Nutritional Significance of the Ultratrace Elements

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Fifteen years ago there was excitement in the air for individuals interested in the importance of trace elements in nutrition. The discovery that glutathione peroxidase is a selenoenzyme had just been made. Evidence indicated that the glucose tolerance factor in brewer’s yeast was a complex composed of chromium, glutamic acid, glycine, a sulfur amino acid, and nicotinic acid. A symposium presented by the American Institute of Nutrition at the 57th Annual Meeting of the Federation of American Societies for Experimental Biology described several new candidates for essential trace element status, specifically fluorine, nickel, silicon, tin, and vanadium. Shortly after that symposium, a number of other elements were suggested to be essential, including arsenic, boron, bromine, cadmium, lead, and lithium. These were designated the “ultratrace” elements because their estimated dietary requirements usually were less than 1 µg/g, and often less than 50 ng/g dry diet. It seemed that within a short period of time one or more of the ultratrace elements would be found as the missing link in some of the unexplained human diseases such as atherosclerosis, osteoporosis, osteoarthritis, and hypertension.

The excitement was premature because the progress of research in the ultratrace element area in the past 15 years can be characterized as disappointing. Selenium has been implicated in only a few human disorders; even in these disorders, selenium deprivation apparently is not the sole explanation. The chromium glucose tolerance factor, if it does exist, still has not been identified. No physiologic function in higher animals has been found for any of the suggested ultratrace elements. In other words, none of the ultratrace elements, except possibly selenium, has been found to be of practical nutritional significance. Does this mean they are not nutritionally significant? Should the ultratrace elements be dismissed and relegated to a footnote or a summary statement in nutrition texts? I believe they should not.

Conditioned Deficiencies

Recent findings with boron, selenium, and chromium suggest that for the ultratrace elements the right questions have not been asked in the past. Emphasis has been placed upon finding simple, or uncomplicated, deficiency syndromes for specific ultratrace elements. Based on the probable nutritional requirements, and considering the diverse sources and types of foods in diets today, finding a severe uncompounded deficiency of any ultratrace element that causes an acute pathology seems unlikely. Situations other than a simple acute deficiency, however, may be possible, which would make an ultratrace element nutritionally significant. In 1982, I listed four areas of potential clinical importance for the ultratrace elements. These were 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)
inadvertent omission from a total parenteral nutrition solution, and 4) 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. Although it was implied, especially by item 2, the following probably should have been on that list: the enhanced requirement for an ultratrace element caused by a sudden or severe change in the system requiring that element. Perhaps boron best exemplifies what is meant by the preceding discussion and especially the last statement.

**Nutritional Significance of Boron**

In 1910, boron was recognized as an element of physiologic importance. In that year findings were reported indicating that boron was essential for higher plants. Conclusive evidence and acceptance of the essentiality of boron for plants dates from studies reported in 1923. A recent review indicated that between 1939 and 1944 several attempts to induce a boron deficiency in rats were unsuccessful, although the diets used apparently contained only 155 to 163 ng boron per gram. In 1945 there was a report that supplemental boron in the diet enhanced survival and maintenance of body fat and elevated liver glycogen in potassium-deficient rats. Those findings were not confirmed in a subsequent study in which rats were fed a different diet with an unknown boron content and different levels of boron supplementation. After those reports, boron was generally accepted as being essential for plants, but not for animals because they did not markedly respond to boron deprivation under optimal conditions. Nonetheless, 70 years after boron was first suggested to be essential for plants, an experiment was done indicating that boron might be essential for chicks. Hunt and Nielsen 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. Since then a number of experiments yielded extensive data that were difficult to interpret because variation in other dietary components caused marked changes in the response of experimental animals to dietary boron.

It was found in both chicks and rats that the response to changes in dietary boron was markedly influenced by the methionine, potassium, magnesium, cholecalciferol, aluminum, and calcium status of the animal. For example, in weaning 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 one of the elements, making the deficiency signs of the other more marked. In the latter case, magnesium deprivation seemed similarly to affect boron-deprived and boron-supplemented rats. Generally, the preceding studies have shown that when the diet was manipulated possibly to 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.
Clinical Investigation of Boron

With these thoughts in mind, I began to search for a situation in humans that might demonstrate an enhanced response to boron. One possibility that emerged was that of the menopausal change in production of estrogen from the reproductive organs to the adrenal cortex with subsequent modification in adipose tissue. Thus in 1986 a study was done to examine the effects of aluminium, magnesium, and boron on major mineral metabolism in postmenopausal women between the ages of 48 and 82 housed in a metabolic unit. In this study a boron supplement of 3 mg/day markedly affected several indices of mineral metabolism of seven women consuming a magnesium-low diet and five women consuming a magnesium-adequate diet. The women had consumed a conventional diet supplying about 0.25 mg boron per day for 119 days. Boron supplementation markedly reduced the urinary excretion of calcium and magnesium; the depression seemed more marked when dietary magnesium was low. Boron supplementation depressed the urinary excretion of phosphorus by the magnesium-low, but not by the magnesium-adequate, women. Boron supplementation also markedly elevated the serum concentrations of estradiol-17β and testosterone. In a manner similar to the changes in the urinary excretion of minerals, the elevation in serum steroids seemed more marked in the magnesium-low women. Although it was not significant, aluminum supplementation tended to reduce the steroid response of the magnesium-adequate women to boron supplementation.

