FLUORIDE, VANADIUM, NICKEL, ARSENIC, AND SILICON IN TOTAL PARENTERAL NUTRITION*

FORREST H. NIELSEN, Ph.D.

United States Department of Agriculture
Agricultural Research Service
Grand Forks Human Nutrition Research Center
Grand Forks, North Dakota

DEFICIENCY in humans has not been described for vanadium, nickel, arsenic, silicon, or fluoride. Thus, at present, the possible importance of these elements for human health and nutrition are only implied from findings with experimental animals. Generally, extrapolation from experimental findings in animals to humans is difficult. For the major trace elements clearly required by humans, however, signs of deficiency often correspond closely with signs observed in experimental animals. Possibly, therefore, the elements under discussion here, which are essential for other animals, also are essential for humans. Further, some of the deficiency signs and requirements described for animals might have counterparts among humans. Thus, those concerned with human nutrition should be aware that further research might prove that vanadium, nickel, arsenic, silicon, and fluoride play more important and widespread roles in human health than are now acknowledged.

FLUORIDE

A beneficial function of fluoride has been known since the late 1930s, when it was discovered that fluoride can play a significant role in the prevention of human dental caries. Subsequently, epidemiologic findings suggested that fluoride is beneficial for the maintenance of a normal skeleton in adults.[1,2] A number of reports describe the treatment response of patients suffering from osteoporosis and other demineralizing diseases to whom substantial amounts of sodium fluoride were given. In some patients, back pain, bone density, and calcium balance were improved.

In the early 1970s several reports suggested fluoride may be necessary

*Presented as part of the *Working Conference in Parenteral Trace Elements-II* held by the Section on Clinical Nutrition of the New York Academy of Medicine and the Department of Foods and Nutrition of the American Medical Association at the Academy September 14 and 15, 1982.

for hematopoiesis, fertility, and growth in mice and rats.[3] However, subsequent findings[4,5] supported the suggestion that fluoride acted on those factors by pharmacologic, not physiologic, mechanisms, and that high dietary fluoride content can improve iron absorption or utilization from a diet marginally sufficient in iron. Thus, unless one considers the caries-preventive action of fluoride as adequate evidence, no evidence unequivocally shows that fluoride is an essential element for animals or humans. This lack of evidence does not mean that an essential function will not be found for fluoride. That fluoride enhances the intestinal absorption of iron[6] and activates some enzyme systems (i.e., adenyl cyclase)[7] indicates that this element may have an essential function in metabolism. At present, however, fluoride probably should be classified as a trace element with beneficial properties.

Because it is not known to be essential, there is no dietary requirement for fluoride. However, 1 to 2 μg. fluoride/g. of diet apparently was beneficial for rats.[8] Recently, the Food and Nutrition Board of the National Research Council estimated adequate and safe daily intakes of 0.1 to 0.5 mg. fluoride for infants less than six months of age, 0.2 to 1.0 mg. for infants between six and 12 months, 0.5 to 1.0 mg. for children between the ages of one and three years, 1.0 to 2.5 mg. for children between the ages of four and six years, 1.5 to 2.5 mg. for children from seven years to adulthood, and 1.5 to 4.0 mg. for adults.[9] These levels were considered to be protective against dental caries and perhaps eventually against osteoporosis.

Soluble fluorides are rapidly and almost completely absorbed from the gastrointestinal tract, even at high intakes. Fluoride contained in dietary substances is also readily absorbed. For example, metabolic balance studies in adult men showed that net fluoride absorption from fish protein concentrate averaged 88%.[10]

Absorbed fluoride is distributed rapidly throughout the body in a pattern similar to that of chloride. Fluoride readily crosses all membranes, including that of the erythrocyte. Bone readily retains absorbed fluoride. In fact, the level of fluoride intake below which all is excreted and none is retained in the bones must be very low, if such a level indeed exists.

