Are nickel, vanadium, silicon, fluorine, and tin essential for man? A review[1,2]

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"A trace element whose deficiency in experimental animals requires unique environments and the preparation of special diets can hardly be of interest to human nutrition." . . . "Nickel is so ubiquitous, it will never be of concern to the human nutritionist." . . . "Research with the 'newer' trace elements is of academic interest but of little relevance."

Investigators concerned with the role of the newer trace elements in nutrition often hear such opinions from colleagues with interests in other aspects of nutrition or metabolism. Such opinions may reflect a lack of appreciation of the fact that a short time ago zinc deficiency was thought to be an esoteric consideration as far as human nutrition is concerned (1). Since then it has been established that zinc deficiency does occur in man. The syndrome has been described in individuals from the United States (2) as well as from Middle Eastern villages (3).

Today, the United States population consumes more highly refined foods, food product analogs, and empty calories than in the past. This change in habits should concern nutrition scientists because an inappropriate, excessive consumption of relatively non-nutritious food items such as certain snack foods, alcoholic beverages, and soft drinks may, in some individuals, contribute to the occurrence of nutritional deficiencies when those foods replace conventional foods to an inordinate degree.

The trace mineral content of such foods is of concern because, at present, knowledge of man's requirements for trace elements is incomplete. This is especially true for five elements, namely, nickel (Ni), vanadium (V), silicon (Si), fluorine (F), and tin (Sn), which recently have been found to be essential, or at least beneficial, in the diets of laboratory animals. It seems probable that some of these elements are also essential or beneficial for man. For the purpose of this report, silicon has been included with the trace elements, even though it is present in the body in relatively large amounts.

Because experimental technology is much improved, trace element research is progressing rapidly. Thus, this review may be out of date by the time it is published and other trace elements, such as lead (Pb), as suggested by Schwarz (4), may have been added to the list of "newer" trace elements which are possibly essential for man.

Nickel

Until recently, only indirect evidence suggested that nickel has a physiological role in living organisms. Now, direct evidence has been provided (5–13) which shows that nickel is indeed essential for some animals. Pathological signs consistent with nickel deficiency have been produced in chicks, rats, and swine.

Day-old chicks fed a diet containing 3 to 4 ng nickel/g and maintained in a trace element-controlled environment for 3.5 weeks showed certain biochemical abnormalities when compared with controls fed 3 μg nickel/g of diet. They included a decreased oxygen uptake by liver homogenates in the presence of α-glycerophosphate (9–11), an increase in liver total lipids (9–11), and an increase in the liver phospholipid and cholesterol fractions (13; Nielsen, F. H., unpublished observations).

Ultrastructural abnormalities in the hepatocytes were also a consistent finding (9–11). They included dilation of the cisterns of the rough endoplasmic reticulum and the swelling of the mitochondria. The swelling of the

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mitochondria was in the compartment of the matrix and was associated with fragmentation of the cristae. Other ultrastructural changes included a dilation of the perinuclear space and pyknotic nuclei. These findings extended earlier work by Sunderman et al. (12) in which they found less severe ultrastructural changes in the livers of chicks deprived of nickel.

Preliminary studies (9–11) were done in successive generations of rats. The animals were exposed to deficiency throughout fetal, neonatal, and adult life. Reproduction was apparently affected; this was indicated when seven first generation, nickel-deficient female rats experienced a 15% fetal death rate, whereas six nickel-adequate control dams showed no fetal mortality. Fetal mortality appeared to be greater in the second generation; nine nickel-deficient, second generation dams experienced a 19% loss of pups. This finding was confounded by the fact that the eight controls had a 10% loss. Loss, in the controls was, however, roughly one-half that observed in the nickel-deficient group. In all generations studied, the pups of the nickel-deficient dams weighed less at 4 days and 24 days (age at weaning) than did those from controls.

During the suckling stage, the nickel-deficient pups generally had a rougher hair coat and appeared less active. Measurements of activity by electronic monitoring of matched litters of second and third generation deficient and control sucklings showed that the nickel-deficient rats were more lethargic.

Nickel deficiency in rats, as in chicks, results in changes in the liver. The livers of the deficient rats were a muddy brown color compared with a red brown color of livers of the controls. They also had a less distinct substructure and were less friable. Homogenates of the liver exhibited a reduced oxidative ability in the presence of α-glycerophosphate. In the nickel-deficient rat liver, sucrose density gradients of liver postmitochondrial supernatants were consistent with a decrease in polysomes and an increase in monosomes. In addition, preliminary studies have shown increased nuclear RNA polymerase activity and increased active alkaline RNase/protein in the liver.

