New Essential Trace Elements for the Life Sciences

FORREST H. NIELSEN

US Department of Agriculture, Agricultural Research Service, Grand Forks Human Nutrition Research Center, Grand Forks, ND 58202

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ABSTRACT

The possible importance of some new essential trace elements in nutrition is discussed. Most likely, insufficient intake of a specific trace element becomes obvious only when the body is stressed in some way that enhances the need for that element; this has been supported by recent findings with selenium. The trace elements boron and copper may be of nutritional significance in a manner similar to selenium. When the diets of animals and humans are manipulated to cause possible changes in cellular integrity or in hormone responsiveness, a large number of responses to dietary boron occur. The findings indicate that boron is important for optimal calcium and, thus, bone metabolism. High dietary cystine and fructose exacerbate the signs of copper deficiency in rats; this indicates that the response to copper deficiency by humans would vary with the amino acid and carbohydrate composition of the diet. There is some evidence that chromium, molybdenum, nickel, arsenic, and vanadium may also be of nutritional significance under stress conditions. In other words, an increasing number of studies have been performed that have examined the importance of trace element nutriture in 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. It is likely that some of the trace elements are more important in human nutrition than is now generally acknowledged.

Index Entries: Trace elements; boron, copper, selenium, chromium, molybdenun, nickel, arsenic, vanadium.

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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, fluorine, 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 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. In the following, it is suggested that 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 physiologic stress have indicated that these are situations in which some of the trace elements may be of nutritional significance.

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 powerful homeostatic mechanisms that the human body possesses. However, there are situations that may make a trace element nutritionally significant. These include:

1. Inborn error of metabolism that affects 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 becomes 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:

$$\text{Pathological Effects} = \text{Stress} \times \text{Organic Vulnerability}$$

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 an inappropriate 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 physiologic stress affected by that element most likely would lead to serious pathological consequences. The preceding concept is supported by findings with selenium.

Selenium was first shown to be nutritionally important by using vitamin E-deficient animals (*2*). Close examination of published data indicates that a very limited number of deficiency signs are caused exclusively by selenium deficiency; most signs appear when vitamin E or antioxidant metabolism is suboptimal (*3,4*). Human diseases involving selenium apparently are not simple selenium deficiencies (*5*). 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 (*6*).

Examining the possibility that other trace elements are important in human nutrition in a manner similar to selenium has revealed several candidates of potential nutritional concern, including boron, chromium, copper, molybdenum, nickel, arsenic, silicon, and vanadium. This is especially true for boron and copper, 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 (*7*), an experiment was conducted indicating that boron might be essential for chicks. Hunt and Nielsen (*8*) 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 (*9*). Since those experiments, it has been found that the response to changes in dietary

boron is markedly influenced by dietary methionine, potassium, magnesium, cholecalciferol, aluminum, and calcium (*10–14*). For example, in weanling rats fed a casein-based diet not supplemented with methionine, but containing luxuriant amounts of arginine (probably methionine-deficient) and marginal potassium, the interaction between magnesium and boron was different from that seen in rats fed optimal amounts of methionine, arginine, and potassium. In the former instance, the interaction was characterized by the deprivation of either boron or magnesium making the deficiency signs (e.g., depressed growth) of the other more marked (*10*). In the latter case, magnesium deprivation similarly affected boron-deprived and boron-supplemented rats (*12*).

Generally, the preceding studies have shown that, when the diet was manipulated to cause possibly 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 occurred. 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.

Human Studies

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 (*15*). After the women had consumed a conventional diet supplying about 0.25 mg boron/d for 119 d, they were given a boron supplement of 3 mg/d for 48 d. As shown in Table 1, boron supplementation markedly reduced the urinary excretion of calcium; the depression seemed more marked when dietary magnesium was low. Boron supplementation also markedly elevated the serum concentrations of estradiol-17β and, as shown in Table 1, 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 (*16*). After the subjects had consumed a

Table 1
Effect in Postmenopausal Women of Boron and Aluminum on Plasma Ionized and Urinary Calcium[a]

Dietary Treatment		Low-Mg Diet		Adequate-Mg Diet	
B	Al	Plasma iCa	Urinary Ca	Plasma iCa	Urinary Ca
mg/day	mg/day	%	g/24 hr	%	g/24 hr
0.25	0	49.7	0.117	49.5	0.132
0.25	1000	49.1	0.124	49.1	0.128
3.25	0	52.1	0.065	51.0	0.104
3.25	1000	51.6	0.073	51.5	0.113
		Analysis of Variance - p Values			
Boron		0.001	0.0001	0.002	0.02
Aluminum		NS	NS	NS	NS
Boron x Aluminum		NS	NS	NS	NS

[a]Experimental conditions described in reference (*15*).

conventional diet supplying about 0.23 mg boron/2000 kcal for 63 d, they were given a boron supplement of 3 mg/d for 49 d. When the last 42 d of depletion and the last 35 d of repletion were compared, several indicators of calcium status were found to be significantly different ($p < 0.05$). As shown in Table 2, plasma ionized calcium was increased and serum osteocalcin was decreased 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 calcitonin (74.1 vs 59.0 pg/mL) and glucose (93 vs 88 mg/dL) were higher during boron depletion than during boron repletion.

