TRACE ELEMENTS EMERGING AS IMPORTANT IN HUMAN NUTRITION

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INTRODUCTION

At present, only seven trace elements have defined essential functions in humans. These elements are cobalt, copper, iodine, iron, molybdenum, selenium and zinc. Essential functions have been identified for manganese in animals, but not in humans. Signs of chromium deficiency have been described for humans, but a specific biochemical role for chromium has not been demonstrated conclusively. A number of other elements in addition to the aforementioned nine elements have been suggested to be essential nutrients including arsenic, boron, bromine, cadmium, fluoride, lead, lithium, nickel, silicon, tin, and vanadium. Deficiencies of only four elements -- cobalt as vitamin B-12, iodine, iron, and zinc -- occur with known sufficient frequency in humans so as to be of concern to health professionals. Nonetheless, the trace elements are often suspected of being the missing link in some of the unexplained human diseases such as atherosclerosis, osteoporosis, osteoarthritis, hypertension, and ischemic heart disease. Efforts to demonstrate that trace element deficiencies are the missing links generally have been unsuccessful. Perhaps some of the failures have occurred because the experimental approach has not been correct in the past. Recent studies examining the need for various trace elements by animals under some form of nutritional, metabolic, hormonal or physiological stress have indicated that these are situations in which some of the trace elements may be of nutritional significance.

Biological Roles of the Trace Elements

Trace elements have four known roles in living organisms. They include: 1) In close association with enzymes, some of the trace elements are an integral part of the catalytic centers at which the reactions of biological chemistry occur. Working in concert with a protein, and frequently with other organic coenzymes, the trace element attracts substrate molecules and facilitates their conversion to a specific endproduct. 2) Some trace elements donate or accept electrons in reactions of reduction or oxidation. These redox reactions are of primary importance in the generation and utilization of metabolic energy through the "burning" of foods in cells. Chemical transformations of molecules frequently involve redox reactions. 3) Some trace elements, especially iron, bind, transport and release oxygen in the body. 4) Some trace elements have structural roles, imparting stability and three dimensional structure to important biological molecules.

Homeostatic Regulation of the Trace Elements

When an essential trace element is absent or too low for adequate activity of an essential function, death occurs. As the intake of the trace element increases, the following occurs: 1) The organism survives but with suboptimal health and well-being. 2) An intake is reached in which optimal health and well-being are maintained. The range of intakes at which this occurs usually is quite large because of powerful homeostatic mechanisms. 3) A decline in health and well-being, and finally death, as regulatory mechanisms are overcome by increasing intakes that become toxic.

Homeostatic regulation involves the processes of absorption, storage and excretion. The relative importance of these three processes varies among the trace elements. The amount absorbed from the gastrointestinal (GI) tract often is the controlling mechanism for cationic trace elements such as copper, iron, and zinc. If the body is low in the trace element, the percent of the element absorbed from the GI tract is increased, and vice versa. Anionic trace elements such as boron, iodine and selenium are usually absorbed quite freely and completely from the gastrointestinal tract. Excretion through the urine, bile, sweat and breath is therefore the major mechanism for controlling the amount of these trace elements in the organism. Some trace elements are prevented from causing adverse reactions when present in high quantities by being stored at inactive sites (e.g., copper as metallothionein; iron as ferritin). Release of a trace element from storage forms also can be important in preventing deficiency.
Factors Affecting Trace Element Requirements

Although trace elements play key roles in a variety of processes necessary for life, the occurrence of overt simple or uncomplicated deficiencies of any of the trace elements is probably relatively uncommon because of the powerful homeostatic mechanisms which the human body possesses. However, there are situations which may make a trace element nutritionally significant. These include: 1) inborn errors of metabolism that affect absorption, retention, or excretion; 2) alterations in metabolism and/or biochemistry as a secondary consequence to malnutrition, disease, injury, or stress; 3) marginal deficiencies (slight deviation from an optimal intake of an essential nutrient) induced by various dietary manipulations or by direct or indirect interaction with another nutrient or drug; and 4) the enhanced requirement for a trace element caused by a sudden or severe change in the system requiring that element. The preceding probably can be summarized by the statement that the insufficient intake of a specific trace element would become obvious only when the body is stressed in some way that enhances the need, or interferes with the utilization, of that element.