It has been reported recently that nickel deficiency can be produced in swine (5). Some of the signs include impaired reproduction and a sparse, rough hair coat. First generation piglets also grew poorly.

Thus, nickel appears to be essential. The major metabolic abnormalities observed so far in nickel deficiency have occurred principally in the liver. Ultramicroscopic morphology, oxidative ability, and lipid levels have been affected. Also observed have been abnormalities in the liver polysomal profile, increased liver nuclear RNA polymerase, and increased active alkaline RNase/protein.

No experimental evidence has been published which shows the level of nickel required by animals to maintain health; thus, this can only be approximated. An intake of 50 to 80 ng nickel/g experimental diet is probably adequate for the rat and chick (Nielsen, F. H., unpublished observations). The experimental diet contained 26% protein, 11% fat, 47% carbohydrates, and 16% fiber, minerals, and vitamins.

Grains and vegetables appear to be good sources for dietary nickel (14). Knowledge concerning the chemical form of nickel in foods of plant origin is limited. It has been shown that nickel translocates in plants as a stable, anionic amino acid complex (15). Whether organic nickel complexes are the usual compounds of nickel in plant tissues, and whether they in any way influence the bioavailability of nickel remains to be determined. Decsy and Sunderman (16) have evidence which suggests that the nickel metalloprotein, nickeloplasmin, preferentially binds nickel in the form of an organic complex which is not synthesized, or is synthesized poorly, by the rabbit in vivo. Grains which are rich in nickel are also high in phytin. Nickel can form a stable complex with phytic acid (17). Thus, it appears possible that the phytate in grains and other vegetables may decrease the availability of dietary nickel for intestinal absorption. In contrast to foods of plant origin, foods of animal origin contain relatively little nickel.

At present it appears that nickel nutriture is not a practical problem for man. If animal data can be extrapolated to man, then the dietary requirement is probably in the range of 50 to 80 ng/g diet. Most diets will provide this amount. However, diets high in foods of animal origin or fats, or both, may be low in nickel. A human diet containing 7 to 22 ng Ni/g was prepared from meat, milk, eggs, refined white bread, butter, and corn oil (14). Protein

supplied 17.4% of the calories, carbohydrate 43.5%, and fat 39.1%. Nickel nutriture may conceivably be of concern in individuals with diseases that interfere with intestinal absorption or who are under extreme physiological stress. It is known that the level of nickel in plasma is decreased in patients with cirrhosis of the liver or with chronic uremia (18). Perhaps, these findings are indicative of nickel depletion. Another consideration is the relatively high concentrations of nickel in sweat (49 μg/liter) (19). Conditions which result in large losses of sweat may conceivably increase the need for nickel. Thus, studies are needed to define the level of nickel required by man, and to ascertain whether nickel deficiency occurs naturally.

Vanadium

Data supporting the view that vanadium is an essential element for animals was first reported by Hopkins and Mohr (20, 21). The initial finding was a significantly reduced growth of wing and tail feathers in chicks fed a diet containing less than 10 ng vanadium/g. Since then, several additional deficiency symptoms attributable to low levels of dietary vanadium have been reported in rats and chicks.

Strasia (22) found that rats fed less than 100 ng vanadium/g of diet exhibited reduced body growth and a significantly increased blood packed cell volume when compared with controls receiving at least 0.5 μg vanadium/g. He also noted an increase in blood and bone iron in deficient rats. Schwarz and Milne (23) found that rats fed a highly purified amino acid diet (containing an unknown amount of vanadium) demonstrated a growth response to 50 to 100 ng vanadium/g of diet. Chicks apparently require more than 30 to 35 ng vanadium/g as depressed growth occurs at that dietary level (Nielsen, F. H., unpublished data).

Vanadium appears to have a role in lipid metabolism. It was found (20, 21) that vanadium-deficient chicks had decreased plasma levels of cholesterol at 28 days of age, but at 49 days their plasma cholesterol concentrations were greater than those of control chicks. With a diet based on peanut meal–sucrose–lard containing 30 to 35 ng vanadium/g, similarly decreased plasma cholesterol levels were found as early as 14 days of deficiency, whereas after only 28 days, significantly increased plasma cholesterol levels occurred (24; Nielsen, F. H., unpublished observations). Other recent data (25, 26) indicate that plasma triglyceride levels are also significantly increased in vanadium-deficient chicks.