Table 2 shows that the subjects who were receiving estrogen therapy to prevent calcium loss from bone had the highest plasma ionized calcium and lowest serum osteocalcin. Boron supplementation after 63 d of boron depletion tended to make the values of the other two groups more similar to those of the women receiving estrogen therapy. These types of changes were the same for serum 25-hydroxycholecalciferol, calcitonin, 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.

Table 2
Effect of Boron on Plasma Ionized Calcium in Individuals Fed a Low Magnesium Diet[a]

Dietary Boron	Plasma iCa		Serum Osteocalcin
mg/day	mg/dL	%	ng/mL
Men over age 45 (n = 5)			
0.25	4.86	52.1	3.7
3.25	4.92	53.2	3.6
p values	0.06	0.004	0.74
Postmenopausal women (n = 4)			
0.25	4.90	52.4	3.8
3.25	4.97	53.6	3.5
p values	0.008	0.06	0.58
Postmenopausal women on estrogen therapy (n = 5)			
0.25	4.95	53.2	2.8
3.25	5.04	54.3	1.8
p values	0.02	0.02	0.08
Above combined plus one premenopausal woman (n = 15)			
0.25	4.91	52.6	3.3
3.25	4.98	53.8	2.8
p values	0.0001	0.0001	0.06

[a]Brief description of experimental conditions in text and in reference (*16*).

NUTRITIONAL SIGNIFICANCE OF COPPER

Animal Studies

Copper deficiency in experimental animals causes many sequelae (*17,18*). A number of abnormalities seem to have implications for human health and include impairment of glucose metabolism, abnormal lipid metabolism and hypercholesteremia, cardiac necrosis, dissecting aneurysms, osteopenia and bone fracture, impaired myelination, anemia and leukopenia, and congenital anomalies. When rats die from copper deficiency, the most common cause is sudden death through structural failure of the heart or arteries.

Recently, a number of dietary factors were found to affect the nature and severity of the signs of copper deficiency. These include sex and genetic makeup of the animal (*19–23*), and dietary carbohydrate and sulfur amino acid content (*22,23*).

Fields and coworkers (*19,20*) have shown that the use of fructose instead of starch as the dietary source of carbohydrate markedly in-

creased the severity and extent of copper deficiency signs in rats. They also reported (*19,20*) 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.

Examples of how genetic makeup, sex, and dietary sulfur amino acids affect copper deficiency are shown in Table 3. 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. In all other groups of males fed supplemental sulfur amino acids, copper deficiency elevated plasma cholesterol; the only exception was the groups of male Long-Evans rats fed the 6 mg cystine/g diet. With the females, adding sulfur amino acids to the diet did not increase plasma cholesterol concentrations. Copper deficiency elevated plasma cholesterol concentrations in all groups of females.

The effect of sex and genetic factors on the hematocrit response to copper deficiency was especially noticeable when the rats were fed the 6 mg cystine/g diet. With this diet, the copper-deficient females and Long-Evans males showed only a mild depression in hematocrit. The copper-deficient Sprague-Dawley males exhibited a more severe depression in hematocrit. The effect of sex on the hematocrit response was also quite apparent when the rats were fed the 16 mg arginine/g diet. The females did not show a depression in hematocrit when deprived of copper, whereas the males did.

Human Studies

Epidemiologic 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 contained substantially less copper than was previously believed (*24*). Apparently less than 25% of diets in the US 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 (25) fed eight men and eight women diets low in copper for periods ranging from 42–120 d in four separate studies. Only one man showed definite signs of copper depletion (*25,26*) with significantly depressed plasma copper and erythrocyte superoxide dismutase, and increased plasma cholesterol. 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 (*27*). No changes in serum ceruloplasmin were found in the men.

Table 3
Effect of Genetic Makeup, Sex, and Dietary Sulfur Amino Acids on Hematocrits and Plasma Cholesterol in Rats[a]

Treatment[b]		Hematocrit			Plasma cholesterol		
Cu	Amino acid	Female SD[c]	Male SD	Male LE[d]	Female SD	Male SD	Male LE
μg/g	mg/g	%			mg/100 mL		
0	16 Arginine	41.4	28.8	27.4	96	99	109
6	16 Arginine	42.3	41.8	38.8	85	90	103
0	2 Methionine	32.3	19.9	–	120	128	–
6	2 Methionine	40.5	41.0	–	89	90	–
0	6 Methionine	31.9	21.3	21.8	124	114	160
6	6 Methionine	41.3	40.5	38.5	82	111	125
0	12 Methionine	24.5	22.6	20.8	120	119	161
6	12 Methionine	41.7	40.5	38.7	78	115	137
0	6 Cystine	38.1	19.0	34.9	94	133	114
6	6 Cystine	41.0	40.5	38.7	81	87	111
0	12 Cystine	26.3	15.2	29.2	116	130	123
6	12 Cystine	41.7	39.9	38.3	78	97	107
0	6 Met + 6 Cys	28.9	18.9	17.7	128	126	160
6	6 Met + 6 Cys	42.2	40.2	38.3	78	112	108
		Analysis of variance—*p* values					
Copper		0.0001	0.0001	0.0001	0.0001	0.0001	0.001
Amino acid (AA)		0.0001	0.0001	0.0001	0.03	0.001	0.0008
Cu × AA		0.0001	0.0001	0.0001	0.006	0.0004	NS
Error mean square		5.1	6.6	7.8	187	171	750

[a]Experimental conditions described in references (22,23).
[b]Amounts of copper (copper sulfate) and specific amino acids supplemented to the diet. Six rats were assigned to each treatment group.
[c]Sprague-Dawley.
[d]Long-Evans.