Recently, Tapp and Natelson\(^1\) presented the formula:

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\text{Pathological Effects} = \text{Stress} \times \text{Organic Vulnerability}
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This formula seems quite applicable to trace element nutrition. In other words, pathological effects are not likely to be seen if a trace element deficiency (organic vulnerability) is not multiplied by some significant stress. Likewise, pathological effects are not likely to be large if stress is not accompanied by an organic vulnerability, or a lack of a trace element. However, the multiplication of a suboptimal intake of a specific trace element times the presence of some nutritional, metabolic, hormonal, or physiological stress affected by that element most likely would lead to serious pathological consequences.

The preceding concept is supported by the knowledge about the need for the established trace elements iron and zinc. Severe signs of iron deficiency most often occur when low dietary intake is combined with the stress of blood loss or rapid growth. Reports of zinc deficiency in humans usually are associated with a condition that enhances the need for zinc; these include rapid growth, malabsorption, inflammatory bowel disease, intestinal parasites, liver disease, renal disease, chronic inflammatory conditions and inborn metabolic errors.

Examining the possibility that other trace elements are of importance for humans under some form of stress has revealed several candidates of potential nutritional concern; these include arsenic, boron, chromium, copper, manganese, molybdenum, nickel, selenium, silicon and vanadium. This is demonstrated by findings with boron, which will be discussed most extensively here.

NUTRITIONAL SIGNIFICANCE OF BORON

Animal Studies

Seventy years after boron was first suggested to be essential for plants,\(^2\) an experiment was done indicating that boron might be essential for chicks. Hunt and Nielsen\(^3\) reported that boron deprivation depressed growth and elevated plasma alkaline phosphatase activity in chicks fed inadequate cholecalciferol. Subsequent experiments suggested that cholecalciferol deficiency enhanced the need for boron and that boron might interact with cholecalciferol metabolism, which in turn affected calcium, phosphorus, or magnesium metabolism.\(^4\) After those experiments it was found that the response to changes in dietary boron is markedly influenced by dietary methionine, potassium, magnesium, cholecalciferol, aluminum, and calcium.\(^5,6,7,8,9\)

Generally, animal studies have shown that when the diet was manipulated to possibly cause changes in cellular membrane integrity (potassium or magnesium deficiency) or in hormone responsiveness (magnesium or cholecalciferol deficiency, aluminum toxicity), a large number of responses to dietary boron occur. On the other hand, when the animal was fed a diet apparently optimal in all respects, the response to dietary boron was not very marked. These findings suggested that the need for boron was not crucial, or was quite low, when the animal was not under any nutritional or metabolic stress, but that there was an enhanced need for
boron when the animal needed to respond to a stressful situation that adversely altered hormonal or cellular membrane status.

Studies with humans also indicate that boron may be of nutritional concern under certain metabolic or nutritional stressful situations, for example, with a low dietary intake of magnesium, or when hormonal changes occur (menopause) which causes an increased loss of calcium from bone. A study done with 12 postmenopausal women housed in a metabolic unit showed that dietary boron markedly affected several indices of mineral metabolism. After the women had consumed a conventional diet supplying about 0.25 mg boron per day for 119 days, they were given a boron supplement of 3 mg per day for 48 days. Boron supplementation reduced the urinary excretion of calcium; the depression seemed more marked when dietary magnesium was low. Boron supplementation also elevated the serum concentrations of estradiol-17\(^{\alpha}\) and ionized calcium; the elevation seemed more marked in the magnesium-low women.

Recently, another study with five men over the age of 45, five postmenopausal women on estrogen therapy, four postmenopausal women not on estrogen therapy, and one premenopausal woman fed a magnesium-low diet (115 mg/2000 kcal) gave findings indicating that boron affects calcium metabolism. After the subjects had consumed a conventional diet supplying about 0.23 mg boron per 2000 kcal for 63 days, they were given a boron supplement of 3 mg per day for 49 days. When compared between the last 42 days of depletion and the last 35 days of repletion, several indicators of calcium status were significantly different (p <0.05). In each group of four or five, plasma ionized calcium was increased by the boron supplementation. When all 15 individuals were used in the comparisons, serum 25-hydroxycholecalciferol (29.1 vs 32.3 ng/ml) was lower, and serum calcitomin (74.1 vs 59.0 pg/ml), osteocalcin (3.41 vs 2.65 ng/ml), and glucose (93 vs 88 mg/dl) were higher during boron depletion than during boron repletion.

The subjects which were receiving estrogen therapy to prevent calcium loss from bone had the highest plasma ionized calcium and lowest serum osteocalcin. Boron supplementation after 63 days of boron depletion tended to make the values of the other two groups more like those of the women receiving estrogen therapy. These types of changes were the same for serum 25-hydroxycholecalciferol, calcitomin and glucose. Thus, the boron supplementation was construed as being beneficial to calcium metabolism. In other words, boron probably has an important role in the maintenance of normal bones. Moreover, this role becomes more apparent under conditions in which increased calcium loss from the bone is quite likely.

