The Historical Evolution of Thought Regarding Multiple Micronutrient Nutrition1–3

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Abstract

Multiple micronutrient nutrition is an idea that originated in the 1940s and exemplifies the iterative nutritional paradigm. In the first four decades of the 20th century, scientists sought to separate and characterize the vitamins that were responsible for xerophthalmia, rickets, pellagra, scurvy, and beriberi. The dietary requirements of the different micronutrients began to be established in the early 1940s. Surveys showed that multiple micronutrient deficiencies were widespread in industrialized countries, and the problem was addressed by use of cod-liver oil, iodized salt, fortified margarine, and flour fortified with multiple micronutrients, and, with rising living standards, the increased availability and consumption of animal source foods. After World War II, surveys showed that multiple micronutrient deficiencies were widespread in developing countries. Approaches to the elimination of multiple micronutrient deficiencies include periodic vitamin A supplementation, iodized salt, targeted iron/folate supplementation, fortified flour, other fortified foods, home fortification with micronutrient powders, and homestead food production. The prevention of multiple micronutrient malnutrition is a key factor in achieving the Millennium Development Goals, given the important effects of micronutrients on health and survival. J. Nutr. 142: 143S–156S, 2012.

Introduction

Although the concept of multiple micronutrient nutrition originated nearly 70 y ago, the idea has received a great deal of attention recently, perhaps owing to a desire to balance what some might view as an excessive emphasis on single micronutrients in the more recent past. For many working in public health nutrition today, it may seem that such thought accelerated rather quickly in the last decade and that a new paradigm suddenly emerged. However, as scientific understanding matured through the 20th century, thinking evolved in an earlier phase toward this broader, encompassing view of multiple micronutrient nutrition. There has been a cyclical nature in the way we have approached certain nutritional problems over time. In the first cycle, we identified and largely solved multiple micronutrient malnutrition in industrialized countries in the mid-20th century. With the recognition of the large disparities in health and resources between industrialized countries and the developing world, attention turned to the problems of developing countries, including reducing mortality, improving health, and, among other challenges, eradicating micronutrient malnutrition. The developing world became the second cycle. In this synthesis, I refer to this cyclical model of thinking as the iterative nutritional paradigm.

The purpose of this article is to provide a brief historical overview of major ideas and events that shaped the evolution of thinking toward multiple micronutrient nutrition from the end of the 19th century to the present day. From a historical standpoint, “micronutrient” is a relatively recent term. It appeared in the 1930s in reference to certain factors that are found in minute amounts and support the growth of plants (1). In the field of plant physiology, micronutrients were originally applied to trace elements, but by the 1950s, micronutrients began to appear in human nutritional textbooks as a term synonymous with essential nutrients, such as trace elements and vitamins (2).

1 Published in a supplement to The Journal of Nutrition. Presented at the workshop “Multiple Micronutrient Nutrition: Evidence from History to Science to Effective Programs,” held at the 2nd World Congress of Public Health Nutrition in Porto, Portugal, September 23–25, 2010. The supplement coordinators were Klaus Kraemer, Sight and Life, Basel, Switzerland and Richard D. Semba, Johns Hopkins University School of Medicine, Baltimore, Maryland. Supplement coordinator disclosures: Klaus Kraemer is employed by Sight and Life, a humanitarian initiative of DSM Nutritional Products Ltd., Basel, Switzerland. Richard D. Semba has no conflicts of interest. The Acting Editor-in-Chief disclosure: Jesse Gregory. Acting Editor-in-Chief disclosure: Jesse Gregory has no conflicts of interest. The supplement is the responsibility of the Guest Editor to whom the Editor of The Journal of Nutrition has delegated supervision of both technical conformity to the published regulations of The Journal of Nutrition and general oversight of the scientific merit of each article. The Guest Editor for the supplement was Marian Neuhouser. Guest Editor disclosure: Marian Neuhouser has no conflicts of interest. The workshop was supported by a grant from Sight and Life, Basel, Switzerland. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the organization of which the organizers are affiliated. Publication costs for this supplement were defrayed in part by the payment of page charges. This publication must hereby be marked “advertisement” in accordance with 18 USC section 1734 solely to indicate this fact. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors or the publisher, Editor, or Editorial Board of The Journal of Nutrition.

2 Author disclosure: R. D. Semba, no conflicts of interest.

3 Supported by a Lew R. Wasserman Merit Award from Research to Prevent Blindness.

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Manuscript received December 24, 2010. Initial review completed May 7, 2011. Revision accepted June 8, 2011.

First published online December 7, 2011; doi:10.3945/jn.110.137745.
State of Knowledge Regarding Micronutrients in the 19th Century

During the 19th century, it was established that trace elements such as iron, iodine, and zinc were important to health. Jean-Baptiste Boussingault (4) showed that iron was an essential nutrient for animals (3). Iron was used to treat anemia in young women. A lack of iodine in drinking water and food was linked to goiter and cretinism (5), and iodine was used to treat goiter (6). Iodine tablets were used to prevent goiter in school children in France (7). Jules Raulin showed that zinc was essential for growth of microorganisms (8). In the latter part of the 19th century, oral zinc was used to treat diarrheal disease in children (9–11).

Major deficiency diseases recognized at the time included scurvy, rickets, beriberi, and xerophthalmia. These diseases were empirically prevented or treated with certain types of foods: citrus fruit, potatoes, and vegetables for scurvy; cod-liver oil for rickets (12); meat, vegetables, and milk for beriberi (13); and cod-liver oil for xerophthalmia (14). The prevailing idea in nutrition was that the essential elements in foods consisted of protein, fats, carbohydrates, and minerals. Many leading scientists in nutrition, including Justus von Liebig at Giessen, Carl von Voit in Munich, Max Rubner in Berlin, and Russell Chittenden at Yale, were focused on proteins and energy. But suspicions were growing that there was something wrong with the ideas that held dominance in nutrition.

