CHAPTER 33

THE ULTRATRACE ELEMENTS: ARSENIC, BORON, CHROMIUM, NICKEL, SELENIUM AND SILICON

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INTRODUCTION

Ultratrace elements are those with an estimated dietary requirement usually less than 1 μg/g, and often less than 50 ng/g of diet for laboratory animals. At least 14 elements have been suggested as fitting into the essential ultratrace element category: arsenic, boron, bromine, cadmium, chromium, fluorine, lead, lithium, molybdenum, nickel, selenium, silicon, tin and vanadium. The quality of the evidence supporting nutritional essentiality varies widely among the ultratrace elements. Here, an element is considered essential if a dietary deficiency of the element consistently results in a suboptimal biologic function that is preventable or reversible by intake of physiologic amounts of that element. Critical reviews (Nielsen 1984, 1988a) of the experimental evidence supporting the suggestion of nutritional essentiality of the ultratrace elements indicated that only arsenic, boron, chromium, molybdenum, nickel, selenium, and silicon meet the criteria for essentiality.

Methods used in assessing the status of a specific ultratrace element can be classified as direct or indirect. The direct method involves the determination of indices that change as status changes. These indices include the specific ultratrace element content in tissues and excreta, the activity or amount of specific biochemical substances in tissues, and the response to specific functional physiological tests. The indirect method involves the removal or supplementation of the ultratrace element in question from the diet and observing whether biochemical or physiological abnormalities are corrected. Both the direct and indirect methods of assessing status are helped by the determination or estimation of the dietary intake of the nutrient of interest.

SELENIUM

Evidence for Essentiality

In 1957, Schwarz and Foltz (1957) reported that sodium selenite prevented liver necrosis in rats fed diets deficient in vitamin E. Since that discovery, many reports have appeared indicating that selenium is nutritionally essential for many animal species including humans. In 1973, Rotruck and co-workers (1973) found that selenium was a component of the active site of the peroxide-destroying enzyme glutathione peroxidase. In 1979, two reports appeared which demonstrated that selenium is required by humans. In China (Keshan Disease Research Group 1979a, 1979b), it was found that Keshan disease, a juvenile cardiomyopathy, was associated with low selenium status. Dietary intervention with sodium selenite tablets prevented the disease. In New Zealand (van Rij *et al.* 1979) a surgical patient on total parenteral nutrition had her plasma selenium concentration drop to 9 ng/ml. While the plasma selenium was low, the patient had bilateral muscular discomfort which disappeared after 7 days of supplementation with 100 μg selenium/day as selenomethionine. Since that time, several other reports (Levander 1987), have appeared indicating a favorable response of humans to selenium supplementation. Thus, selenium is well accepted as an essential nutrient for humans.

Assessment of Status

Levander (1985) reviewed the techniques for assessing selenium status. They are summarized in the following discussion.

Selenium Content In Tissue And Excreta

Plasma. Although the plasma selenium concentration reflects large body selenium pools during static long-term intakes of selenium, its use for assessing selenium status in individuals is limited because people usually do not consume a diet very consistent in selenium content. Plasma selenium concentration can vary markedly with short-term shifts in selenium intake. Plasma selenium concentrations are probably satisfactory for assessing long-term status of specific groups of people because random fluctuations caused by dietary intake would tend to be nullified.

Assignment of selenium values for plasma which indicates a deficient, adequate or toxic state is difficult. However, recently reviewed findings (Levander 1985) suggest that plasma selenium concentrations less than 0.02 μg/ml indicate deficient status and concentrations near 0.09 μg/ml indicate adequate status. Thus, values significantly higher than 0.09 μg/ml should indicate a high dietary intake of selenium. In a high se-

lenium area of China, where people exhibited signs of chronic selenosis, mean blood selenium concentrations were found to be 3.2 μg/ml.

Erythrocytes. Erythrocyte selenium concentrations apparently are more suitable than plasma or serum concentrations for assessing long-term selenium status because of the slow turnover of the erythrocyte. However, care must be used with cellular material because there are findings indicating that erythrocytes did not accurately reflect the status of rats fed toxic amounts of selenium as selenized yeast (Levander and Morris 1980).

Hair. Hair selenium could serve as an indicator of selenium status because a close relationship between hair and blood selenium levels was reported for people living in China (Chen *et al.* 1980). However, because hair color (Wahlstrom *et al.* 1984), and the use of selenium-containing shampoos (Davies 1982) affect the selenium content of hair, assignment of hair selenium values that would indicate deficient, normal and toxic status is difficult in Western countries.