NUTRITIONAL SIGNIFICANCE OF OTHER TRACE ELEMENTS

Arsenic

Studies with rats, chicks, and hamsters have revealed that the nature and severity of the signs of arsenic deprivation are affected by several dietary manipulations, including variations in the concentrations of zinc, arginine, choline, methionine, taurine, and guanidoacetic acid, all of which can affect methyl-group metabolism and thus polyamino synthesis in which arsenic apparently has a role. Most likely, arsenic is needed by humans. Furthermore, evidence for this need will probably be obtained under conditions in which lipid or methyl-group metabolism is stressed such that there is an enhanced need for arsenic.

Chromium

Chromium is another trace element whose need by humans apparently is influenced by nutritional or physiological stress. The dietary need for chromium seems to change when normal insulin-dependent metabolism of carbohydrate, protein and fat is upset. Stress, including trauma, infection, surgery, and intense heat or cold, elevates the secretion of hormones, which alters glucose metabolism and apparently affects chromium metabolism. In experimental animals, the stress of a low-protein diet, controlled exercise, acute blood loss, or infection aggravated the signs of depressed growth and survival caused by chromium-deficient diets. In humans, severe trauma and exercise elevated the excretion of chromium in urine.
Copper

Epidemiological studies and observations on experimental animals indicating that a low intake of dietary copper can adversely affect cardiovascular health, and affect the metabolism of some predictors of heart disease including plasma cholesterol $^{17,18}$ became of interest to nutritionists when it was found that many diets contain substantially less copper than was previously believed. $^{19}$ Apparently less than 25% of diets in the United States contain the 2 mg of copper thought to be required daily. However, attempts to produce signs of copper deficiency in adult humans have not yielded consistent changes in examined copper status indicators, e.g., plasma cholesterol. Milne and coworkers $^{20}$ fed eight men and eight women diets low in copper for periods ranging from 42 days to 120 days in four separate studies. Only one man showed definite signs of copper depletion similar to those observed in animals; the signs were significantly depressed plasma copper and erythrocyte superoxide dismutase, and increased plasma cholesterol $^{20,21}$. Only two of the other men exhibited similar trends; however, the changes were not significant and were within the normal range. Two men also showed impaired glucose tolerance. $^{22}$ No changes in serum ceruloplasmin were found in the men.

In the one study with women, plasma copper, cholesterol, and erythrocyte superoxide dismutase were unaffected by the dietary copper manipulations. However, copper depletion depressed enzymatic ceruloplasmin and cytochrome-c oxidase in platelets and mononucleated white cells. $^{22}$

Animal studies suggest that the inability to obtain consistent signs of copper deficiency in adult humans may be caused by factors of sex, genetic makeup, dietary sulfur amino acids, and dietary carbohydrate. For example, Fields and co-workers $^{23,24}$ have shown that fructose instead of starch as the dietary source of carbohydrate markedly increases the severity and extent of copper deficiency signs in rats. They $^{23,24}$ also reported that male Sprague-Dawley rats fed a copper-deficient high-fructose diet displayed anemia, hypertrophic hearts, and mortality; female rats fed the same diet did not. Nielsen $^{25,26}$ found that, with males, regardless of copper status, a supplement of 6 or 12 mg of methionine/g diet elevated plasma cholesterol. In these groups, copper deficiency did not cause a noteworthy additional increase in plasma cholesterol in the male Sprague-Dawley rats, but did cause an apparent increase in the male Long-Evans rats. On the other hand, copper deficiency did not elevate plasma cholesterol in male Long-Evans rats fed a supplement of 6 mg cystine/g diet. With the females, adding sulfur amino acids to the diet did not increase plasma cholesterol concentrations. Regardless of dietary sulfur amino acids, copper deficiency elevated plasma cholesterol concentrations in females.

Thus, copper is another trace element whose nutritional need is apparently markedly influenced by several nutritional, metabolic and physiologic factors. Most likely, the practical importance of copper in human nutrition will be established only after stressors which enhance the need for copper have been identified.