The Emergence of the Vitamins

In 1906, Frederick Gowland Hopkins of Cambridge University made a prophetic statement in an address to the Society of Public Analysts in London:

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 still cannot flourish. The animal body is adjusted to live either upon plant tissues or the tissues of other animals, and these contain countless substances other than the proteins, carbohydrates, and fats. Scurvy and rickets are conditions so severe that they force themselves upon our attention; but many other nutritive errors affect the health of individuals to a degree most important to themselves, and some of them depend upon unsuspected dietetic factors.

When Hopkins made his speech in London, he already had results that suggested the existence of certain unknown dietetic factors in milk that supported growth in mice. He finally published his work in 1912, calling these unsuspected substances "accessory factors" (16).

The challenge to scientists at the time was to identify the specific accessory factors and distinguish how these factors were related to health. Investigators attempted to separate and characterize the effects of single nutrients through controlled feeding experiments in animal models. Axel Holst and Theodor Frohlich (17) developed the guinea pig model for scurvy in 1907, representing a major step toward the understanding of vitamin C. In the Dutch East Indies, Christiaan Eijkman and Gerrit Grijns (18,19) studied beriberi by feeding chickens a diet of polished rice; the chickens developed polyneuritis, a neurological condition resembling human beriberi. For many vitamins, it took one or two decades of work to identify the accessory factors and distinguish how these factors were important to health.

### TABLE 1

Characterization of five major vitamins, 1880s to 1930s

<table>
<thead>
<tr>
<th>Vitamin A</th>
<th>Vitamin C</th>
<th>Vitamin D</th>
<th>Thiamin</th>
<th>Niacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syndrome</td>
<td>Night blindness</td>
<td>Corneal ulcers</td>
<td>Blindness</td>
<td>Immune suppression</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Vitamin A deficiency disorders</td>
<td>Scurvy</td>
<td>Rickets</td>
<td>Beriberi</td>
</tr>
<tr>
<td>Food sources</td>
<td>Liver, butter, cheese, egg yolk, dark green leafy vegetables, orange 1 and yellow fruit and vegetables</td>
<td>Citrus fruits, peppers, broccoli, spinach, potatoes</td>
<td>Oily fish, liver</td>
<td>Beans, peas, lentils, brown rice, wheat germ, pork</td>
</tr>
<tr>
<td>Empirical remedy</td>
<td>Cod-liver oil</td>
<td>Lemons</td>
<td>Cod-liver oil</td>
<td>Meat, milk</td>
</tr>
<tr>
<td>Animal model</td>
<td>Rats, mice</td>
<td>Guinea pig</td>
<td>Dog</td>
<td>Pigeon, chicken</td>
</tr>
<tr>
<td>Basic studies of deficiency effects in animals</td>
<td>1880s–1920s</td>
<td>1907–1920s</td>
<td>1918–1920s</td>
<td>1897–1920s</td>
</tr>
<tr>
<td>Vitamin isolated or crystallized</td>
<td>1937</td>
<td>1932</td>
<td>1931</td>
<td>1926</td>
</tr>
<tr>
<td>Chemical structure described</td>
<td>1931</td>
<td>1937</td>
<td>1936</td>
<td>1936</td>
</tr>
<tr>
<td>Synthesis of vitamin</td>
<td>1947</td>
<td>1937</td>
<td>1924</td>
<td>1936</td>
</tr>
</tbody>
</table>

1 Excluding fortified foods.
with experimental animal models to reach a fundamental understanding of the effects of single vitamin deficiencies. The term “vitamine” was introduced by Casimir Funk in 1912 for the substances of which a deficiency produced beriberi, scurvy, and pellagra (20).

In 1911 nicotinic acid was isolated by Funk (21), who initially thought it was the anti-beriberi vitamin. Nicotinic acid was synthesized from nicotine in the 1870s and its chemical formula was deduced (22). Pellagra was widespread in some communities in the southern U.S. and a major cause of death. Joseph Goldberger (23) of the U.S. Public Health Service conducted extensive epidemiological investigations and demonstrated that pellagra was associated with a poor diet and could be prevented by providing milk, eggs, fresh meat, beans, peas, and oatmeal in the diet.

In 1913, Elmer McCollum and Marguerite Davis at the University of Wisconsin and Thomas Osborne and Lafayette Mendel (24,25) at Yale showed that fats were not equivalent in supporting growth, because a fat-soluble factor in butter or egg yolk supported growth in rats whereas lard did not. The application of the alphabet to vitamins began in 1916, when McCollum (26) proposed abandoning the term “vitamine” in favor of using “water-soluble B” to an unknown substance that caused polyneuritis in pigeons, in contrast to “fat-soluble A” that supported growth in rats. It was not known at the time that fat-soluble A actually contained both vitamins A and D. In 1918, Edward Mellanby (27,28) at King’s College showed that lack of fat-soluble A or a substance “with a similar distribution” caused rickets in dogs.