The excretion of fluoride is rapid, and urine is the major route of elimination. An elevation in fluoride intake is associated with a prompt and marked elevation in urinary fluoride excretion. Excretion from the intestinal tract is low. Average individuals on ordinary diets excrete 80% or more of their ingested fluoride in the urine.[11]

Chronic ingestion of excessive fluoride adversely affects teeth, bone, tendons, and ligaments. Osteosclerosis (elevated bone calcium and overgrowth) and calcification of ligaments and tendons are caused by the chronic ingestion of high-fluoride water.[12] Roholm[13] estimated that the daily ingestion of 20 to 80 mg of fluoride for 10 to 20 years would result in crippling skeletal fluorosis. At lower levels of intake from drinking water, excessive fluoride can lead to tooth mottling (dental fluorosis) in children.[14] The occurrence depends on the diet and ambient temperature. Some children will develop changes when fluoride levels in water exceed approximately 0.7 to 1.3 mg./liter.[15] These levels are very close to the level at which water supplies are fluoridated to prevent tooth decay. Generally, however, fluoride intakes that may eventually be toxic produce no early, observable adverse effects. The reasons for this latent period are that urinary fluoride excretion responds to elevated intake and retained fluoride is deposited in the skeleton, which can accept relatively large amounts of that ion before saturation is reached.

The lack of conclusive evidence supporting the essentiality or physiological function of fluoride makes it difficult to comment on its use in parenteral fluids. Perhaps the most useful comment is a word of caution because of the adverse effects of high intakes of fluoride on bone and teeth. Parenteral fluids should not supply more fluoride than that usually supplied by normal consumption of food and water. No evidence available supports supplementation of parenteral fluids with fluoride. It is presently unknown if fluoride should be included in parenteral fluids of patients on long-term, home maintenance. If fluoride is given to such patients, it should be given cautiously, in amounts that do not exceed usual daily intakes. Range of average fluoride intake has been found to be 0.78 to 3.44 mg. daily.[16]

VANADIUM

A recent summary described the evidence for the nutritional essentiality of vanadium from whole animal experiments as inconclusive.[17] Basically, several laboratory groups found after many experiements that vanadium deprivation adversely affected growth, feathering, hematocrits, plasma cholesterol, bone development, and liver lipid, phospholipid, and cholesterol content in chicks, and perinatal survival, growth, physical appearance, hematocrits, plasma cholesterol, and liver lipid and phospholipid content in rats. Unfortunately, no sign of vanadium deprivation in either

chicks or rats was found consistently throughout all experiments. At present, therefore, based on published findings, vanadium cannot be unequivocally classified as an essential nutrient for any animal.

Recent *in vitro* studies have indicated that vanadium may have a specific physiological role as a regulator of (Na,K)-ATPase and other phosphoryl transfer enzymes. Since 1977, when Cantley et al.[18] found that pentavalent orthovanadate was a naturally occurring inhibitor of (Na,K)-ATPase, the number of reports concerned with the effect of vanadium on (Na,K)-ATPase and similar enzymes has increased. Only a few highlights of those reports are presented here.

Vanadates, apparently because they structurally resemble inorganic phosphates, affect many enzyme reactions in which phosphate is a critical component. Orthovanadate, for example, is a potent inhibitor of human alkaline phosphatase. Possibly that ion, through hydration or chelation, resembles a transition-state analogue of phosphate in the mechanism that involves a phosphoryl-enzyme intermediate and phosphoryl transfer.[19] One of the transition states might be a trigonal bipyramidal species, and vanadate can form this structure.[20]

The finding that vanadate is a potent inhibitor of (Na,K)-ATPase has aroused considerable interest in the possibility that vanadium might function *in vivo* to control the activity of the enzyme, and thus regulate the sodium pump.[21,22] Vanadate (V^{5+}) inhibits (Na,K)-ATPase by binding to the ATP hydrolysis site, but reduction of vanadate to the vanadyl ion (V^{4+}) reverses that inhibition.[23] Shifts in the redox state of a cell might shift the equilibrium concentrations of endogenous V^{4+} and V^{5+} sufficiently to alter the activity of the sodium pump, which is operated through (Na,K)-ATPase.[21,22] However, this hypothesis is clouded because the predominant oxidation state of vanadium in tissue is not 5+ but 4+. For example, in the erythrocyte, vanadate (V^{5+}) is reduced to vanadyl (V^{4+}), which then binds to hemoglobin,[24] a reaction that apparently is almost quantitatively driven by glutathione.[22] Thus, further studies are required before it can be stated that vanadium oxidation-reduction equilibrium regulates cation flow across cell membranes.