Urine. Another possible indicator of selenium status is the urinary excretion of selenium. Blood selenium concentrations apparently are reflected by the urinary excretion of the element (Griffiths and Thomson 1974). Also, the excretion of trimethylselenonium ion apparently is affected by dietary selenium (Nahapetian *et al.* 1983). Thus, quantification of urinary metabolites may be useful in assessing selenium status. However, like plasma selenium, short-term shifts in dietary selenium are likely to affect the urinary excretion of selenium and, therefore, limit its usefulness in assessing status.

Activity/Amount of Specific Biochemical Substances

Glutathione Peroxidase. The one known biochemical function for selenium in humans is as an integral part of the enzyme glutathione peroxidase. In New Zealand, where the dietary selenium intake is low, it was found that whole-blood glutathione peroxidase activity correlated with the selenium concentration when the latter was less than 0.10 μg/ml in whole blood (Thomson *et al.* 1977) or less than 0.14 μg/ml in erythrocytes (Rea *et al.* 1979). Above these concentrations the enzyme activity tended to plateau. Thus, low blood glutathione peroxidase apparently can be an indicator of low selenium status; its use as an indicator of high status is limited.

Perhaps a better indicator of selenium status than blood glutathione peroxidase is the activity of the enzyme in platelets. Platelets have a high selenium content, relatively fast turnover, and contain no hemoglobin. Hemoglobin might interfere with the determination of glutathione

peroxidase activity. Moreover, animal and human studies have shown that platelet glutathione peroxidase activity responds to dietary selenium (Levander *et al.* 1983a, b).

One must be aware that the use of glutathione peroxidase as an index of selenium status can be affected by a number of variables including age, sex, exposure to pro-oxidants, toxicants or heavy metals, and deficiencies of iron or vitamin B_{12} (Ganther *et al.* 1976).

Functional Physiological Tests

A number of functional physiological tests have been suggested as possible indicators of selenium status; these include erythrocyte hemolysis, erythrocyte selenium uptake, exhalation of hydrocarbons and bactericidal capacity of neutrophils. However, none of these techniques has been extensively developed.

CHROMIUM

Evidence for Essentiality

In 1959, Schwarz and Mertz (1959) reported that chromium was necessary for normal glucose utilization; chromium-deficient rats exhibited a glucose intolerance similar to clinical diabetes mellitus. Since that discovery, a number of reports have appeared indicating that chromium is needed for normal carbohydrate, lipid and protein metabolism; these were recently reviewed (Saner 1986; Borel and Anderson 1984). In 1977, Jeejeebhoy and co-workers (1977) reported the first case of human chromium deficiency. A subject on total parenteral nutrition for 3½ yr exhibited impaired glucose tolerance and glucose utilization, weight loss, neuropathy, elevated plasma free fatty acids, depressed respiratory quotient, and abnormalities in nitrogen metabolism. These abnormalities were alleviated by chromium supplementation.

It is apparent from the preceding that chromium is an essential nutrient which influences insulin sensitivity, and thus carbohydrate, lipid and protein metabolism. However, the specific biochemical function of chromium has not been clearly identified; that is, the chemical nature of the relationship between chromium and insulin function has not been defined. Lack of this critical knowledge has retarded progress in the establishment of the nutritional importance of chromium, and of indices for assessing chromium status. Because exceedingly high oral intakes are necessary to achieve chromium toxicity, only possible indices of low and normal chromium status are presented here.

Assessment of Status

Chromium Content In Tissue And Excreta. The chromium concentrations in tissue are 10–100 times higher than those in blood. Tissue chromium stores apparently are not in equilibrium with blood chromium.

Plasma. Fasting plasma or serum chromium concentrations probably are not good indices of chromium status (Borel and Anderson 1984; Saner 1986). Nonetheless, the relative content of chromium in plasma was markedly lower in the aforementioned chromium-deficient woman, maintained on total parenteral nutrition for 3½ yr, than in normal adults (Jeejeebhoy *et al.* 1977). Also, the fasting concentration of serum chromium was depressed in association with impaired glucose tolerance during induced acute infection (Pekarek *et al.* 1975). These reports suggest that concentrations of chromium much lower than the normal value of 0.14–0.15 ng/ml for serum or 0.26 or 0.28 ng/ml for plasma (Offenbacher *et al.* 1986) might indicate the presence of a severe chromium deficiency.