Manganese

The essentiality of manganese for various animal species is well established. Thus, it is surprising that an unequivocal case of manganese deficiency in humans has not been described. Manganese may be another trace element whose importance is manifested under special situations. There are a few manganese metalloenzymes; they include arginase, pyruvate carboxylase and manganese-superoxide dismutase. Perhaps stressing humans so that they have an enhanced need for one of these enzymes will be the situation which will show the nutritional importance of manganese. This suggestion is supported by findings which show that conditions causing the production of superoxide radicals, including exposure to hyperbaric oxygen, ozone, or ethanol, increases the activity of manganese superoxide dismutase in rats and monkeys $^{27,28,29}$. Also, manganese-deficient rats are more susceptible to ethanol toxicity than normal rats $^{30}$; ethanol toxicity increases superoxide production.
Molybdenum

A patient receiving prolonged parenteral nutrition therapy developed a syndrome described as acquired molybdenum deficiency. This syndrome, exacerbated by methionine administration, was characterized by hypermethioninemia, hypouricemia, hyperoxypurinemia, hypouricosuria and very low urinary sulfate excretion.\(^{31}\) In addition, the patient suffered mental disturbances that progressed to coma. Supplementation of the patient with ammonium molybdate improved the clinical condition, reversed the sulfur handling defect, and normalized uric acid production. Thus, an excessive intake of methionine, or other situations requiring the enhanced activity of the molybdoenzyme sulfite oxidase, may be the stress which makes molybdenum nutrition of concern.

Epidemiologic findings have implicated molybdenum deficiency in the incidence of esophageal cancer in Africa, China, and Russia.\(^{32}\) Cancer is often caused by xenobiotic compounds. The molybdoenzymes xanthine oxidase, aldehyde oxidase, and sulfite oxidase may be involved in the detoxification of xenobiotic compounds.\(^{33}\) Possibly, humans stressed by an exposure to certain xenobiotics also have an enhanced need for molybdenum.

Nickel

Vitamin B-12 status was found to affect the response of methionine/methyl group-depleted rats to nickel deprivation.\(^{34}\) An interaction between nickel and vitamin B-12 affected growth, kidney weight/body weight ratio, plasma concentrations of copper, iron and molybdenum, liver concentrations of calcium, copper, and molybdenum, and kidney concentrations of copper, manganese, and nickel. With almost all the variables affected by dietary nickel, the effects were influenced by vitamin B-12 status. With many of the variables, vitamin B-12 deprivation made, or tended to make, the nickel-supplemented rats essentially the same as the nickel-deprived rats. As a result, it was suggested that vitamin B-12 is necessary for the optimal expression of the biological role of nickel. Thus, the need for nickel by humans may become evident under situations in which one of the vitamin B12-dependent enzyme systems is functioning suboptimally.

Selenium

Selenium was first shown to be nutritionally important by using vitamin E-deficient animals.\(^{35}\) Close examination of the data indicates that a very limited number of deficiency signs are caused exclusively by selenium deficiency; most signs are enhanced by the lack of either vitamin E or antioxidants.\(^{36,37}\) Human diseases involving selenium apparently are not simple selenium deficiencies.\(^{38}\) For example, it has been suggested that Keshan disease, which responds to selenium supplementation, also involves another factor. Suggested possibilities include various toxins, hypoxia, or infectious agents, particularly viruses.\(^{39}\)

Silicon

Signs of silicon deficiency have not been described for humans. Nonetheless, the nature of the signs of silicon deficiency in animals has resulted in the speculation that the lack of silicon is involved in several human disorders, including atherosclerosis, osteoarthritis, and hypertension, as well as the aging process. Recently, findings have been obtained which suggest that silicon protects rats against aluminum-induced abnormal behavior.\(^{40}\) The findings included that high dietary aluminum decreases the silicon content in selected regions of the brain, including those thought to be involved in Alzheimer’s disease, and that brain aluminum content was elevated by aluminum supplementation of rats maintained on a low-silicon diet; no elevation occurred in rats maintained on a silicon-supplemented diet. Perhaps as humans age, the need for silicon increases, especially with unusual dietary habits such as the high consumption of aluminum.

Vanadium

Recently it was found that some haloperoxidases from red and brown algae\(^{41,42}\) and from lichens\(^{43}\) require vanadium to be active. In rats, it was found that as dietary iodine increased from 0 to 0.33 \(\mu g/g\) diet, thyroid
peroxidase activity decreased, with the decrease more marked in vanadium-supplemented (38.1 to 12.3 units/mg protein) than vanadium-deprived (18.7 to 10.3 units/mg protein) rats. Perhaps there is an enhanced need for vanadium in animals and humans with subnormal thyroid status.