Vanadium is present in tissues at concentrations that might generally inhibit phosphoryl transfer enzymes *in vivo,* and such inhibition could reflect a regulatory function for vanadium in addition to, or other than, inhibition of (Na,K)-ATPase. However, the proposal of that function, like that proposal for (Na,K)-ATPase, would be strengthened immensely by evidence of an *in vivo* mechanism whereby the vanadium in tissue, which

apparently exists as the 4+ oxidation state complexed to protein or small molecules, would be converted to vanadium in the 5+ state. The oxidation of the vanadyl ion by cytochrome c oxidase from mitochondrial membrane *in vitro*[25] suggests that such a mechanism may be present in tissue.

In addition to its possible regulatory role, vanadium might be a cofactor for some enzyme. Possibly vanadium activates δ-ALA transaminase, which converts 4,5-dioxovaleric acid to δ-aminolevulinic acid in *Chlorella pyrenoidosa*.[26] Vanadium also stimulates adenyl cyclase of cardiac tissue.[27]

There is also a possibility that vanadium might be involved in the expression of some endocrine function. Vanadium metabolism in rats is disturbed in endocrine deficiency induced by hypophysectomy or thyroidectomy-parathyroidectomy.[28] Glucose oxidation is further stimulated by the addition of vanadate or vanadyl to a submaximally effective concentration of insulin in isolated rat adipocytes.[29]

It is difficult to suggest a vanadium requirement for any animal species, including humans, because of incomplete knowledge of conditions necessary to produce consistent vanadium deficiency and of the dietary components that affect vanadium metabolism. However, it has been found that feeding diets containing 10-25 ng. of vanadium/g. adversely affect rats and chicks under certain conditions. If these animal data could be extrapolated to humans, the calculated daily requirement for vanadium would be about 10-25 μg. under certain dietary conditions.

Most ingested vanadium remains unabsorbed by the gastrointestinal tract and is excreted in the feces. The very low levels of vanadium in urine in comparison to the estimated dietary intake and fecal level of vanadium indicate that $\leq 1\%$ of vanadium ingested is absorbed.[30] This level is lower than the estimated absorption of 5 to 12% of vanadium given as a salt,[31] but the availability or absorption of vanadium is markedly affected by food or dietary composition. For example, vanadium toxicity in chicks was alleviated by corn, dehydrated grass, cottonseed meal, ascorbic acid, EDTA, chromate, and protein.[32-36] Perhaps these various dietary ingredients were partly effective in altering absorption or availability of vanadium by affecting its form in the gastrointestinal tract. Parker and Sharma[37] found that the tissue residue of vanadium was always higher in animals fed 50 μg. of vanadium as sodium orthovanadate/g. of diet than in those given the same dose as vanadyl sulfate. Possibly this difference in tissue distribution was due to differences between the two

oxidation states of vanadium in respect to solubility in biological fluids, absorption from the gut, or metabolism and elimination by the animal. Moreover, the apparent difference in metabolism between vanadate and vanadyl and the probable effect of diet on which form predominates in the gastrointestinal tract probably explains the inconsistent findings in studies of deficiency and toxicity.

Under certain dietary conditions, 10 mg. of vanadium/kg of diet was found to be slightly toxic to chickens.[38] That level of dietary vanadium is approximately 450 to 500 times the level at which apparent vanadium deficiency signs occurred in some studies of chicks. If animal data can be extrapolated to humans, a daily dose of 10 mg. of vanadium may be slightly toxic in humans under certain conditions. That extrapolation is supported by Dimond et al.,[39] who gave oral doses of 4.5 to 18 mg. vanadium per day to volunteers for six to 16 weeks. Cramps and diarrhea were produced only by the larger dose. Schroeder et al.[40] fed up to 9 mg. of vanadium per day for six to 16 months to older individuals who were confined to a mental institution, and observed no ill effects due to the vanadium supplementation.

