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"Newer" Trace Elements In Human Nutrition

Recent research indicates that vanadium, nickel, silicon, fluorine, and tin are essential in animal nutrition. They may also be essential in human nutrition. . . .

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□ THE ULTIMATE GOAL of nutrition research is to assure the population of an optimal dietary intake of essential nutrients and to prevent overexposure to others. For some time, it was believed that this goal had been obtained and that a diet including a reasonable variety of foods would furnish an adequate intake of all the essential nutrients. However, the era of affluence we are experiencing today has resulted in the increased consumption of highly refined foods, food product analogs, and empty calories. Examples of the latter include some snack foods, alcoholic beverages, and soft drinks. Inappropriate excessive consumption of these non-nutritious food items may lead to nutritional deficiencies through their replacement of conventional foods.

It is also possible that deficiencies may occur when refined foods or food product analogs which are incomplete in nutrient content are used as the major constituents of the diet. The trace mineral content of such foods is of particular concern because, at the present time, knowledge of man's requirements for trace elements is incomplete. This is especially true for five elements—vanadium, nickel, silicon, fluorine, and tin—which have been found to be essential for laboratory animals since 1970. It seems probable that these elements are also essential for man. For the purpose of this report, silicon is considered as a trace element, even though it is apparently required in relatively high amounts.

VANADIUM ESSENTIAL FOR ANIMALS

Data supporting the view that vanadium is an essential element for animals was first reported by Hopkins and Mohr (1971a;b). The initial finding was a significantly reduced growth of wing and tail feathers in chicks fed a diet containing less than 10 ppb vanadium. Since then, several additional deficiency symptoms attributable to low levels of dietary vanadium have been reported in rats and chicks.

Strasia (1971) found that rats fed less than 100 ppb vanadium in the diet exhibited reduced body growth and a significantly increased blood packed cell volume when compared with controls receiving at least 0.5 ppm vanadium. He also noted an increase in blood and bone iron in deficient rats. About the same time, Schwarz and Milne (1971) found that rats fed a highly purified amino acid diet (containing an unknown amount of vanadium) demonstrated a growth response to 50–100 ppb vanadium. Chicks apparently require more than 30–35 ppb vanadium, as depressed growth occurs at that dietary level (Nielsen, 1973).

Vanadium appears to have a role in lipid metabolism, as shown in Table 1. Hopkins and Mohr (1971a;b) found that vanadium-deficient chicks had decreased plasma levels of cholesterol at 28 days of age, but that at 49 days their plasma cholesterol concentrations were greater than those of control chicks. Recently, increased plasma cholesterol levels have been found in vanadium-deficient chicks after only 28 days of deficiency (Nielsen and Ollerich, 1973a). Other recent data (Hopkins and Mohr, 1973) indicate that plasma triglyceride levels are also significantly increased in vanadium-deficient chicks.

In rats, reproductive performance is impaired by vanadium deprivation (Hopkins and Mohr, 1973). 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.

Another recent finding has been the demonstration that vanadium deficiency retards bone development in chicks (Nielsen and Ollerich, 1973a). Histologically, the vanadium-deficient chick tibia shows severe disorganization of the cells in the epiphysis. The cells

Table 1—**EFFECT OF VANADIUM DEFICIENCY** *on chick plasma lipids*

Lipid	Vanadium-deficient diet	Vanadium-supplemented diet
Cholesterol, mg/100 ml		
(28 days)[a]	178	206
(49 days)[a]	249	224
(28 days)[b]	158 (12)[c]	145 (12)
(28 days)[d]	182 (10)	163 (10)
Triglycerides, mg/100 ml[e]	48.7 (9)	25.4 (9)

[a] Hopkins and Mohr (1971b)
[b] Nielsen and Ollerich (1973a)
[c] Number of chicks
[d] Nielsen (1973)
[e] Hopkins and Mohr (1973)

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Table 2—**LEVELS OF TRACE ELEMENTS** *in selected fresh foods*