STATUS OF TRACE ELEMENTS IN NUTRIENT DATABANKS

The preceding shows that an increasing number of studies have been performed to examine the importance of trace element nutriture with various forms of nutritional, metabolic, hormonal, or physiologic stress in animals and humans. These studies indicate that situations will be found in which a trace element is of nutritional significance. Thus, many of the elements described in the preceding should be considered as desirable inclusions in nutrient data banks. However, at present, trace element data in nutrient data banks are quite limited. Of the elements discussed, the USDA Standard Reference Tape or the Revised Handbook No. 8 series includes food composition data only for iron, zinc, copper and manganese. The revision of Handbook No. 8 is still incomplete and the 1963 Handbook No. 8 did not list zinc, copper or manganese (also magnesium) in foods. Thus, values for these nutrients are not available on the USDA Standard Reference tape for food groups that remain to be released; these foods include lamb, snacks, sweets and baked products. Furthermore, copper and manganese were late additions to the nutrients included in the Handbook No. 8 revision. As a result copper is missing from the first two sections, and manganese did not appear until the 5th section of the revision.

Other major nutrient databases released to the public which include trace element values include the Continuing Survey of Food Intake by Individuals (CSFII), release 2.1, and McCance and Widdowson's The Composition of Foods; both of these sources contain values for copper and zinc (and magnesium). Although these nutrient databases can be used to fill holes in the USDA Standard Reference Tape, this proves to be a difficult task. Food descriptions rarely match exactly, thus the nutrient data manager is faced with imputing values for foods described more specifically, less specifically, or merely similar to a food for which data are available. If the imputing has not been done conservatively, with a sound basis and with a flag to identify values as imputed, the "complete" hole-free nutrient database may be less valuable than the original incomplete one. By imputing data, several private nutrient databases have developed "complete" data for several trace elements which are not complete on the USDA Standard Reference Tape. However, the quality of this "complete" data depends upon the specific procedures used for imputing.

The only other sources of information about trace elements beyond the major nutrient databases are literature reports which contain a limited number of foods -- from a few to about 200. Some of this literature can be useful for roughly evaluating whole diets, if the literature includes both foods highly concentrated in the element of interest and foods which supply substantial amounts of the element because they are widely consumed. An example of a report which may allow a rough evaluation of whole diets is that by Pennington et al. This report lists the trace elements iron, zinc, copper, manganese and selenium contained in 234 foods in the FDA total diet study. The foods in this study were sampled to be geographically representative for the United States. This report provides copper, manganese and selenium (and iodine) data not available from the USDA Standard Reference Tape, and for enough representative foods that contents of total diets can be estimated.

Schubert et al. compiled data from other primary sources, systematically evaluated for quality, on the selenium contents of 114 foods chosen for selenium concentration and frequency of consumption in the USDA 1977-78 Nationwide Food Consumption Survey. Because this food list is intended to include all significant sources of selenium in the U.S. diet, it also can be useful for estimating the selenium contents of whole diets. A group of Finnish scientists issued a report which may allow a rough evaluation of the trace elements molybdenum, nickel, chromium, selenium, silicon, boron, and arsenic in whole diets. Two reports which provide the vanadium content of a limited number of foods, but which would be less useful for evaluating diets are those by Pennington and Jones, and by Byrne and Kosta.
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It should be recognized that using these abbreviated food lists to estimate the trace element contents of diets involves extensive approximations comparable to inputting values into a large database. Although working with condensed food lists involves substantial approximations, this process is still more desirable than trying to estimate the trace element contents of diets using a variety of publications listing only a few foods. These reports may vary widely in analytical methods, sample handling, sampling plans, and analytical quality control. Generally, for the trace elements arsenic, boron, nickel, silicon, vanadium, chromium, and selenium, food composition values published before 1975 should be viewed with a great suspicion or distrust. Even today, methods to determine accurately the concentration of some trace elements in biological material are still being developed, e.g. boron and vanadium. Thus, even recent publications indicating the content of some trace elements in foods can be accepted only with caution.

Basically, the preceding discussion should indicate that, except for a few major trace elements, only sparse data of uncertain reliability are available to evaluate the dietary content of trace elements emerging as important in human nutrition. The data for some of these trace elements, especially boron, chromium and selenium, are likely to be in great demand by nutrient databank users in the near future. Thus, the theme of this conference ‘A decade of progress meets a decade of challenge’ seems quite appropriate for the trace elements. Although some progress has been made in recognizing the importance of trace elements in nutrition to the point that some are included in major nutrient databases, a major challenge lies ahead. More trace element data is needed. Nutrient databank managers are going to become vividly aware that trace elements other than copper, iron and zinc are important in human nutrition.

REFERENCES