In the one study with women, plasma copper 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 (25).

The described 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. This suggestion is supported by a recent study conducted at the Grand Forks Human Nutrition Research Center (unpublished observations). In this study, ten healthy men were fed a mixed Western diet that supplied about 0.6 mg copper/2500 kcal. The diet contained a high amount of dairy and casein-based products; thus, it contained 2.4 g methionine and 0.7 g cystine/2500 kcal. After an equilibration period of 15 d, the men were placed on four dietary periods of 36 d each when the following treatments were presented:

1. Basal diet
2. Basal diet supplemented with 2 mg copper/d
3. Basal diet supplemented with 2 g cystine/d and
4. Basal diet supplemented with 2 mg copper and 2 g cystine/d.

When comparisons were made that contained all ten subjects, there were very few statistically significant changes in the variables examined. However, the subjects seemed to separate into two groups; the groups were those whose serum cholesterol did not increase during copper depletion with the high cystine diet (dubbed the nonresponders) and those whose serum cholesterol increased at least 15 mg/dL during copper depletion with the high cystine diet (dubbed the responders). Performing statistical comparisons on the two groups separately yielded a number of significant differences. An example is shown in Table 4.

Table 4 shows that, if genetic variability is accepted as being present (responders and nonresponders), serum cholesterol is affected by an interaction between dietary copper and cystine. When the nonresponders were fed high cystine, copper deficiency decreased serum cholesterol, but when they were fed low cystine, copper deficiency tended to increase serum cholesterol. When the responders were fed high cystine, copper deficiency increased serum cholesterol, but when they were fed low cystine, copper deficiency had no effect.

The preceding discussion indicates that copper is another trace element whose nutritional need is markedly influenced by several nutritional, metabolic, and physiologic factors. Future research is needed to identify clearly the stressors in humans that enhance the need for copper.

Table 4
Effect in Men of Copper, Cystine, and Their Interaction on Serum Cholesterol

	Total Cholesterol, mg/dL		
Dietary Period[a]	All Subjects	Non-responders[b]	Responders[c]
LoCu LoCys	220	223	214
LoCu HiCys	220	214	229
HiCu LoCys	215	214	216
HiCu HiCys	225	239	204
Analysis of Variance - p Values			
Copper	NS	NS	0.05
Cystine	NS	NS	NS
Cu x Cys	NS	0.01	0.03

[a]LoCu = 0.6 mg copper/d; HiCu = 2.6 mg copper/d; LoCys = 0.7 g cystine/d; HiCys = 2.7 g cystine/d.
[b]Nonresponders were subjects whose serum cholesterol did not increase during copper depletion with the high cystine diet.
[c]Responders were subjects whose serum cholesterol increased at least 15 mg/dL during copper depletion with the high cystine diet.

NUTRITIONAL SIGNIFICANCE OF OTHER TRACE ELEMENTS

Chromium

Chromium is another trace element whose need by humans apparently is influenced by nutritional or physiologic 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 chro-

mium 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 (*28*). In humans, severe trauma and exercise elevated the excretion of chromium in urine (*29*).

Molybdenum

Epidemiologic findings have implicated molybdenum deficiency in the incidence of esophageal cancer in Africa, China, and Russia (*30*). 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 (*31*). Possibly, animals and humans stressed by an exposure to certain xenobiotics 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 (*32*). 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. Moreover, the findings indicate that animals or humans with suboptimal vitamin B-12 or methionine metabolism may have an enhanced need for dietary nickel.

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 (*33,34*) and, thus, polyamine synthesis in which arsenic apparently has a role (*35*). It seems possible that situations might occur that would enhance the dietary need for arsenic.

Vanadium

Recently it was found that some haloperoxidases from red and brown algae (*36,37*) and from lichens (*38*) require vanadium to be active.

In rats, it was found that, as dietary iodine increased from 0 to 0.33 μg/g diet, thyroid peroxidase activity decreased, with the decrease more marked in vanadium-supplemented (38.1 to 12.3 μ/mg protein) than vanadium-deprived (18.7 to 10.3 μ/mg protein) rats (*39*). Perhaps there is an enhanced need for vanadium in animals and humans with subnormal thyroid status.

CONCLUDING STATEMENT

An increasing number of studies have been performed examining the importance of trace element nutriture in 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, it is likely that some of the trace elements are more important in human nutrition than is now generally accepted.

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