The lack of precisely defined conditions that induce reproducible deficiency or toxicity signs in animals prevents any comments about requirement for vanadium by the intravenous route or the composition of vanadium-containing parenteral solutions. Nutritional and absorption studies indicate that any absolute human requirement for vanadium is probably very small—1 μg. or 2 μg. daily. Thus, an appropriate level of vanadium in parenteral fluids probably would supply a few micrograms daily.

NICKEL

Signs of nickel deprivation have been described for six animal species—chick, cow, goat, minipig, rat, and sheep. These signs include depressed growth and hematopoiesis and alterations in the content of iron, copper, and zinc in liver.[41] The establishment of nickel as an essential nutrient through nutritional experiments has not clearly defined its biochemical function. At present, findings indicate that nickel functions either as a cofactor or structural component in specific metalloenzymes or metalloproteins or as a bioligand cofactor facilitating the intestinal absorption of the Fe^{3+} ion.

A nickel-containing macroglobulin, nickeloplasmin, has been found in human and rabbit serum.[42] Unfortunately, there is no clear indication as to the physiological significance or function of nickeloplasmin. In methano-

genic bacteria, a low-molecular-weight yellow compound named factor F_{430} apparently contains a nickel tetrapyrrole structure.[43] Like nickeloplasmin, the function of factor F_{430} is unknown.

The hypothesis that nickel in animals may function as an enzyme cofactor has been stimulated by the discovery of several nickel-containing enzymes in plants and microorganisms. These enzymes include urease from several plants and microorganisms,[41] carbon monoxide dehydrogenase from acetogenic bacteria,[44] and hydrogenases of nickel-requiring "Knallgas" bacteria.[44] Nickel can activate many enzymes *in vitro*,[17] but its role as a specific cofactor or component for any animal enzyme has not been demonstrated.

The hypothesis that nickel may function as a bioligand cofactor facilitating intestinal absorption of the Fe^{3+} ion has been supported by findings that, depending upon the form of dietary iron, nickel interacts with iron in the rat.[41] The interaction between nickel and iron affected hematopoiesis when dietary iron was ferric sulfate only, but not when dietary iron was a mixture of ferric and ferrous sulfates. Further, when low levels of ferric sulfate only were fed, $^{59}Fe^{3+}$ retention in whole body, blood, and kidney was apparently less in nickel-deprived, even though they were more anemic, than in nickel-supplemented rats, whereas, $^{59}Fe^{2+}$ retention was not affected by dietary nickel. Those findings show that nickel enhances the absorption of iron present in the diet in less than adequate, but not severely inadequate, levels and in a relatively unavailable form, and suggest that nickel is essential for the enzymatic formation, or structural integrity, of a molecule involved in ferric ion absorption.

By extrapolation from animal data, it is reasonable to suggest the importance of nickel in human nutrition. However, extrapolation of a nickel requirement from one species to another should be done with extreme caution because trace element requirements usually vary among species. Nonetheless, the nickel requirement of animals should give a general idea of magnitude of nickel required by humans. For rats and chicks, the nickel requirement apparently is about 50 μg./kg. of diet or slightly less.[45,46] For cows and goats this requirement may be higher ($>$100 μg./kg. of diet),[47,48] possibly because some rumen bacteria use nickel as part of their enzyme urease. Calculated from data for monogastric animals, a suggested dietary nickel requirement for humans would be near 50 μg./kg. of diet, or 16 μg./1,000 Cal.[49] It should be noted that this suggested requirement could be either increased or decreased by factors that affect nickel absorption or excretion.

Most ingested nickel is unabsorbed by the intestinal mucosa and is excreted in the feces.[50] Some fecal nickel may come from the bile, as nickel was excreted in bile of rats and rabbits injected with $^{63}Ni^{2+}$.[51] Limited studies suggest that typically less than 10% of ingested nickel is absorbed.[52] Intravenously injected nickel is excreted mainly in the urine.[51] Because nickel is poorly absorbed, its absolute requirement probably is very low for humans, less than 5 μg. daily.

Nickel is a very ubiquitous element. The nickel content in purified proteins, amino acids, and minerals often is near 0.1-1.0 μg./g. Thus, for those concerned with parenteral nutrition, nickel toxicity may be a greater problem than deficiency.