The first expert group on vitamins, the Accessory Food Factors Committee, was established by the Medical Research Council in 1918. The Committee consisted of five nutritionists: Hopkins, Mellanby, Jack Drummond from University College, and Harriette Chick and Arthur Harden from the Lister Institute. The Committee stated: “It is now established that . . . certain unidentified principles, known as accessory food factors or ‘vitamines,’ must also be present in order to maintain health and prevent the occurrence of deficiency diseases” (29). The following year, Harry Steenbock (30) at the University of Wisconsin began a large series of investigations that showed that yellow and orange plant foods had the same biological effects as vitamin A in animal fats. Drummond (31) proposed using the term “vitamin” instead of “vitamine,” noting “the substances should be spoken of as vitamin A, B, C, etc. This simplified scheme should be quite sufficient until such time as the factors are isolated, and their true nature identified.” In 1922, McCollum (32) showed that cod-liver oil contained not only fat-soluble A but another substance that promoted bone growth. The substance was initially called the “anti-rachitic factor” or simply “X,” and it eventually became known as vitamin D (33). Steenbock (34) discovered that the vitamin D concentration of certain foods could be increased by irradiating the foods with UV light. In 1926, two Dutch chemists, Barend Jansen and Willem Donath (35), crystallized “water-soluble B” and identified it as thiamin. In Hungary, Albert Szent-Györgyi (36) isolated vitamin C from various plants and adrenal cortex in 1928. The League of Nations, an intergovernmental organization founded in the wake of World War I, sponsored the first International Conference on Vitamin Standards in London in 1931. The Committee was convened to develop standards and measurement units for “fat-soluble vitamin A, anti-rachitic vitamin D, antineuritic vitamin B, and antiscorbutic vitamin C.” Mellanby was chair of the Committee, which included Drummond, Chick, Steenbock, McCollum, and Adolf Windaus from Göttingen (37). The vitamin field was moving rapidly; scientists were closing in on the chemical identity of each of the vitamins. In 1931, ergocalciferol, or vitamin D2, was purified and crystallized by three independent groups (38–40), and Paul Karrer (41,42), a Swiss biochemist, described the chemical structure of vitamin A. In 1932, Szent-Györgyi (43) crystallized vitamin C and Norman Haworth (44) synthesized vitamin C at the University of Birmingham the following year. In 1936, Windaus (45,46) described the structure of both ergocalciferol, or vitamin D2, and cholecalciferol, or vitamin D3. The same year, Robert Williams (47,48) of Columbia University crystallized thiamin and described its chemical structure. In 1937, vitamin A was crystallized by Harry Holmes and Ruth Corbet (49) at Oberlin College. Conrad Elvehjem (50) isolated nicotinamide from liver concentrates and used it to cure black tongue in dogs, thus showing that niacin was the “anti-pellagra vitamin.” By the end of the 1930s, the chemical structures of major vitamins were known, the vitamins had been isolated and crystallized, and most could be synthesized. Vitamin A proved to be a harder problem to solve; it was finally synthesized by Otto Isler (51) at Hoffmann-La Roche in 1947.

Progress with Iodine and Iron

During the same period in which there was remarkable growth of knowledge of the vitamins, progress was being made in combating iodine deficiency and iron deficiency caused by hookworm infection. David Marine and Oliver Kimball (52–55) showed that iodine could prevent goiter in schoolgirls. Iodized salt was introduced in Switzerland in 1922 and in Michigan state in the US in 1924 (56). In Michigan, the iodized salt program required the cooperation of the salt producers, grocers, and the State Department of Health. The new state regulations prohibited any advertisement promoting the feature of added iodine by the salt producers. The USDA originally insisted but later dropped their demand that iodized salt be labeled with a skull and crossbones symbol because they considered iodine to be a poison (57). Eventually, >90% of homes were reached with iodized salt and endemic goiter practically disappeared in Michigan (56).

The Rockefeller Sanitary Commission for Eradication of Hookworm was established in 1909 to combat hookworm and anemia in the southern US. The commission had 3 goals: to determine the geographical distribution of the disease and degree of infection, to cure those who were infected, and to take measures to improve sanitation with latrines to remove the source of infection (58). In a survey of over one-half million rural school children in 11 states in the American South, nearly 40% were infected with hookworm (59). From 1911 through 1914, the Rockefeller Sanitary Commission sponsored a dispensary campaign, conducting examinations and providing treatment for over 1 million persons (59).

In 1926, Wilson Smillie (60,61) demonstrated that deworming of heavily infected school children improved hemoglobin concentrations and increased growth. Hookworm infection was associated with poor mental development (62,63), and children treated for hookworm infection performed better on mental development tests than untreated children (64). In heavily affected areas, school-based programs of mass treatment with anthelmintics and provision of sanitary toilets were undertaken (65).
Progress with Vitamin A

In Denmark from 1910–1920, Carl Bloch and Olaf Blegvad (66) observed high mortality in children who were hospitalized with vitamin A deficiency. The mortality rate of vitamin A-deficient children was reduced by ~54% by treating the children with cod-liver oil and whole milk, two rich sources of vitamin A. In the late 1920s, vitamin A was recognized to have an effect on immunity to infection, and vitamin A became known as the antieucliptic vitamin (67). Largely through the influence of Mellanby, vitamin A underwent a period of intense clinical investigation. Between 1920 and 1940, at least 30 trials were conducted to determine whether vitamin A could reduce the morbidity and mortality from infectious diseases, including respiratory disease, measles, puerperal sepsis, and tuberculosis (67). By the 1930s, it was established that vitamin A supplementation could reduce morbidity and mortality in young children. In 1932, Joseph Ellison (68,69) showed that vitamin A supplementation reduced the mortality of vitamin A-deficient children with measles by nearly 60%. Vitamin A became a mainstream preventive measure; cod-liver oil was part of the morning routine for millions of children and was acknowledged in saving the lives of children from poor families in England (70).

League of Nations Mixed Committee on the Problem of Nutrition

The League of Nations Mixed Committee on the Problem of Nutrition was established in 1935 by resolution of the 16th assembly of the League of Nations. The Committee was made up of experts in agriculture, economics, and nutrition, and their mandate was to improve nutrition in the world. The Committee was mostly limited to gathering data from industrialized countries, but they also recognized:

Disease and ill-health due to vitamin deficiency are common throughout the tropics and the Far East. Nightblindness and keratomalacia, due to vitamin A deficiency, have been observed in many parts of Asia and Africa. . . .[T]here can be little doubt that a vast amount of ill-health in the tropics and the East is due to the consumption of a diet deficient in vitamins. (71)

The Committee divided foods into highly protective, less protective, and nonprotective foods. The protective foods were thought to provide vitamins and essential nutrients and the nonprotective foods provided mostly energy. Thus, the highly protective foods were milk, cheese, eggs, liver, fat fish, vegetables and fruit, butter, and cod-liver oil. Legumes, cereals, nuts, sugars, margarine, and olive oil were considered nonprotective. The recommendation of the Committee was: “Take all possible steps to make food supplies, and especially protective foods, so far as possible, available at prices within the reach of all classes of the community, while at the same time safeguarding the interests of the producers” (71). For people living in poverty, the “protective foods” were usually beyond their meager budgets (72). The Committee acknowledged the conceptual gap in addressing nutritional problems in developing countries:

At present, the suggestions made [with a view to improving nutrition] are too often based merely upon . . . observations from Europe, and consequently they frequently prove to be quite wrong or economically impracticable. In Europe and America, for instance, one suggested means of improvement is to increase the consumption of milk, eggs, butter, meat, vegetables and fruit, but in most Asiatic countries, any considerable developments in regard to the first three items are out of the question. In Asia, therefore, entirely different solutions will have to be sought. (73)

The League of Nations began to establish guidelines and principles for conducting dietary surveys in different populations worldwide (74). The survey methods included assessment for various micronutrient deficiencies, including night blindness or impaired dark adaptation (vitamin A), anemia (iron), urinary ascorbic acid (vitamin C), and blood phosphatase (vitamin D). The British government attempted to address the paucity of data regarding nutrition in its colonial possessions by compiling a report from the respective colonies in the monograph Nutrition in the Colonial Empire (1939). The overseas colonies consisted of 48 territories with a combined area of >2 million square miles. The report echoed the League of Nations: “one of the most striking things about our inquiry, namely the almost complete absence from tropical diets (with a few exceptions) of milk and indeed of animal products generally, and the impossibility of supplying them in anything like the quantities which are normally regarded adequate in European conditions. There may be those who say ‘How then can anyone in the tropics ever be properly nourished?’” (75). To address some of the micronutrient deficiencies, the report recommended use of fish liver oils, red palm oil, consumption of local beers in moderation, and use of iodized salt. The outbreak of World War II effectively interrupted any coordinated international efforts to investigate nutritional status in large populations. However, two effects of the war were to increase the focus on food security and on the harmful effects of micronutrient deficiencies on both the armed forces and civilians.

Fortification of Foods with Micronutrients

In the late 1930s and during World War II in Great Britain and the United States, considerable efforts were made to fortify foods with different micronutrients. The idea of fortification was not new. As early as 1873 in France, bakers fortified bread with cod-liver oil to improve health in hospitalized children (76). In Great Britain, Helen Mackay (77) showed that iron-fortified milk could reduce anemia in infants. By the late 1920s, some margarine in Europe was fortified with vitamin A; various patented procedures had been developed to add cod-liver oil, liver oil, or extracts of cod-liver oil to the margarine (78). In the United States, the Council on Foods and Nutrition (then known as the Committee on Foods) met in 1936 to discuss fortified foods, in which it was generally understood that fortification meant increasing the percentage of mineral or vitamins beyond that found in the same food as exists in nature (79). In December 1938, the AMA’s joint committee of the Council on Foods and Nutrition and the Council on Pharmacy and Chemistry adopted a resolution, which stated in part, “to encourage the restorative addition of vitamins and minerals or other dietary essentials, in such amounts as will raise the content of vitamin or mineral or other dietary essential of general purpose foods to recognized high natural levels . . . for which a wider distribution is considered by the Council to be in the interest of public health” (80). The council recognized that the fortification of milk with vitamin D, margarine with vitamin A, table salt with iodine, and cereal products with calcium and iron was in the interest of public health. They also encouraged further work on the
additions of thiamin, riboflavin, and iron to flour and white bread (80).

In July 1940, the British government decided to fortify their flour and bread with thiamin, but it was not put into effect except for the armed forces, because controversy arose that fortification would benefit the vitamin manufacturers (79). In the U.S., the Subcommittee on Medical Nutrition, established by the NRC in 1940, recommended the fortification of flour with thiamin for use by the armed forces. The Committee on Food and Nutrition (which later became the Food and Nutrition Board) of the NRC held its first meeting in November 1940. The board was to provide scientific direction for the national nutrition program and they promptly recommended that flour be fortified with “thiamin, nicotinic acid, and other nutrients” (79). In 1941, President Franklin D. Roosevelt called for a national conference, the National Nutrition Conference for Defense, to address the problem of poor nutrition in the U.S. The attendees endorsed the fortification of flour and bread at the meeting (81).

Under the Food, Drug, and Cosmetic Act of 1938, the U.S. FDA had authority over the standards of identity for flour that had been nutritionally improved by fortification. The fortified flour became known as “enriched” flour, and by 1943, standards were established for the concentrations of thiamin, riboflavin, niacin, iron, calcium, and vitamin D to “enriched” flour (with calcium and vitamin D considered optional) (79). The War Food Administration required that all white bread be enriched with the existing standard for enriched flour in 1943 with their Food Order Number 1. After wartime emergency powers ceased in 1946, fortification of white bread and flour was no longer compulsory. Many states passed regulations requiring the fortification of flour, and the national millers and baking associations had decided to continue fortification voluntarily. By the late 1950s, 80–90% of all white bread and white “family flour” was fortified in the U.S. (82).

Origins of Dietary Standards for Micronutrients

The scientific rationale for fortification of bread, flour, milk, table salt, and margarine was to prevent or eliminate the prevalence of multiple micronutrient deficiencies in the population. On the basis of surveys in the U.S. by Hazel Stiebeling and others (83,84) that showed inadequate intakes of many vitamins and minerals, especially in low-income populations, the NRC concluded that “deficiency states are rife throughout the nation” (85). Stiebeling (86) was an early pioneer in attempts to establish dietary requirements for micronutrients. In 1933, she used the term “dietary allowances” for quantitative estimates of individual dietary intake for several vitamins and minerals. The USDA attempted to summarize current knowledge of human nutrition and dietary requirements for protein, fats, carbohydrates, vitamins, and minerals in their 1939 Yearbook of Agriculture (87).

In 1940, the first Committee on RDA was established by the Food and Nutrition Board. The committee was chaired by Lydia Roberts and included Stiebeling, who proposed dietary allowances that were 50% more than the average requirement. The larger requirement in the allowances was an attempt to account for variability in the population and was considered to cover most normal individuals. Their recommendations were presented and accepted at the 1941 National Nutrition Conference for Defense and published shortly afterwards (88,89). In the meantime, the Canadian Dietary Standard was introduced, with figures that were somewhat lower than the U.S. RDA, because the Canadian standards took into consideration body size or weight (90).