In the late 1970's, the "relative chromium response" (RCR) or the 1-h serum chromium concentration after an oral glucose load divided by the fasting serum chromium concentration times 100, was considered an index of chromium status. However, recent studies (Anderson *et al.* 1985; Offenbacher *et al.* 1985) have refuted the RCR as a meaningful indicator of chromium status.

Hair. Hambidge *et al.* (1972) concluded that hair chromium reflects endogenous chromium available to hair follicle cells provided that before analysis the hair was carefully washed and was not exposed to dyes, bleach, or other environmental contaminants. Hair chromium concentration is affected by many variables including hair growth rate, age, pregnancy, diabetes and arteriosclerosis (Borel and Anderson 1984). Reported hair chromium concentrations range from less than 200 ng/g to over 900 ng/g. Saner (1986) suggested that hair chromium concentrations lower than 200 ng/g might be considered an indication of marginal chromium deficiency in older people.

Urine. Because urine is the major excretory route of absorbed chromium and because urinary chromium may be derived from a biologically active component of plasma chromium, urinary chromium has been closely examined as a possible index of chromium status. The urinary excretion of chromium by normal healthy adults is very low, about 0.2 μg/day. This low level makes the precise measurement of urinary chromium very difficult. The chromium/creatinine ratio in a 4-h urine sample has been suggested as a reliable index of the chromium excretion rate (Gurson and Saner 1978). Because of the difficulty with analyzing for chromium at very low concentrations, increases, not decreases, in urinary

chromium have been examined as an index of chromium status. Urinary chromium excretion often increases after a glucose load or glucose utilization (Saner 1986). Thus, it was thought this test could be used to assess chromium status. However, it has been reported that urinary excretion after a glucose challenge was not predictable and did not indicate chromium status (Offenbacher *et al.* 1985; Anderson *et al.* 1982).

Activity/Amount of Specific Biochemical Substances

Because the specific biochemical function of chromium has not been identified, the determination of the amount or activity of some substance directly involving chromium can not be ascertained. Thus, there is no known specific biochemical measure of chromium status.

Functional Physiological Tests

Supplementation of chromium has been shown to improve glucose tolerance in children with protein-calorie malnutrition, some diabetics, and some people with marginally elevated blood glucose (Borel and Anderson 1984). Thus, an abnormal glucose tolerance can possibly indicate a low chromium status and improvement in glucose tolerance after chromium supplementation may be a valid indicator of chromium deficiency.

SILICON

Evidence for Essentiality

After the discovery of the essentiality of chromium, 10 yr passed before evidence began to accumulate suggesting that another element, silicon, might also be essential. In 1969–1970, Carlisle (1969, 1970) reported that silicon is localized in the active growth areas in bones of young mice and rats, and suggested that silicon might be needed for bone calcification. Subsequently, several reports appeared describing signs of silicon deprivation in chicks and rats. These early studies were summarized by Carlisle (1975). Most of the signs of silicon deficiency indicated aberrant metabolism of connective tissue and bone. Animals in those early studies were fed crystalline amino acid diets that did not produce optimal growth in controls. Carlisle (1980a, b) developed a semisynthetic, silicon-deficient diet that produced near optimal growth in chicks. With this diet, in contrast to amino acid diets, silicon deprivation did not affect chick growth or outward appearance but did affect connective tissue and bone. Abnormalities included structural abnormalities of the skull associated with depressed collagen in bone, and long bone abnormalities characterized by small, poorly formed joints and defective endochondrial bone growth.

Silicon-deficient chick tibiae exhibited depressed contents of articular cartilage, water, hexosamine, and collagen. Thus, although some of the early evidence for the essentiality of silicon may have been disputable because of the poor growth of the experimental animals, Carlisle's (1980a, b, 1984) more recent findings clarify the issue and indicate that silicon can be accepted as an essential nutrient.

Assessment of Status

More work is needed to clarify the consequences of silicon deficiency in humans. To date, a syndrome of silicon deficiency in humans has not been described. The form needed and minimum requirement of silicon have not been ascertained for any animal, so there is no basis for conjecture concerning possible human requirements. Without knowledge of a sign of deficiency or what constitutes a low intake of silicon, methods for assessing status can not be established. Speculation (Carlisle 1975, 1984) that silicon might be involved in several human disorders including atherosclerosis, osteoarthritis, hypertension, and in the process of aging demonstrates the critical need for the study of silicon nutrition and status assessment, especially in aging humans.

The chronic oral ingestion of small amounts of many silicious materials is generally considered safe as evidenced by the number of silicates on the Food and Drug Administration's Generally Recognized as Safe list. Thus, there does not seem to be an immediate concern about establishing indices indicating an excessive oral intake of silicon.