Food	Vanadium (ppb)	Nickel[e] (ppb)	Silicon[f] (ppm)	Fluorine (ppm)	Tin[i] (ppm)
Milk	<0.1[a]	0.0	1.4	0.1– 0.2[g]	0.19–0.68
Eggs	370–680[b]	30	20–40	0.8– 0.9[h]	0.91
Red meat	<0.1[a,b]	0– 20	5–15	≃2.0[h]	0.3 –3.0
Fish	0.0[b]	20– 50	≃5	5 –10[g,h]	0.49–3.0
Oysters	110[b]	1,500	—	—	1.38
Corn oil	119[c]	0.0	0.0	—	4.10
Rice	230–820[b]	300–650	10,000 (dry)	1 – 3[g]	0.28
Oats	1,630[b]	1,710	5,700 (dry)	1 – 3[g]	2.28
Wheat	0.0[b]	0–160	200 (dry)	1 – 3[g]	0.0
Bread	70[b]	1,130	—	—	2.48
Peanuts	0.0[b]	—	200 (meal)	—	—
Peas	<0.1[a]	300	—	—	1.06
Lettuce	20[a]	140	—	—	0.07
Apples	0.0[b]	0–80	—	—	—
Sucrose	5[d]	30	5–7	—	—

[a] Soremark (1967)
[b] Schroeder et al. (1963)
[c] Welch (1973)
[d] Nielsen (1973)
[e] Schroeder et al. (1962)
[f] Carlisle (1973b)
[g] Schwarz (1971)
[h] Underwood (1971)
[i] Schroeder et al. (1964)

appear compressed and their nuclei seem flattened. These abnormalities apparently 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 4 different laboratories, and on 2 different species, have established that vanadium is an essential nutrient for higher animals.

VANADIUM INTAKE MAY BE INSUFFICIENT

Due to limited data, the level of vanadium required by rats and chicks to maintain health can only be estimated, but it appears that an intake of approximately 100 ppb is probably adequate. This is equivalent to about 34 μg/1,000 calories of experimental diet composed of 26% protein, 6% fat, and 57% carbohydrate (balance: minerals, vitamins, and nonnutritive fiber).

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 (1967) reported values obtained by activation analysis. These range from less than 0.1 ppb vanadium in peas, beets, carrots, and pears to 52 ppb in radishes. Milk generally contains less than 0.1 ppb (fresh basis), and liver, fish, and meat contain up to 10 ppb. Schroeder et al. (1963) found few foods rich in vanadium—these include bread, some grains and nuts, and a few root vegetables. These limited data indicate that many dietary items contain amounts of vanadium which are below 100 ppb. Table 2 gives representative levels of vanadium found in some foods.

Obviously, many additional data are needed before firm conclusions can be drawn; but enough data are available to suggest that the required intake of vanadium for animals will not necessarily be consumed in an ordinary diet. 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 34 μg of vanadium per 1,000 calories.

Although the extrapolation of animal data to man can be misleading, the observation of altered lipid metabolism (i.e., increased plasma cholesterol and triglycerides) in vanadium-deficient animals makes one wonder if marginal vanadium deficiency indeed occurs in man and if it is in part responsible for the increased serum lipid concentrations which occur in some individuals. Obviously, this is highly speculative at present, as there are no data available which test the hypothesis.

NICKEL HAS PHYSIOLOGICAL ROLE

Until recently, only indirect evidence suggested that nickel has a physiological role in living organisms. Now, direct evidence has been provided which supports the hypothesis (Nielsen and Sauberlich, 1970; Nielsen, 1971; Nielsen and Higgs, 1971; Nielsen and Ollerich, 1973b). By using a diet containing 3–4 ppb nickel, and a trace element controlled environment, pathologic signs consistent with nickel deficiency have been produced in chicks and rats.

Day-old chicks fed the nickel-deficient diet for 3½ weeks showed few gross signs when compared with controls fed 3 ppm nickel. Their shank skin pigmentation was altered, and their livers were less friable than those of the controls. Other gross signs were inconsistent. In contrast, certain biochemical abnormalities were more consistently found. These included a decreased oxygen uptake by liver homogenates in the presence of α-glycerophosphate, an increase in liver total lipids, and a decrease in the liver phospholipid fraction (Table 3). The total lipids and the phospholipids of the heart were both increased (Table 3).

