 10% of energy intake it becomes effective at lowering LDL-cholesterol.

Dr. Richardson: What do you think of the current interest both in scientific circles and in the popular press about the use of pro-vitamins such as β-carotene to scavenge free radicals?

Dr. Olson: Carotene as a radical scavenger—singlet O₂—acts at very low oxygen tensions and probably accounts for a small percentage of the body’s total antioxidant potential. Because antioxidants may prevent DNA damage, carotene is being studied as a chemopreventive agent against cancer. Sir Richard Doll did a study in Brazil to determine cancer incidence in a population eating large amounts of palm oil rich in β-carotene compared to another population of a low carotene diet, but there was no difference in the cancer incidence. Other studies are in progress.

Dr. Schiffman: I am concerned that we should not assign a negative value to supplementation. Primitive man appears to have eaten more vitamin C and calcium than modern man. Perhaps supplementation with these nutrients has a positive value for substantial numbers of people in the developed world.

Dr. Olson: Eaton and Konner calculated that Paleolithic man consumed around 400 mg of vitamin C and 1500 g of calcium daily (1). These amounts are clearly within the range of current intakes in the USA. There is a rationale for fortifying the diet of women with calcium up to 2 g per day to increase bone salt density.

REFERENCE