After the release of the RDA, Russell Wilder (91), the chairman of the Food and Nutrition Board, noted that the RDA were often misinterpreted in that failure of any diet to provide the nutrients at the level of the RDA was “ipso facto evidence of dietary inadequacy.” He noted that such conclusions were unwarranted and that the figures were often misused by advertisers of vitamin products. Popular books began to appear, such as The National Malnutrition, which proclaimed “999 out of every 1000 people lack the proper nutrition” and gave dire warning that “hidden hunger is starving millions . . . are you a victim?” (92).

Multiple Micronutrient Nutrition in the 1940s

In the 1940s, John Youmans (93) at Vanderbilt University noted: “A characteristic feature of nutritional deficiencies in humans is their multiple nature. Single deficiencies are uncommon, multiple deficiencies are the rule.” Given the high prevalence of vitamin and mineral deficiencies found by surveys conducted in different segments of the population, especially among the poor, various investigators sought to address these multiple deficiencies by using daily multiple micronutrient supplements. Clinical trials, many using placebo controls, were undertaken with daily multiple micronutrient supplements in aircraft workers (94), school children (95–98), and blacks in the Harlem neighborhood of New York City (99). In retrospect, many of these trials lacked sufficient power to detect effects of multiple micronutrient supplements on morbidity and growth. Outcome measures of the trials included absenteeism, endurance, fatigue, oral health, and resting vital capacity.

There was also growing recognition of interactions between micronutrients. Edgar Gordon and Elmer Sevringhaus (100) at the University of Wisconsin remarked: “There are important vitamin interrelationships that are only now beginning to be uncovered. Thus, the absorption, metabolism and excretion of one factor may be conditioned in part by the nutritional status of the organism relative to other (perhaps all other) nutrients.” Thomas Moore (101) summarized the somewhat limited state of knowledge regarding the interactions of the vitamins that had accumulated by 1945.

By the 1940s, the U.S., Canada, Great Britain, and some countries of continental Europe were addressing the problems of micronutrient deficiencies through fortification of foods such as wheat, margarine, milk, and salt. In places were fortification was practiced, florid clinical cases of pellagra, beriberi, vitamin A deficiency, and goiter became rare. Fortification continued because of concerns about subclinical micronutrient deficiencies, which affected a much larger portion of the population than clinical deficiencies. Vitamins were also widely available to consumers in the form of pills, cod-liver oil, and other liquid preparations sold by grocery stores and pharmacies (102).

International Organizations Emphasize Protein Following World War II

The aftermath of World War II saw the establishment of major international organizations such as the FAO of the United

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Nations in 1945, the UNICEF in 1946, and the WHO in 1948. A joint expert committee was established between the FAO and WHO. At their first international meeting in 1949, the committee declared that “kwashiorkor” was “one of the most widespread nutrition disorders in tropical and suburban areas” (103). The Jamaican pediatrician, Cicely Williams, previously brought attention to a dramatic condition called kwashiorkor, which in the Gold Coast of Africa, referred to the “disease the deposed baby gets when the next one is born.” The syndrome consisted of peripheral edema and skin lesions and it was associated with high mortality. Kwashiorkor was usually seen in the second year of life when complementary foods were introduced (104).

At their second meeting, the joint committee recommended further studies of kwashiorkor (105). In accordance with the recommendations of the committee, John Brock and Marcel Autret (106) undertook at survey of kwashiorkor in central and tropical Africa. The term “protein malnutrition” was introduced in 1952 at the third meeting of the joint committee held in the Gambia, West Africa (107), and “protein malnutrition” soon became a dominant theme for nutrition policymakers (108). Subsequent international meetings on protein malnutrition were held at Princeton (109) and Cuernavaca (110) with a focus on the lack of animal food products, notably milk and meat, in the diet. Little emphasis was placed on vitamin or mineral deficiencies at these proceedings. In August 1960, an international conference, “Progress in Meeting Protein Needs of Infants and Preschool Children,” was held in Washington, DC under the auspices of the Committee on Protein Malnutrition of the Food and Nutrition Board and the NIH (111). The U.S. government sponsored the publication of the influential handbook *Child Nutrition in Developing Countries* by Derrick Jelliffe (112). Jelliffe thought that the main nutritional problems in developing countries were kwashiorkor and marasmus (starvation with severely reduced energy intake). He advocated the “three plank protein bridge” consisting of prolonged breastfeeding and increased consumption of animal and plant proteins. Beans, lentils, and groundnuts were considered to be main sources of plant protein. Jelliffe suggested that eggs, fish, meat, and cow milk be incorporated into weaning foods and mixed in with all meals for young children each day. Partly in response to the lack of protein in the diet of young children, UNICEF provided dried skimmed milk fortified with vitamins A and D to developing countries as one of their major activities (113).

Further Research on Multiple Micronutrient Nutrition

During the time at which some nutritionists and policymakers were focusing primarily on protein malnutrition, it is important to note that many scientists continued to conduct research on micronutrient deficiencies. In 1948, the Department of Health of the Government of the Philippines, with support from the U.S. Public Health Service, conducted an experimental intervention with micronutrient-fortified rice in Bataan province (114). The rice was fortified with thiamin, niacin, and iron. After 1951, fortified rice was introduced on a commercial basis in Bataan and Tarlac provinces and was associated with a drop in beriberi-related mortality (115). In 1952, a national rice enrichment law was passed in the Philippines. Rice millers soon organized opposition to fortification. By law, all manufactured products in the Philippines, including milled rice, were subject to taxation, but most millers had previously avoided paying taxes. Government supervision of rice fortification allowed inspectors to calculate the mill output and levy taxes accordingly (116). Rice fortification eventually failed because of a lack of cooperation by the rice millers and lax enforcement of the law.