In rats, reproductive performance is impaired by vanadium deprivation (25, 26). When five, fourth generation female rats were mated, there were significantly fewer live births and significantly more deaths of neonatal pups than with vanadium-sufficient controls.

Vanadium deficiency also has adverse effects on bone development in the chick (24). Histologically, the vanadium-deficient chick tibia shows severe disorganization of the cells of the epiphysis. The cells appear compressed and their nuclei flattened. These abnormalities result in a shortened, thickened leg structure. The uptake and distribution of $^{35}SO_4^{=}$ and hexosamine concentrations in the epiphysis are similar to those of the controls. It seems, therefore, that mucopolysaccharide metabolism is not affected by vanadium deficiency.

These data from four different laboratories and on two different species have established that vanadium is an essential nutrient for higher animals.

Due to limited data, the level of vanadium required by rats and chicks to maintain health can only be estimated. It appears that an intake of approximately 100 ng/g for chicks is probably adequate with an experimental diet composed of 26% protein, 6% fat, and 57% carbohydrate (balance minerals, vitamins, and non-nutritive fiber) (Nielsen, F. H., unpublished observations). Information as to the amount of vanadium in natural feeds and foods is limited. This is in part due to the difficulty in accurately analyzing for low levels of vanadium. Soremark (27) reported values obtained by activation analysis. These range from less than 0.1 vanadium/g in peas, beets, carrots, and pears to 52 ng/g in radishes. Milk generally contains less than 0.1 ng/g (fresh basis) and liver, fish, and meat contain up to 10 ng/g. Schroeder et al. (28) found few foods rich in vanadium. They include bread, some grains and nuts, vegetable oils, and a few root vegetables. These limited data indicate that many dietary items contain amounts of vanadium which are below 100 ng/g.

Obviously, many additional data are needed

before firm conclusions can be drawn; but, if man has a vanadium requirement which is similar to that of rats and chicks, adequate vanadium nutrition should not be taken for granted. A diet exclusively of milk, meat, and certain vegetables could contain less than 100 ng V/g.

Silicon

Silicon is one of the newest elements to be shown essential for animals. It was first reported (29, 30) that silicon is necessary for an early stage of bone calcification in rats and chicks. The first clear evidence that silicon is essential for animals was reported in 1972 (31, 32). Chicks fed a silicon-deficient diet had depressed growth. Pallor of the legs, comb, skin, and mucous membranes occurred. The subcutaneous tissue had a muddy to yellowish color in contrast to the white-pinkish subcutaneous tissue of the silicon-adequate control animals. The deficient chicks had no wattles and their comb was severely attenuated. Feathering was retarded. Leg bones had a thinner cortex and were shorter and of smaller circumference than were those of controls. Femurs and tibias fractured more easily, cranial bones were flatter, and beaks were more flexible. These latter gross signs supported the earlier suggestion that silicon is involved in some aspect of bone calcification.

It also was found (33) that silicon deficiency in rats results in depressed growth and skull deformations.

More recently, it has been shown (34) that the skeletal alterations involve the cartilage matrix. In the silicon-deficient chick metatarsus and tibial epiphyses, epiphyseal plates, and spongiosae, there is a significant decrease in hexosamines.

A role for silicon in mucopolysaccharide metabolism is further supported by the finding that silicon is a constituent of certain glycosaminoglycans and polyuronides where it is apparently bound to the polysaccharide matrix (35). Schwarz (35) reported 330 to 554 μg of bound silicon/g of purified hyaluronic acid from the umbilical cord, chondroitin 4-sulfate, dermatan sulfate, and heparan sulfate. These levels correspond to 1 atom of silicon per 50,000 to 85,000 molecular weight or 130 to 280 repeating units. Lesser amounts (57 to 191 μg/g) were found in chondroitin 6-sulfate, heparin, and keratan sulfate-2 from cartilage. Hyaluronic acid from vitreous humor and keratan sulfate-1 from cornea were silicon-free. Schwarz concluded from various biochemical studies that silicon is present as a silanolate, i.e., an ether (or ester-like) derivative of silicic acid, and postulated that silicon has a structural role in the glycosaminoglycans and polyuronides. Silicon may link portions of the same polysaccharides to each other, or acid mucopolysaccharides to proteins. Thus, Schwarz suggested that silicon may function as a biological crosslinking agent and may contribute to the structure and resilience of connective tissue.