The mechanism behind the boron responses of the postmenopausal women is unknown. Some findings, however, suggest that boron may affect the formation of the active or hydroxylated forms of some specific steroid hormones. Because boron deficiency was found to exacerbate the signs of cholecalciferol deficiency, including abnormal bone formation and poor growth, it was suggested that boron might be needed for a hydroxylation step that forms the active or hydroxylated form of cholecalciferol. The formation of testosterone and estradiol-17β from precursors involves hydroxylation of the ring structure. As described, these blood-borne steroids were elevated in serum of postmenopausal women given boron supplementation. Moreover, boron has chemical properties that give it the ability to complex with bioorganic compounds containing hydroxyl groups. If boron is found to affect the hydroxylation of biologic substances in the body, it could have a role in several disorders of unknown etiology, for example, osteoporosis. These hints of possible boron involvement in some such disorders show that boron is probably of nutritional significance under some stress situations, and that there is an urgent need for further research on the nutritional, biochemical, and clinical aspects of boron.

Nutritional Significance of Other Ultratrace Elements

Selenium. Boron is not the only ultratrace element that seems to be of nutritional significance when an organism is subjected to nutritional or metabolic stress. Selenium was first shown to be nutritionally important by using vitamin E-deficient animals. If one examines the data closely, it appears that a very limited number of signs of deficiency caused exclusively by selenium deficiency have been described; most all signs described are affected by vitamin E or other antioxidants. The human diseases in which selenium plays a role apparently are also not simple selenium deficiencies. 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.

Chromium. Chromium is another ultratrace 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 carbohy-
drate, protein, and fat is upset. Stress, including trauma, infection, surgery, 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.

If boron, selenium, and chromium are most nutritionally significant when an organism is under some form of stress that enhances the need for the element, perhaps some of the other ultratrace elements may be nutritionally significant in a similar way. In other words, perhaps elements such as arsenic, molybdenum, nickel, silicon, and vanadium have not yet been studied under conditions that allow higher animals, including humans, to respond markedly. Thus, to consider the ultratrace elements nutritionally insignificant may be a bit premature. Those concerned with nutrition should consider some of the following recent findings.

**Molybdenum.** Epidemiologic findings have implicated molybdenum deficiency in the incidence of esophageal cancer in Africa, China, and Russia. Xanthine oxidase and aldehyde oxidase, both molybdoenzymes, may be involved in the detoxification of xenobiotic compounds. Is it possible that animals and humans exposed to certain xenobiotics have an enhanced need for molybdenum?

**Nickel.** Dietary nickel was found to affect the growth, kidney weight/body weight ratio (KW/BW), and plasma urea response to vitamin B₁₂ deprivation in the methyl-group-depleted rat. Omitting vitamin B₁₂ from the diet enhanced growth and decreased the KW/BW in the nickel-deprived rat, but depressed growth and increased the KW/BW in the nickel-supplemented rat. Plasma urea was higher in vitamin B₁₂-deprived than vitamin B₁₂-supplemented nickel-deprived rats. Plasma urea was unaffected by dietary vitamin B₁₂ in the nickel-supplemented rat. These findings indicate that nickel may have a physiologic role related to vitamin B₁₂ metabolism. Is it possible that animals and humans with suboptimal vitamin B₁₂ status have an enhanced need for dietary nickel?

**Arsenic.** Studies with rats, chicks, and hamsters have revealed that the extent, severity, and direction 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. It therefore, seems quite possible that arsenic is important physiologically as a methylated compound or is involved in labile methyl-group metabolism, suggesting 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 require vanadium to be active. Is it possible that vanadium has an effect on the mammalian haloperoxidase, thyroid peroxidase? Perhaps vanadium nutrition should be examined in animals and humans with subnormal thyroid status.

**Summary and Conclusions**

Progress in showing the nutritional significance of the ultratrace elements has been disappointingly slow. There are, however, indications that progress may be more rapid in the future. Findings with boron, selenium, and chromium suggest that the right situations and questions are just beginning to be addressed for the ultratrace elements. In other words, it has taken time to change the attitude that an element can be nutritionally significant only if a response to a deficiency of that element occurs when all other variables are optimal. An increasing number of studies have been described that examined the interaction of specific ultratrace elements.
with various forms of nutritional, metabolic, hormonal, or physiologic stress in animals. These studies indicate that there are situations in which some of the ultratrace elements are of nutritional significance. Thus it is likely that some of the ultratrace elements are more important in humans than is now generally acknowledged. Those who are concerned with human nutrition should be cognizant of this possibility, and therefore should not dismiss the ultratrace elements as esoteric when considering the adequacy of diets.

1. JT Rotruck, AL Pope, HE Ganther, AB Swanson, DG Hafeman, and WG Hoekstra, Science 179: 588-590, 1973
17. FH Nielsen, Proc ND Acad Sci 40: 82, 1986
27. W Mertz and EE Roginski, J Nutr 97: 531-536, 1969
29. XM Luo, HJ Wei, and SP Yang, JNCI 71: 75-80, 1983