Life-threatening toxicity of nickel or nickel salts through oral intake is low, ranking with such elements as zinc, chromium, and manganese. Nickel salts exert their toxic action mainly by gastrointestinal irritation and not by inherent toxicity. The relative nontoxicity of nickel is apparently related to its low absorption by the intestinal mucosa.

Nickel also has little tendency to accumulate in tissues during lifetime exposure. Large oral doses of nickel salts are necessary to overcome the homeostatic control of nickel. Generally, 250 μg. or more of nickel per gram of diet is required to produce signs of nickel toxicity in rats, mice, chicks, rabbits, and monkeys.[53] Thus, the ratio of the minimum toxic dose and the minimum dietary requirement for chicks and rats is approximately 5,000. If animal data can be extrapolated to humans, this translates into a daily dose of 250 mg. of soluble nickel to produce toxic symptoms in humans.

Recent findings, however, suggest that oral nickel in not particularly high doses can adversely affect human health under certain conditions. These include nickel allergy, copper deficiency, and severe iron deficiency.

Nickel dermatitis is a relatively common form of nickel toxicity in humans. Several surveys have shown that the incidence of sensitivity to nickel is between 4% and 13%.[54] Reviews[53,54] attributed nickel dermatitis to percutaneous absorption of nickel. However, Christenson and Moller[55] suggested that the ingestion of small amounts of nickel may be of greater importance than external contacts in maintaining hand eczema. They observed that an oral dose of 5.6 mg. of nickel as nickel sulfate ($NiSO_4$) produced a positive reaction in nickel-sensitive individuals within one to 20 hours after ingestion. That dose is only 112 times as high as the human daily requirement projected from animal studies.

An antagonistic interaction between nickel and copper was found in rats.[56,57] The findings showed that if copper deprivation was not too severe, signs of copper deficiency in rats were more severe with, than without, supplemental nickel (diet contained 16-20 ng./g.), and that effect was greater when dietary nickel was 50 μg./g. rather than 5 μg./g. Nickel supplementation did not depress the level of copper in the liver or plasma of copper-deficient rats, thus indicating that nickel probably exacerbated copper deficiency by a mechanism other than interfering with copper absorption. The antagonism between copper and nickel was probably due to the isomorphous replacement of copper by nickel at various functional sites. At those sites nickel did not perform, or less efficiently performed, the functions of copper, thus resulting in a more severe copper deficiency.

The synergistic relationship between nickel and iron (as Fe^{3+}) was emphasized during the discussion of nickel essentiality. This appears to be the appropriate place to mention the antagonistic relationship between those elements. Severe iron deficiency was found to be more detrimental to nickel-supplemented than to nickel-deficient rats, as growth was more severely depressed and perinatal mortality was higher in nickel-supplemented rats.[58] Like the synergistic relationship, the antagonistic interaction between nickel and iron (this time as Fe^{2+}) occurs during absorption. Recent findings suggest that nickel is transported across the mucosal epithelium through the iron active transport system.[59] Active transport of iron is relatively specific for the divalent cation. Thus, when dietary iron is absorbed as the divalent cation, competition probably occurs between it and the Ni^{2+} ion for the active transport system.

In summary, dermatological and animal studies show that adverse effects in humans could result from too little or too much intake of nickel by either the oral or intravenous route. These possibilities for adverse effects stress the need to determine for humans adequate but safe nickel intakes that would permit optimal health throughout a lifetime.

Despite growing knowledge about nickel metabolism and nutrition, essentially nothing is known about its requirement by the intravenous route. Thus, it may be inappropriate to make recommendations for its inclusion in solutions for parenteral use. On the basis of present knowledge, the most reasonable recommendation is that the nickel content of solutions for parenteral use should be measured. If the solutions contain extremely low levels, or levels abnormally above those which would supply 5 μg. of nickel daily, the recipient of the solution should be

closely observed for possible adverse effects similar to those found in nickel-deprived or nickel-poisoned experimental animals.

ARSENIC

Signs of arsenic deprivation have been described for four animal species —chick, goat, minipig, and rat. These signs include depressed growth and abnormal reproduction characterized by impaired fertility and elevated perinatal mortality.[60] The establishment of arsenic as an essential nutrient through nutritional experiments has not clearly defined its biochemical function. Thus, the mode of action of arsenic is open to conjecture.