In spite of the above, one should be aware that silicon in blood might be found as an index of silicon status. The silicon concentration in human serum usually falls in a narrow range, near a mean of 50 μg/dl, and is similar to the concentration of silicon in other body fluids except urine (Carlisle 1984). Although the concentration of silicon in blood is quite consistent, findings with rats indicate that it can be moderately changed over time by feeding metasilicate or markedly changed by feeding organic silicates (Carlisle 1984). Moreover, increased blood silicon has been associated with increased silicon in certain tissues (Carlisle 1980b). Urinary silicon most likely will not be found useful in assessing silicon status because it apparently reflects current dietary intake (Carlisle 1984).

NICKEL

Evidence for Essentiality

The first evidence that nickel might have a physiological function appeared in 1970 (Nielsen and Sauberlich 1970). However, it has been only

since 1975 that diets and environments that allow for optimal growth and survival of experimental animals have been used in studies of nickel nutrition and metabolism. Up until 1984, it was believed that clear signs of nickel deprivation had been described for six animal species (Nielsen 1984). Many of the signs indicated that nickel was important for iron absorption and for zinc and iron utilization. In 1984, Nielsen and coworkers (1984) reported findings showing that dietary nickel in quantities not considered particularly high, or about the amounts used for supplementing control diets in some studies, could have pharmacologic and toxicologic effects in iron-deficient rats. In other words, the most evident actions of nickel on iron metabolism occurred when nickel intakes far exceeded the amounts suggested to meet requirements (about 50 ng/g diet). Apparently the signs of nickel deficiency need redefinition. Nonetheless, examination of studies done to date reveals that some were done in a manner which makes one believe the reported deficiency signs were real. In other words, the nickel-deprived animals were compared to controls which were growing optimally and receiving a nonpharmacologic nickel supplement. Under these conditions, nickel deprivation impaired iron utilization and altered the trace element profiles of bone and liver. Thus, there still is good evidence to indicate that nickel is an essential nutrient. Further support of the postulate that nickel is essential is the finding that nickel is a component of a number of enzymes found in plants and microorganisms (Nielsen 1984).

Assessment of Status

The physiological role of nickel in animals or humans is still unclear. Moreover, a syndrome of nickel deficiency for humans has not been described. Finding or inducing a nickel deficiency in a human may be difficult because the hypothetical nickel requirement, based on animal data, of near 35 μg daily is much less than the indicated usual dietary intake of humans, which ranges between 170–700 μg daily (Nielsen 1987). Thus, finding indices indicating a nickel deficiency in humans has not received any attention.

The chances for occurrence of a life-threatening toxicity of nickel through oral intake is low, ranking with such elements as zinc and chromium. However, because of nickel ubiquity, and avidity for proteins and amino acids, some solutions used for parenteral nutrition may contain enough nickel to cause adverse reactions. Recently reviewed findings (Nielsen 1987) suggest that the infusion of solutions highly contaminated with nickel could cause undesirable changes in cardiac and uterine function and allergic reactions. Moreover, because embryonic tissue retains greater amounts of parenterally administered nickel than maternal tissue, anomalies could occur in the embryo without recognizable effects in

the mother. Thus, serum values above the reported normal range should be of concern in people on total parenteral nutrition. For humans, the reported range of nickel concentration in serum of healthy humans is 0.8–5.2 μg/l (Nielsen 1987).

ARSENIC

Evidence for Essentiality

In 1975–1976, the first findings showing that arsenic is essential came from two laboratories. Reviews by Nielsen and Uthus (1984), and Anke (1986) summarized the signs of arsenic deprivation found in four animal species–chick, goat, pig and rat. In the goat, pig and rat, the most consistent signs of arsenic deprivation were depressed growth and abnormal reproduction characterized by impaired fertility and elevated perinatal mortality. Other notable signs of deprivation in goats were depressed serum triglycerides and death during lactation. Histological examination revealed myocardial damage in the lactating goats that died. 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 metabolism (Nielsen 1988b). Thus, it seems quite possible arsenic is important physiologically as a methylated compound or is involved in labile methyl metabolism.

Assessment of Status

Like silicon and nickel, the specific biochemical function of arsenic still needs clarification. Also, a syndrome of arsenic deficiency for humans has not been described. Thus, the establishment of indices of low-arsenic status in humans has not received any attention. Perhaps this lack of attention should be of concern because animal studies indicate it is likely that there are safe and necessary levels of arsenic intake that would permit optimal health for humans throughout a lifetime. Animal studies also indicate that the human arsenic requirement might be near 12–25 μg daily (Nielsen 1988b). This intake may be difficult to achieve if efforts are mounted to eliminate as much arsenic as possible from dietary sources because of its tenuous reputation for being a poison or a carcinogen.