Ultrastructural abnormalities in the hepatocytes were also a consistent finding. These included dilation of the cisterns of the rough endoplasmic reticulum and swelling of the mitochondria. The swelling of the mitochondria was in the compartment of the matrix and was associated with fragmentation of the cristae. Other ultrastructural changes included a dilation of the peri-

nuclear space and pyknotic nuclei. These findings extend earlier work in which Sunderman et al. (1972) found less severe ultrastructural changes in the livers of chicks deprived of nickel.

NICKEL APPEARS TO BE ESSENTIAL

Results from rat studies are more preliminary (Nielsen and Ollerich, 1973b; Nielsen, 1973). Successive generations of rats have been raised. Thus, the animals have been exposed to deficiency throughout fetal, neonatal, and adult life. Reproduction apparently is affected, as seven first-generation nickel-deficient dams had a significant number of dead pups (15%), compared with no mortality in the young of six controls. Nine second-generation nickel-deficient dams had a 19% loss of pups. This finding was confounded by the fact that the eight controls had a 10% loss of pups; this was, however, roughly half the loss in the deficient group. The pups of the nickel-deficient dams also weighed less at 4 days and 24 days than those of the controls. In the third generation, the nickel-deficient pups showed a generally less thrifty appearance and were less active.

Nickel deficiency in rats, as in chicks, results in a decreased in-vitro liver oxidation of α-glycerophosphate. In addition, in the nickel-deficient rat liver, preliminary sucrose density gradients of liver postmitochondrial supernatants have been consistent with a decrease in polysomes and an increase in monosomes.

Thus, nickel also appears to be essential. The major effects of deficiency so far identified have occurred principally in the liver. Ultramicroscopic morphology, oxidative ability, and lipid levels have been affected.

NICKEL DEFICIENCY NOT A PROBLEM

As with vanadium, the level of nickel required by animals to maintain health can only be approximated. It has been suggested that an intake of 50–80 ppb of nickel, or approximately 16–25 μg/1,000 calories of experimental diet, is probably adequate for the rat and chick. The experimental diet contained 26% proteins, 11% fat, 47% carbohydrates, and 16% fiber, minerals, and vitamins.

Nickel is ubiquitous. Grains and vegetables are particularly rich in nickel (Table 2). Knowledge concerning the chemical form of nickel in foods of plant origin is limited (Tiffin, 1971). It has been shown that nickel translocates in plants as a stable anionic amino acid complex. Whether organic nickel complexes are the usual compounds of nickel in plant tissues, and whether they in any way influence the bioavailability of nickel, remain to be determined. It is important to note that grains, which are indeed rich in nickel, are also high in phytin. Nickel can form a stable complex with phytic acid (Vohra et al., 1965). 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, those 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 16–25 μg/1,000 calories. Most diets will provide this amount. On the other hand, nickel nutriture may conceivably be of concern in individuals with diseases which interfere with intestinal absorption, or who are under extreme physiological stress, or who have unusual dietary habits. It is known that the level of nickel in plasma is decreased in patients with cirrhosis of the liver or with chronic uremia (McNeely et al., 1971). Perhaps these findings are indicative of nickel depletion.

Another consideration is the relatively high concentrations of nickel in sweat (Horak and Sunderman, 1973). Conditions which result in large losses of sweat may conceivably increase the need for nickel. Finally, diets high in foods of animal origin and/or fats may be low in nickel. A human diet containing 1.3–4.3 μg of nickel per 1,000 calories has been prepared from meat, milk, eggs, refined white bread, butter, and corn oil (Schroeder et al., 1962); protein supplied 17.4% of the calories, carbohydrate 43.5%, and fat 39.1%.

Studies are needed to define the level of nickel required by man, and to ascertain whether nickel deficiency occurs naturally.