Recent findings suggest that arsenic might have a role in arginine metabolism. This is exemplified by findings from experiments with chicks.[60] Arsenic deprivation apparently elevated kidney arginase activity and plasma uric acid in chicks fed a normal level of arginine. When dietary arginine was increased to 34 mg./g. by a supplement of 20 mg./g., kidney arginase and plasma urea were substantially elevated. However, the elevation of these two factors was markedly influenced by dietary arsenic and zinc. Zinc deficiency alleviated the elevation in plasma urea and kidney arginase activity in arsenic-deprived chicks. On the other hand, zinc deficiency exacerbated their elevation in arsenic-supplemented chicks. In addition to these findings, others not described here suggest that arsenic strongly influences arginine metabolism. Further, because arginine metabolism is affected by arginine, manganese, and zinc nutriture, these nutrients may modify the role of arsenic, thus affecting the extent, severity, or direction of the signs of arsenic deprivation.

Perhaps arsenic, arginine, manganese, and zinc interact to affect the reaction:

$$\text{arginine} \xrightarrow[\text{arginase}]{} \text{urea} + \text{ornithine}$$

The enzyme arginase is composed of four subunits, to each of which is bound one atom of Mn^{2+} and is specific for L-arginine. The mechanism of action through which arsenic affects arginase activity is most likely indirect because arsenic deprivation elevates or depresses chick kidney arginase activity with the direction determined by the zinc and arginine status of the chick.

Possibly, the indirect effect merely reflects a general role for arsenic in the utilization of amino acids for protein synthesis or in the control of

protein degradation. Findings which support this possibility include: Arsenic deprivation increased plasma uric acid levels in chicks fed normal levels of arginine.[60] Excess amino acid nitrogen is usually eliminated from the chick as uric acid. Arsenic deprivation depressed the total microsomal protein level in the liver of rats.[60] Arsenic deprivation depressed the level of arginine and elevated levels of cystine, glutamine, glycine, and histidine in plasma of chicks.[61]

The preceding discussion shows that, even though a specific biochemical basis for arsenic essentially is not known, enough evidence is accumulating to indicate that arsenic probably has an essential role in humans. However, only data from animal studies are available for estimation of the magnitude of arsenic that humans possibly require. The arsenic requirement for chicks and rats apparently is less than 50 ng./g. of diet and probably near 25 ng./g.[63] Calculated from data for animals, a suggested dietary arsenic requirement of humans would be near 6 μg./1,000 calories or 12 to 25 μg. daily.

As with other elements, any requirement for arsenic could be altered by several factors. Absorption, retention, and excretion are influenced by the chemical form and level of the arsenic ingested. All forms of arsenic are well absorbed; however, organo-arsenic may be less well absorbed than inorganic arsenic. Human subjects fed radioactive arsenic present in tissues of chickens fed arsanilic-^{74}As acid rapidly excreted the isotope (60 to 80%) in feces.[62] Perhaps some of the fecal arsenic, however, represented that absorbed and excreted through the bile.[63] But much of the fecal arsenic probably was that unabsorbed. In contrast, 58% of an oral dose of inorganic arsenic given to humans was excreted in the urine five days after dosing.[64] Because arsenic is well absorbed, its absolute requirement might be near the nutritional requirement.

Excretion of ingested arsenic is quite rapid and both urine and feces are major routes of elimination. The chemical form of the ingested arsenic influences the form of the eliminated arsenic. Organo-arsenic that is absorbed apparently undergoes no chemical change because, after the ingestion of such arsenic-rich foods as lobster and crab, most of the arsenic in urine is organically bound.[65] Arsenic ingested as an inorganic form appears in the urine in both the inorganic and methylated forms. Tam et al.[64] found that the chemical species of arsenic in human urine was 51% dimethylarsenic acid, 21% monomethylarsenic compound, and 27% inorganic arsenic. Crecelius[65] suggested that two different processes with different rates were involved in the removal of ingested As^{3+}. The