In 1953, a nutrition survey was conducted among Republic of Korea Army troops. The survey showed evidence of a high prevalence of many micronutrient deficiencies, prompting worries about the health and performance of the Korean and other U.S. allies (117). In 1953, the ICNNND4 was thus created, one part of the Cold War strategy against Russia (117). The ICNNND conducted nutritional surveys in 33 foreign countries in which the United States had such strategic interests, including Vietnam, Thailand, Bangladesh, Philippines, Jordan, Ethiopia, Guatemala, Panama, and Brazil. The survey manual used by the ICNNND included clinical descriptions of the signs of various micronutrient deficiencies, in addition to kwashiorkor and marasmus. The survey instruments included assessment of Bitot’s spots, goiter, pellagrous dermatitis, and laboratory analyses of hemoglobin, serum vitamins A and C, and urine thiamin and riboflavin (118). The results of these surveys, which were published as separate monographs mostly between 1956 and 1966, showed that anemia and micronutrient deficiencies were highly prevalent in many countries, especially that of vitamin A and iodine. There was no cross-tabulation of results, that is, the existence of multiple deficiencies in the same individuals was not reported. Notably, the overall results demonstrated that micronutrient deficiencies were far more common than kwashiorkor or marasmus, which were also enumerated in the same surveys.

Further research on micronutrients was stimulated by a conference on beriberi, goiter, and vitamin A deficiency that was held by the NIH in Princeton, NJ in 1958. At the conference, the Dutch physician H.A.P.C. (“Janus”) Oomen (119), who worked for many years in Sumatra, Sulawesi, and Java, made a notable remark that the prevalence of vitamin A deficiency was so high in parts of Indonesia “to be responsible for a considerable part of toddler mortality.” A major goal of the conference was to identify priorities for research and training on beriberi, iodine deficiency, and vitamin A deficiency. Nevin Scrimshaw (119) perceived that a theme emerging from the conference was that nutrition and infectious diseases were interrelated, but nutritionists tended to neglect infectious diseases, whereas infectious disease specialists generally ignored nutrition.

In 1963, the FAO held a conference in Bellagio, Italy with the theme “How to Reach the Pre-School Child,” because the mortality rate in preschool-aged children was from 10 to 40 times higher in developing countries than developed countries (120). The attendees urged that a “crash” program was needed to reach these children (121). The Bellagio conference was followed with another conference sponsored by the NIH in Washington DC. Among the conference conclusions were that vitamin A deficiency accounted for widespread blindness and high child mortality, iron deficiency was common and contributed to the debility of the child, and iodine deficiency was

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prevalent and resulted in cretinism, imbecility, and dwarfism (122).

In 1968, a seminal monograph, *Interactions of Nutrition and Infection*, was published by Scrimshaw, Carl Taylor, and John Gordon (123). The work, undertaken for the WHO, was a comprehensive review of the relationship between nutrition and infection. The authors analyzed the world’s literature on experimental animal models and human studies and the effects of single micronutrient and multiple micronutrient deficiencies. Scrimshaw et al. (123) concluded: “Synergism between malnutrition and infection is responsible for much of the excess mortality among infants and pre-school children in less developed regions.” They declared “no nutritional deficiency is more consistently synergistic with infectious disease than that of vitamin A.” Two years later, on the occasion of the Second World Food Congress, Wallace Aykroyd (124) published *Conquest of Deficiency Diseases: Achievements and Prospects*. Aykroyd noted that progress had been made in reducing the prevalence of beriberi, pellagra, rickets, and scurvy but that protein-energy malnutrition, vitamin A deficiency, goiter, and iron deficiency were still major unresolved problems.

Deficiencies of micronutrients, including vitamin A, vitamin C, iron, riboflavin, thiamin, and iodine were soon characterized in the U.S. From 1968 to 1970, the Ten State Nutrition Survey was undertaken in five low-income states (Kentucky, Louisiana, South Carolina, Texas, and West Virginia) and five high-income states (California, Massachusetts, Michigan, New York, and Washington) (125). The survey was conducted at the request of Congress during the Johnson administration to identify the prevalence, magnitude, and distribution of malnutrition and related health problems in the U.S. It was the largest nutritional survey ever undertaken in the country and involved detailed nutritional assessment in nearly 40,000 individuals. The Ten State Nutrition Survey proved to be a political bombshell; it showed widespread micronutrient deficiencies and hunger among the poor in the U.S., especially in the south. Arnold Schaefer, the director of the survey, was attacked for collecting data on childhood immunizations. The study revealed that hundreds of schoolchildren in Texas were not immunized against polio and diphtheria, a shocking violation of the law (126). The newly inaugurated, conservative Nixon administration attempted to limit the embarrassing revelations by curtailing the survey in early 1969. Schaefer resigned in disgust (127). The following year in Texas, a large outbreak of diphtheria occurred and an outbreak of paralytic poliomyelitis affected 22 children, the largest number of cases reported for any state in the U.S. (128).

By the mid-1970s, it became apparent that a lack of protein was not really a major nutritional problem worldwide, despite all the attention of many international policymaking groups. In 1975, John Waterlow (129), one of the main proponents of the idea of widespread protein deficiency, conceded: “The concept of a worldwide protein gap, derived from the diagnosis of kwashiorkor as a protein deficiency state, is no longer tenable. Current estimates of children’s protein and energy requirements are considered realistic, and by these criteria the problem is mainly one of quantity rather than quality of food.” Waterlow’s revelation brought to close an era over two decades in which policymakers had been led to believe that the “protein gap” was the major nutritional problem in developing countries. The policy groups had brought much attention to the lack of animal foods in the diet of the poor in developing countries. The issue of the lack of animal foods did not disappear but instead emerged again with subsequent scientific investigations on micronutrient deficiencies, because animal foods are rich sources of vitamin A, zinc, and iron.

**Organization of Expertise in Micronutrients: Vitamin A, Iron, and Iodine**

The so-called “big three” micronutrient groups were soon established. In 1975, the IVACG was founded. The following year saw the founding of the INACG. The ICCIDD was established in 1985 with support from the UNICEF, WHO, and the Australian government. The main common denominators behind the big three were that all three deficiencies were highly prevalent and resulted in serious consequences for health. Both IVACG and INACG were funded by the USAID and maintained their secretariats at the International Life Sciences Institute Human Nutrition Institute in Washington, DC. The micronutrient groups, along with the WHO and UNICEF, provided much of the impetus for the iterative nutritional paradigm (Fig. 1). One exception to the model shown for “developing countries” is the case of early mandatory iodization of salt that occurred in Brazil in the 1950s (130).