It was estimated (Carlisle, E. M., personal communication) that the chick requirement for silicon as sodium silicate is in the range of 100 to 200 μg/g of experimental diet containing 26% amino acids, 5% fat, 62% carbohydrate, and 7% minerals and vitamins. It is probable that other forms of silicon are more available than the silicate. Thus, the absolute requirement probably is lower than 100 to 200 μg/g. Foods high in silicon include unrefined grains such as unpolished rice. For those who drink their calories, it should be reassuring that beer is a saturated solution of silicon containing approximately 1,200 μg/g. Dietary items of animal origin, except skin (i.e., chicken) are relatively low in silicon.

Fluorine

A beneficial function of fluorine has been known since the late 1930's when it was discovered that the fluoride ion can play a significant role in the prevention of human dental caries. In the 1960's, it was reported that treating patients suffering from osteoporosis and other demineralizing diseases with substantial amounts of sodium fluoride may result in beneficial effects upon back pain, bone density, and calcium balance. Epidemiological studies have shown that there is substantially less osteoporosis in some high-fluoride areas than in low-fluoride areas. Apparently, fluorine is not only beneficial for the maintenance of teeth, but also for the maintenance of a normal skeleton in the adult. These effects of fluorine have been reviewed by Underwood (36). If an essential element were defined as one which has a beneficial effect on health and well-being,

under the usual conditions in which individuals live, then in the light of the above evidence, fluorine would be considered an essential element in human nutrition.

Recently, interest in fluorine has been stimulated by unconfirmed reports that fluorine may be necessary for normal hematocrit levels, fertility, and growth. It has been found that during the stress of pregnancy, feeding diets low in fluoride may result in decreased hematocrits in mice (37). Also, a decrease in fertility apparently occurs (38). The number of litters produced by first and second generation females was reduced, but litter size was not affected. The condition was prevented by the addition of 50 μg fluorine/ml drinking water. Although this amount is toxic for man, it is not an unusual amount to be fed to rodents.

It also has been reported that fluorine stimulates the growth of rats fed a highly purified amino acid diet and maintained in trace element-controlled isolators (39). This observation must, until confirmed, be viewed with reservation for the following reasons: *1*) The control rats grew suboptimally, even though they were supplemented with F. *2*) Although significant, the differences in weight gain between the deficient and the control animals were small, approximately 6 g over 26 days, even though the diet contained all known essential elements including V, Si, and Sn. *3*) Others have not been able to confirm this finding even though they have fed diets containing less fluorine (36). Clearly more research will be necessary before it can be stated that fluorine is essential for growth.

At present, a requirement for fluorine cannot be estimated. However, 1 to 2 μg/g of diet (39) appears beneficial. Foods high in fluorine include sea foods (5 to 10 μg/g) and tea (100 μg/g). Cereal and other grains contain 1 to 3 μg/g. Cow's milk usually contains 1 to 2 μg/g (dry basis) (36). An important source of fluorine is drinking water. On the basis of the above experimental studies in animals and studies in man with osteoporosis, it seems possible that fluoridation of city water supplies is beneficial in ways other than in the prevention of caries.

Tin

Trace amounts of tin occur in many tissues and dietary items, but until recently, the element has been considered an "environmental contaminant" instead of a possible essential dietary factor. In 1970, it was reported that tin is essential for the growth of rats maintained on purified amino acid diets in a trace element-controlled environment (40). Rats required 1 μg tin as stannic sulfate per gram of experimental diet for optimal growth. This observation has not been confirmed.

Tin has a number of chemical properties that offer possibilities for biological function. Tetravalent tin has a strong tendency to form coordination complexes with 4, 5, 6, and possibly 8 ligands. Thus, it has been suggested (40) that tin may contribute to the tertiary structure of proteins or other components of biological importance. It also has been speculated (40) that tin may participate in oxidation-reduction reactions in biological systems because the $Sn^{2+} \leftrightarrows Sn^{4+}$ potential of 0.13 volts is within the physiological range. In fact, it is near the oxidation-reduction potential of flavine enzymes.

The levels of tin reported to promote growth in rats are similar to the amounts found in many foods of plant and animal origin (40).

Summary

Three new elements (nickel, vanadium, and silicon) have been found essential and two (fluorine and tin) possibly essential for animals. To date, these elements have not been shown essential for man. However, from animal data, it seems probable that they have an essential function in human nutrition and metabolism.

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