first process involved the removal of arsenic as As^{3+} by the kidneys and began at 5 hours, diminished at 20 hours, and was not evident at 60 hours after ingestion. The second process involved the methylation of ingested As^{3+} to methylarsonic acid and dimethylarsenic acid. The excretion of methylated arsenic began within 5 hours after ingestion of As^{3+}, but reached maximum levels much later than excretion of As^{3+}. Most of the arsenic ingested was excreted within 85 hours, and the apparent biological half-life was approximately 30 hours. Arsenite might have been oxidized to arsenate before it was methylated.[64] Crecelius[65] found the excretion of ingested As^{5+} was difficult to assess, but suggested that some unchanged As^{5+} was rapidly excreted from the body. Part of the ingested As^{5+} was methylated and excreted within several days.

The toxicity of a given arsenical is related to how rapidly it is cleared from the body and to what degree it may accumulate in tissues. The general pattern toxicity is as follows:

$$As^{3+} > As^{5+} > RAs\text{-}x$$

which is approximately the reverse order of excretion. Elemental arsenic, being insoluble, is essentially nontoxic.

A considerable body of literature provides qualitative descriptions of the signs of arsenic toxicity in humans. It is beyond the scope of this discussion to review that literature here. Fowler[67] gives a brief account of this literature.

Although arsenic is generally considered to be highly toxic, it is actually much less toxic than selenium, a trace element with established nutritional value. Toxic quantities of arsenic generally are measured in milligrams, and the ratio of the toxic to nutritional dose for rats has been calculated to be approximately 1,250.[68] Nonetheless, arsenic has been synonymous with poison for centuries, and a number of reports have associated arsenic with some forms of cancer. As a result, the concept that arsenic is an element beneficial for human health may be difficult for some individuals to accept.

Of the elements not established to be, but suggested as essential for humans, arsenic may be of most practical concern. Beliefs that any form or amount of arsenic is unnecessary, toxic, or carcinogenic might lead to efforts for a zero-base exposure to arsenic, or for elimination of as much arsenic as possible from nutritional sources for humans. Thus, there is an urgent need to determine for humans adequate but safe arsenic intakes that

would permit optimal health throughout a lifetime. This is especially important for individuals receiving total parenteral nutrition because arsenic can be removed much more readily from parenteral fluids than from the diet.

Until more is known about its physiological function, it may be inappropriate to suggest a requirement for arsenic by the intravenous route or to make recommendations for the inclusion of arsenic in parenteral solutions. It is even difficult to recommend that the arsenic content of parenteral solutions should be measured because, if it is found in any quantity, attempts might be made to eliminate it. Nonetheless, such determinations should be done. Hopefully, reason will prevail, and the finding of arsenic in parenteral fluids in quantities which would supply 10 to 15 μg. daily will be accepted as nonhazardous and possibly beneficial for human health. The possibility of abnormal arginine or amino acid metabolism must be considered if parenteral fluids contain less than 10 to 15 μg. daily.

Silicon

Early silicon deficiency studies were done using crystalline amino acid diets that did not give optimal growth in control animals. Recently, Carlisle[69,70] 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 growth or outward appearance. However, connective tissue and bone abnormalities occurred, including skull structural abnormalities associated with depressed collagen content in bone, and long bone abnormalities characterized by small, poorly formed joints and defective endochondral bone growth. Silicon-deficient chick tibiae exhibited depressed water, hexosamine, and collagen in articular cartilage. Thus, although some of the early evidence for the nutritional essentiality of silicon may have been disputable because of poor growth of the experimental animals, the latter findings of Carlisle tend to resolve these problems.

Both the distribution of silicon in the organism and the effect of silicon deficiency on connective tissue form and composition support the view that silicon functions as a biological cross-linking agent and contributes to the architecture and resilience of connective tissue. Schwarz[71] found that silicon is a constituent of certain glycosaminoglycans and polyuronides where it is apparently bound to the polysaccharide matrix. In his review of

the possible biochemistry of silicon, Schwarz[71,72] concluded that silicon is present as a silanolate, an etherlike or esterlike derivative of silicic acid, in mucopolysaccharides. Thus, silicon could link portions of the same polysaccharide chain, different polysaccharides to each other, or acid mucopolysaccharides to proteins. Unfortunately, none of the proposed structures have been rigorously identified.