For 30 y, IVACG provided the main global leadership for the eradication of vitamin A deficiency. During the tenure of IVACG, there was notable progress in knowledge and control of vitamin A deficiency. The organization disseminated information on the advances in nutritional assessment of vitamin A deficiency, the safe use of vitamin A, and vitamin A fortification of foods. In 1986, Alfred Sommer et al. (131) showed that periodic high-dose vitamin A supplementation reduced the mortality of preschool-aged children in Indonesia by 34%. The implications of the findings for child health were enormous. Soon, many independent groups of investigators conducted randomized, placebo-controlled, doubled-masked, community-based trials in Asia and Africa to confirm whether vitamin A supplementation reduced morbidity and mortality in young children. For the historical record, it should be noted that some of the investigators of the trials were initially skeptical that vitamin A supplementation could reduce child mortality but were later convinced when their study codes were broken and the data were analyzed.

The IVACG meetings served as a forum for dissemination of the results of the studies. Seven of eight population-based intervention trials with vitamin A that included >165,000 children in Indonesia (131,132), India (133,134), Nepal (135,136), and Africa (137) showed that improving vitamin A status by periodic high-dose supplementation, weekly supplementation, or fortification reduced mortality by 6–54%. The greatest reduction in mortality was in the trial conducted in India (133). A trial conducted in the Sudan was the only study that did not show a reduction in mortality (138). Many questions have been raised as to why this trial was the only exception to the other major vitamin A trials. During the middle of the trial in the Sudan, a huge natural disaster struck; the Khartoum region received the highest recorded rainfall in history. Along the Nile River, massive flooding occurred that destroyed the homes of 1.5 million people (139,140). A large proportion of the study population was displaced by the floods and, inadvertently, emergency relief agencies further compromised the integrity of the trial because mobile medical teams provided vitamin A supplements to all preschool children from displaced families (141,142).

The trials showed that periodic high-dose vitamin A supplementation reduced child mortality by 23%, as shown in an...
independent meta-analysis conducted by George Beaton et al. (143). The meta-analysis became the basis for official WHO and UNICEF policy of periodic high-dose vitamin A supplementation for child survival. More than 100 developing countries have adopted vitamin A supplementation programs to improve child survival (144). Other results presented at the IVACG meeting were the findings that vitamin A supplementation reduced the severity of diarrheal disease (145–148) and improved immune function (149–151). These important findings demonstrate that the reduction of child mortality from vitamin A supplementation occurs through improving immunity and reducing the morbidity from diarrheal disease.

Another important research finding with enormous implications that was discussed extensively at the IVACG meetings concerned the bioavailability of vitamin A in fruit and vegetables. Saskia de Pee, Clive West, and Muhilal, working in Indonesia, showed that the bioavailability of vitamin A in fruits and vegetables was lower than previously thought (152). Further recent stable isotope studies and dietary interventions have confirmed their findings that the bioavailability of provitamin A carotenoids is much lower than previously thought (152). The Food and Nutrition Board of the Institute of Medicine subsequently revised their estimates regarding the bioavailability of vitamin A from provitamin A carotenoids in fruit and vegetables (157). These findings demonstrate that it would be difficult to meet the dietary needs for vitamin A in children through fruit and vegetable intake alone. These seminal findings reinforced the importance of having animal source foods such as milk, liver, cheese, and eggs as sources of vitamin A in the diet.

During the existence of INACG, there was a compilation of global data on anemia (158) and a shift in thinking toward “iron deficiency” rather than “iron deficiency anemia” (159). INACG provided guidelines on the use of iron supplements and disseminated information on the bioavailability of iron and the iron fortification of foods. Further studies were conducted on the impact of iron supplementation on child health (160,161). One trial showed that iron supplementation increased morbidity and mortality among iron-replete children in a malaria-endemic region (161). These cautionary findings led to new recommendations regarding the use of iron supplements for children where malaria is present (162).

The ICCIDD has fostered widespread advocacy and awareness of the iodine deficiency disorders. ICCIDD disseminated information on the assessment of iodine status and guidelines for monitoring salt iodization programs and reported the progress in various countries regarding salt iodization. There was the rapid expansion of salt iodization (notably with 70% of world’s population now having access to iodized salt) and a major reduction in iodine deficiency disorders worldwide (163,164). Improvement of iodine status has also affected child survival, because trials conducted in different parts of the world show that improving iodine status in the form of iodized oil injections, oral iodized oil, or iodinated water supply can reduce neonatal, infant, and child mortality (165–168).

At the 1990 World Summit for Children, 71 heads of state and senior policy makers from 80 other countries convened (169). Among the goals that were announced at the meeting was the elimination or significant reduction in iodine, vitamin A, and iron deficiencies by 2000. On the heels of the summit, in 1991, a meeting, “Ending Hidden Hunger,” was held in Montreal (170). The purpose of the meeting, which was well attended by ministers, scientists, and policymakers, was to pursue the goals of the World’s Summit for Children to reduce micronutrient malnutrition. The presenters highlighted the challenges of vitamin A, iron, and iodine deficiencies.

Another micronutrient expert group, the IZiNCG was founded in 2000. The secretariat for IZiNCG is based at the University of California, Davis. Among the goals of IZiNCG are to promote and assist efforts to reduce zinc deficiency worldwide, provide technical assistance, and disseminate information regarding new research findings for programs and interventions aimed at reducing zinc deficiency. Advances in the knowledge of

**FIGURE 1** The iterative nutritional paradigm: two temporal cycles of action in nutrition.
zinc nutrition were recently summarized by Sonja Hess et al. (171). Results of multiple, community-based trials showed that zinc supplementation lowered the incidence of diarrhea and pneumonia among young children (172), reduced diarrhea morbidity when given during an episode (173), and increased young child survival (174).

In September 2000, 189 member states of the United Nations adopted the Millennium Declaration. The Millennium Development Goals included reducing child mortality by two-thirds between 1990 and 2015 (175,176). The prevention of micronutrient deficiencies is an important part of the strategy to reduce child mortality, given the strong association of vitamin A with child survival, iodine with infant health and survival, and zinc with pneumonia, diarrhea, and child survival.