SILICON ESSENTIAL FOR ANIMALS

Silicon is one of the newest elements to be shown essential for animals. It was first reported (Carlisle, 1970; 1971) that silicon is necessary for an early stage

Table 3—**EFFECT OF NICKEL DEFICIENCY** *on liver oxidative ability and liver and heart lipids of chicks*[a]

Group	No. of chicks	O_2 uptake[b] (μl/hr/mg protein)	Total lipid, liver[c] (%)	Lipid phosphorus, liver[c] (mg/g)	Total lipid, heart[c] (%)	Lipid phosphorus, heart[c] (mg/g)
Experiment 1						
Ni-def. (3 ppb)	12	4.7[d] ± 0.2[e]	6.21[f] ± 0.10	—	—	—
+ 3 ppm Ni	12	5.5 ± 0.2	5.78 ± 0.11	—	—	—
Experiment 2						
Ni-def. (4 ppb)	11	5.4[g] ± 0.2	6.27[f] ± 0.18	1.327[d] ± 0.016	4.09[f] ± 0.06	0.942[g] ± 0.007
+ 3 ppm Ni	11	6.0 ± 0.2	5.87 ± 0.05	1.379 ± 0.016	3.85 ± 0.11	0.898 ± 0.010
Experiment 3						
Ni-def. (14 ppb)	12	5.5[g] ± 0.1	5.71 ± 0.09	1.318 ± 0.016	—	—
+ 3 ppm	12	5.9 ± 0.1	5.55 ± 0.10	1.335 ± 0.015	—	—

[a] Nielsen and Ollerich (1973b) and Nielsen (1973)
[b] Using liver homogenates and with α-glycerophosphate as the substrate
[c] Fresh weight basis
[d] Significantly different ($P < 0.025$) from +3 ppm Ni group
[e] ± Standard error of the mean
[f] Significantly different ($P < 0.05$) from +3 ppm Ni group
[g] Significantly different ($P < 0.10$) from +3 ppm Ni group

of bone calcification in rats and chicks. The first clear evidence that silicon is essential for animals was reported in 1972 (Carlisle, 1972a;b). Chicks fed a silicon-deficient diet had depressed growth. Pallor of the legs, combs, skin, and mucous membranes occurred. The subcutaneous tissue had a muddy to yellowish color in contrast to the white-pinkish subcutanous tissue of the silicon-adequate control animals. The deficient chicks had no wattles, and their combs were 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 tibiae 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 (Schwarz and Milne, 1972a) that silicon deficiency in rats results in depressed growth and skull deformations. Recently, it has been shown (Carlisle, 1973a) 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 (Schwarz, 1973). Schwarz (1973) has reported 330–554 ppm of bound silicon in purified hyaluronic acid from umbilical cord, chondroitin 4-sulfate, dermatan sulfate, and heparan sulfate. These levels correspond to 1 atom of silicon per 50,000–85,000 molecular weight, or 130–280 repeating units. Lesser amounts (57–191 ppm) 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 has concluded from various biochemical studies that silicon is present as a silanolate, i.e., an ether (or ester-like) derivative of silicic acid, and has 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, it has been suggested that silicon may function as a biological crosslinking agent, and may contribute to the structure and resilience of connective tissue.

SHOULD STUDY SILICON ROLE IN HUMANS

Carlisle (1973b) has estimated that the chick requirement for silicon as sodium silicate is in the range of 100–200 ppm, or approximately 26–52 mg/1,000 calories 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 suggested above. Foods high in silicon include unrefined grains such as unpolished rice (Carlisle, 1973b). For those who drink their calories, it should be reassuring that beer is a saturated solution of silicon, containing approximately 1,200 ppm. Dietary items of animal origin, except skin (i.e., chicken), are relatively low in silicon.

At present, a role for silicon in human nutrition can only be postulated. Its possible function in mucopolysaccharide metabolism suggests that certain connective tissue diseases should be studied with regard to their effects on silicon metabolism and the possibility that abnormal silicon metabolism may be a contributory factor in their occurrence. In addition, the effects of aging on silicon status should be assessed. Observations in the rat indicate that silicon levels of some tissues decrease with age (Charnot and Peres, 1971).