Proteins in connective tissue, notably collagen and elastin, also contain bound, or are affected by, silicon. Silicon was found in all four solubility classes of collagen in young skin,[73] and as a bound component of a variety of collagens.[74] Silicon is also a constituent of elastin.[75] Carlisle[69,70,76] found that silicon-deficient chick skull, tibia, and tibial cartilage contained depressed levels of collagen. Loeper et al.[75,77] found that silicon preserved the integrity of elastic tissue in rabbits fed an atherogenous diet. The elastic fibers of aortic tissue from rabbits fed high amounts of cholesterol were depleted, thin, and fragmented. With silicon supplementation, the elastic fibers were dense, regular, and often thickened. These findings suggest that silicon has a role in the cross-linking phenomenon of collagen and elastin.

Silicon apparently is involved in bone calcification; however, the mechanism is unknown. Some findings suggest a catalytic function for silicon. On the other hand, the marked influence of silicon on collagen and mucopolysaccharide formation and structure suggests that the influence of silicon on bone calcification is an indirect consequence of changes in these matrix components. Support for this latter view is that, in silicon-deficient animals, the formation of organic matrix, whether cartilage or bone, apparently is affected more severely than the mineralization process.[70] Nonetheless, in bone formation, apatite crystallization in matrices apparently occurs on sites that form specific nucleation centers at which calcium binding is probably the most important and first event. Silicon may be associated with calcium in this early stage of bone calcification because, as mineralization progresses, the silicon and calcium contents rise congruently in osteoid tissue. In the more advanced stages of mineralization, the silicon concentration falls markedly, whereas calcium concentrations approach proportions found in bone apatite.[78] Mehard and Volcani[79,80] proposed that the interrelationship between silicon and calcium in bone formation occurs in the mitochondria, which may be involved in the calcification process[81] because they consistently found silicon in that cell organelle.

Little is known about whether silicon has a physiological function in

soft tissue. The finding of silicon in centrioles suggests a role in the morphogenesis or function of centrioles or "microtubules organizing centers" of primitive cells.[82] Perhaps in any tissue, not just in bone and connective tissues, silicon has a role as a cross-linking agent.

Little is known about the nutritional requirements and metabolism of silicon. The form and minimum requirement of silicon have not been ascertained for any animal. The estimated requirement of chicks for silicon, as sodium silicate, is in the range of 100 to 200 μg./g. of diet, or approximately 52 mg./1,000 calories.[49] Schwarz[83] indicated that he found other silicon compounds that were five to 10 times as effective, per atom of silicon, as silicate in preventing nutritional deficiency. Thus, the minimum requirement for chicks probably is much lower than 26 to 52 mg./1,000 calories.

The preceding findings and the study of Benke and Osborn[84] show that the form of dietary silicon is a control factor in its absorption. This probably reflects the rate of production of soluble or absorbable silicon in the gastrointestinal tract. Other factors that probably affect silicon absorption are dietary fiber[85] and age, sex, and the activity of various endocrine glands of the animal.[86]

Increasing the intake of silicon increases urinary silicon output up to fairly well-defined limits in man, rats, and guinea pigs.[68] The upper limits of urinary silicon excretion apparently are not set by the excretory ability of the kidney because urinary excretion can be elevated above these upper limits upon peritoneal injections of silicon.[87,88] Thus, the limits apparently are set by the rate and extent of silicon absorption from the gastrointestinal tract. The experiments of Jones and Handreck[89] indicate most ingested silicon remains unabsorbed and is excreted in the feces. Probably less than 4% of silicon ingested is absorbed. Silicon is essentially a nontoxic element when taken orally. However, ruminants consuming plants with a high silicon content may develop silicious renal calculi.[90] Renal calculi in humans may also contain silicates.[90]

While knowledge of silicon in human metabolism is very preliminary, this has not prevented speculation that silicon deprivation might be involved in several human disorders, including atherosclerosis, osteoarthritis, hypertension, and the aging process.[91] These speculations demonstrate the critical need for study of the importance of silicon nutrition for humans. Until such studies are done, knowledge will be insufficient to suggest a need for silicon in parenteral nutrition.

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