Signs of chronic arsenicalism in humans include the development of dermatosis of various types including hyperpigmentation, hyperkeratosis, desquamation and loss of hair; hematopoietic depression; anhydremia because of the loss of fluids from blood; liver damage characterized by jaundice, portal cirrhosis and ascites; sensory disturbances and peripheral

neuritis; anorexia and loss of weight (Squibb and Fowler 1983). Confirming that a person presenting these signs is suffering from arsenic toxicity usually can be done by finding elevated amounts of arsenic in body fluids and tissues. Tissues rich in keratin, which contains sulfhydryl groups to which inorganic arsenic may bind, probably are most useful to assess arsenic toxicity; these include skin, hair and nails. Arsenic concentrations markedly in excess of 1 μg/g for these tissues would indicate an elevated exposure to arsenic (Ishinishi *et al.* 1986; Vahter 1983; Anke 1986). Arsenic in urine may be useful as an index of exposure (Ishinishi *et al.* 1986; Vahter 1983; Anke 1986), but dietary habits must be known. Eating a diet high in seafood can markedly elevate the arsenic concentration in urine. Normal concentrations of arsenic in urine of people with no known high exposure are apparently in the range of 5–50 μg/l; ingestion of seafood containing high amounts, but nontoxic, organic arsenic, can increase the concentration to more than 1 mg/l (Ishinishi *et al.* 1986). Arsenic in blood increases with increasing exposure (Vahter 1983), thus, it may be helpful in diagnosing excessive arsenic exposure. The concentrations of arsenic in blood has been found to be 2.5–5.1 μg/l for healthy persons not exposed to excessive arsenic (Vahter 1983; Anke 1986).

BORON

Evidence for Essentiality

Hunt and Nielsen (1981) 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 interacts in some manner, other than through a direct effect on cholecalciferol metabolism, with the metabolism of calcium, phosphorous, and magnesium (Nielsen 1988b). A series of experiments were done with rats which gave further evidence that boron is involved in major mineral (calcium, phosphate, magnesium) metabolism (Nielsen 1988b). Among the signs of boron deprivation exhibited by rats fed marginal methionine were depressed growth and bone magnesium concentration, and elevated kidney weight/body weight ratio.

The first evidence that boron has a beneficial, if not essential, role in humans was presented by Nielsen *et al.* (1987). A boron supplement of 3 mg/day markedly affected several indices of mineral metabolism of 7 women consuming a magnesium-low diet and 5 women consuming a magnesium-adequate diet; the women had consumed a conventional diet supplying about 0.25 mg boron/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 markedly elevated the serum concentrations of estradiol-17β and testosterone; the elevation seemed more marked when dietary magnesium was low. The findings indicated that supplementation of a boron-low diet with an amount of boron commonly found in diets high in fruits and vegetables induces in postmenopausal women changes consistent with the prevention of calcium loss and bone demineralization.

Assessment of Status

The finding that boron may be nutritionally important for humans is so new that there has been no opportunity to investigate possible indicators of inadequate boron status. The determination of boron in biological material has been inhibited by the lack of precise and sensitive analytical methods. Thus, even recent animal studies on boron essentiality have not indicated any useful indices for assessing human boron status. Moreover, because boron is not a particularly toxic element, indices for chronic excessive boron intake are not well defined. There is a need to find indicators for boron status because it seems likely that boron will be found to be a contributing factor to some disorders characterized by abnormal mineral metabolism. It is quite possible that persons consuming diets low in foods of plant origin might not be consuming adequate boron (Nielsen 1988b; Nielsen *et al.* 1987).

CONCLUSIONS

At present, no single isolated measurement can assess the status of any ultratrace element. The assessment of status requires careful planning and interpretation, and involves three approaches. These are: (1) analytical determinations (tissue concentrations and excreta amounts), (2) biochemical measurements, and (3) functional physiological tests. To establish the deficiency state, the best approach is to find a low concentration of the ultratrace element in a body fluid and/or tissue and to combine that observation with a finding of suboptimal biochemical and/or physiological function. A subtoxic-to-toxic state usually can be confirmed by a finding of high concentrations in blood and urine.

For the ultratrace elements, much work needs to be done. Future progress in understanding the extent of suboptimal status of specific ultratrace elements in humans depends largely on the successful development of valid assessment criteria.

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