In 2006, the Micronutrient Forum was established to replace the IVACG and INACG. The different interest groups working on vitamin A, iron, iodine, and zinc agreed on one joint meeting, the first of which took place in Istanbul in 2007 and the second in Beijing in 2009. At these meetings, there was some emphasis on multiple micronutrient deficiencies and micronutrient interactions. Further support for the Micronutrient Forum was withdrawn by the USAID and the next meeting that was scheduled in Dakar, Senegal was subsequently cancelled. The lack of support from the USAID for scientific groups working on micronutrients is likely to have a negative impact on future work in micronutrients. The IVACG, the INACG, and the Micronutrient Forum also provided an important opportunity for younger scientists from around the world to enter the field and interact in a positive environment that fostered new careers and further strengthened work on micronutrients.

**Multiple Micronutrient Nutrition: Recent Findings, Future Directions**

In a report sponsored by the Micronutrient Initiative, John Mason (177) noted: “we can expect only limited success in controlling the effects of micronutrient deficiencies by tackling one micronutrient at a time . . . this analysis argues for a multifaceted approach incorporating supplementation and fortification with several micronutrients, supported where feasible with increased micronutrient intake from the diet.” At the time of the report in 2001, 28 countries had policies for addressing all three deficiencies (vitamin A, iron, and iodine) that were discussed in the report. Mason (177) predicted that “[a]lthough these policies may not yet have been translated into multiple approaches (such as multiple supplementation and fortification), this would be a logical next step.” Multiple micronutrient supplementation has been evaluated by Parul Christian, James Tielsch, and colleagues in pregnant women in south Asia, as discussed separately in this issue (178).

Nutritional and health surveillance systems undertaken in Bangladesh and Indonesia provided important data on the relationships of poverty with dietary diversity and malnutrition, as shown in a model in Figure 2. This model provides a context for the various and multiple approaches that are being implemented to combat multiple micronutrient deficiencies. For micronutrient-fortified foods to reach even the poorest families, such fortified foods would need to be those that were affordable and used by all, such as cooking oil or sugar. Given the limited bioavailability of vitamin A from fruit and vegetables (152–156), until adequate dietary diversity is attained by poor families, i.e., greater access to vitamin A-rich animal source foods and fortified foods, vertical intervention with vitamin A capsules remains the best evidence-driven strategy for protecting children against vitamin A deficiency and improving child survival.

Home fortification in the form of a micronutrient powder was originally developed by Stanley Zlotkin et al. (179,180) in the late 1990s as a strategy to combat nutritional anemia. Home fortification is also known as “point of use” fortification. A small sachet of the powder is opened and sprinkled on an individual serving of food prior to consumption. The formulation was initially made to reduce nutritional anemia, but a formulation with multiple micronutrients has followed (181). Micronutrient powders are now being used in large-scale programs, mainly in development settings, but also in a few emergency and refugee settings, including in Aceh, Indonesia (182). Other places where micronutrient powders are under evaluation include refugee camps in Kenya, Nepal, and Bangladesh, and in disaster relief in Bangladesh and the Philippines, as reviewed by Rah et al. (183) in this issue. One of the advantages of home fortification is that it can reach the poorest families, or the lowest levels shown in Figure 2.
nutrients can be sprinkled on the most basic bowl or plate of food.

As noted previously, the fortification of flour with micronutrients was implemented in some places in the early 1940s. The fortification of maize and wheat flour with vitamin A (184), iron (185), zinc (186), folate, and possibly vitamin B-12 are starting to be implemented in developing countries (187). Triple fortification of salt with iodine, iron, and vitamin A has been shown to be effective in reducing these respective micronutrient deficiencies in schoolchildren (188). Fortification of fish sauce with iron (189) or with both iron and iodine (190) are being considered in areas where fish sauce is more commonly used as a condiment than table salt. Sugar has been fortified with vitamin A in Guatemala continuously since 1988, with fortified sugar reaching 95% of households (191). Vitamin A-fortified sugar is also implemented in other Latin American and a few African countries.

Homestead food production has been advocated by Martin Bloem, Aminuzzaman Talukder, and Saskia de Pee (192–194) as one way to combat micronutrient malnutrition and poverty. Helen Keller International has worked with local nongovernmental organization partners to establish model farms in selected target communities. The farms provide seeds, seedlings, saplings, and chicks to participating households. The homestead food production pilot projects were first initiated by Helen Keller International in Bangladesh in 1990. The model has been adapted, refined, and expanded in Bangladesh and in Cambodia, Nepal, and the Philippines. The program has now reached over 1 million households that represent ~5.5 million beneficiaries (195). Homestead food production appears to lower the risk of clinical vitamin A deficiency among children in Kiribati and Bangladesh, especially when they missed the most recent vitamin A capsule distribution (194,196,197). Rigorous controlled studies are needed to measure the impact of homestead food production on multiple micronutrient status in women and young children.

Homestead food production is appropriate for some settings but may be problematic for poor families who are landless or have no access to land. Homestead food production is not a viable strategy in arid environments with limited availability of water. Although purely food-based approaches have been advocated to address vitamin A deficiency in India, there are alarming results from the recent Demographic and Health Survey that show that >40% of children, aged 12–35 mo, did not receive vitamin A-rich foods in the previous 24 h, as assessed by dietary recall (199). Children who did not receive any vitamin A-rich foods were also more likely to have missed vitamin A supplementation in the last 6 mo (198). India has made little progress toward the Millennium Development Goal of reducing under-five child mortality (199). India accounts for the largest number of under-five child deaths worldwide, and effective leadership is needed in nutrition to address the problem of vitamin A and other micronutrient deficiencies.

The Copenhagen Consensus is a think tank based in Denmark that uses sound economic science to advise governments on the best ways to spend aid and development money. In 2004, this panel of economists noted that “investments in micronutrients have higher returns than those from investments in trade liberalization, in malaria, or in water and sanitation. . . . No other technology offers as large an opportunity to improve lives at such low cost and in such a short time” (200).

In April 2010, the governments of Canada and Japan, the USAID, and the World Bank hosted a high-level meeting on “Scaling Up Nutrition” with the objective of mobilizing invest-
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