FLUORINE MUST BE CONSIDERED ESSENTIAL

A beneficial function of fluorine has been known since the late 1930s, when it was discovered that the fluoride ion can play a significant role in the prevention of human dental caries. In the 1960s, 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 pains, bone density, and calcium balance. Epidemiological studies have shown that there is substantially less osteoporosis in 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 (1971). If an essential element is defined as one which is ordinarily required for health and well-being under the usual conditions in which individuals live, then in the light of the above evidence, fluorine must be considered as an essential element in human nutrition.

MORE FLUORINE RESEARCH NEEDED

Recently, interest in fluorine has been stimulated by unconfirmed reports that fluorine may be necessary for normal hematocrit levels, fertility, and growth. It was found that during the stress of pregnancy, feeding diets low in fluoride resulted in decreased hematocrits in mice (Messer et al., 1972b). Also, a marked decrease in fertility apparently occurred (Messer et al., 1972a). 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 ppm of fluorine in the drinking water.

It also was reported that fluorine could stimulate the growth of rats fed a highly purified amino acid diet and maintained in trace element controlled isolators (Schwarz and Milne, 1972b). This observation was received with reservation for the following reasons: • Experimental methods were inadequately described. • The control rats grew suboptimally, even though they were supplemented with fluorine. • 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 vanadium, silicon, and tin. • Others have not been able to confirm this finding even though they have fed diets containing less fluorine (Underwood, 1971). 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, 1–2 ppm (0.23–0.46 mg/1,000 calories) in the diet (Schwarz, 1971; Schwarz and Milne, 1972b) or water (Underwood, 1971) appears beneficial. Foods high in fluorine include seafoods (5–10 ppm) and tea (100 ppm). Cereal and other grains

contain 1–3 ppm. Cow's milk usually contains 1–2 ppm on a dry basis (Schwarz, 1971; Underwood, 1971).

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 may well be that fluoridation of city water supplies is beneficial in ways other than the prevention of caries.

SUFFICIENT TIN IN CURRENT FOODS

Trace amounts of tin occur in many tissues and dietary items, but until recently, the element has been considered an "environmental contaminant" instead of an 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 (Schwarz et al., 1970). Rats required 1 ppm tin as stannic sulfate, or approximately 0.23 mg of tin per 1,000 calories of experimental diet, for optimal growth.

Tin has a number of chemical properties which 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 by Schwarz et al. (1970) that tin many contribute to the tertiary structure of proteins or other components of biological importance. Schwarz et al. (1970) have also speculated that tin may participate in oxidation-reduction reactions in biological systems because the $Sn^{2+} \leftrightarrows Sn^{4+}$ potential of 0.13 volt is within the physiological range. In fact, it is near the oxidation-reduction potential of flavine enzymes.

The levels of tin found to promote growth in rats are similar to the amounts found in many foods of plant and animal origin (Schwarz et al., 1970). Therefore, tin nutriture is not of concern at present. On the other hand, increased use of highly refined foods, or food product analogs containing little or no tin, may alter this judgment in the future.

SHOULD INCLUDE TRACE ELEMENTS IN FOODS

In summary, four new elements—vanadium, nickel, silicon, and tin—have been found essential and one—fluorine—possibly essential for animals. To date, these elements have not been shown essential for man. However, by extrapolation from animal data, it is possible to postulate their importance in human nutrition. Moreover, the recognition of human deficiencies of other trace elements, such as zinc and copper, in certain populations and in patients with specific diseases, supports the concept that these less understood trace elements are probably also important for man.

Thus, human deficiency of one, or more, of the trace elements discussed in this paper may be observed in the future. If people are consuming diets low in any of these elements, it is currently not clinically recognized. It is also unknown whether subclinical or marginal deficiencies occur. In any case, prevention of marginal deficiencies may be prudent. Inclusion of reasonable amounts of these less well understood trace elements in food product analogs and their replacement in refined foods may be desirable.

It is my opinion that the speculations and suppositions I have made today may be established as true in the not too distant future. In addition, thanks to improved experimental technology, trace element research is moving so rapidly that this discussion may be out of date by the time it is published and other trace elements will have been added to the list of "newer" trace elements which are probably essential for man.

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