Chapter 23

The Nutritional Essentiality and Physiological Metabolism of Vanadium in Higher Animals

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In vitro, pharmacological, and lower life form findings have stimulated speculations about the nutritional importance of vanadium. Between 1971 and 1985 several research groups described possible signs of vanadium deficiency for some animals. However, it was difficult to determine whether the changes caused by vanadium deprivation in these early experiments, which used questionable diets, were true deficiency signs, or manifestations of a pharmacological action of vanadium. Since 1985, studies with goats and rats apparently have found true responses to low intakes of vanadium. Responses of goats fed a vanadium-deficient diet included skeletal deformations and death within 90 days of birth. In rats, vanadium deprivation affected changes in thyroid weight and plasma thyroxine and triiodothyronine concentrations caused by feeding deficient or luxuriant iodine. Vanadium deprivation also depressed the activity of pancreatic amylase, and affected serum lactate dehydrogenase in an opposite manner when dietary iodine was deficient than when it was luxuriant. These findings indicate physiological amounts of vanadium affect thyroid hormone and carbohydrate metabolism, and when combined with the knowledge that homeostatic mechanisms exist for vanadium, and that vanadium has functional roles in lower forms of life, provide circumstantial evidence that vanadium is an essential element for higher forms of life. A daily dietary intake of 10 μg of vanadium probably will meet any postulated vanadium requirements of humans.

Since the turn of the nineteenth century, when some French physicians suggested vanadium was a panacea for human disorders (*1,2*), vanadium has been proposed numerous times to be of pharmacological or nutritional importance. Through the years, enthusiasm has risen and fallen for the possible use of vanadium as a pharmaceutical for such things as treating syphilis (*3*), reducing serum cholesterol (*4,5*), and preventing caries (*6*). Currently, attempts are being made to create a pharmaceutical that can safely take advantage of its insulin mimetic properties (*7*). However, the thought that vanadium salts might be useful as antidiabetic agents is not

new; this thought existed 100 years ago (*1*). The hypothesis that vanadium has a physiological or essential role in higher animals including humans has gone through periods where it has received much credence then followed by much skepticism. In 1931 it was found that vanadium was superior to copper as a dietary supplement with an incompletely effective dose of iron in alleviating anemia caused by feeding a milk diet to rats; vanadium also improved growth of the rats (*8,9*). Apparently because other elements in addition to vanadium had similar effects, these findings neither stimulated further research nor resulted in the acceptance of vanadium as an essential element. In 1949, Rygh (*10*) suggested that vanadium may be nutritionally important because it stimulated the mineralization of bones and teeth in rats and guinea pigs. However, almost 20 years later, Schroeder and coworkers (*11*) stated that, although vanadium behaves like an essential trace metal, final proof of essentiality for mammals was still lacking. Findings reported between 1971 and 1974 by four different research groups led many to conclude that vanadium is an essential nutrient. In a 1974 review of those findings, Hopkins and Mohr (*12*) stated "we are secure in the concept that vanadium is an essential nutrient." However, in a review 11 years later (*13*) a convincing argument was presented for the judgement that the evidence for the nutritional essentiality of vanadium was still inconclusive. The argument was that the findings accepted as evidence for vanadium essentiality were mostly manifestations of high vanadium supplements that had pharmacological actions in animals fed nutritionally unbalanced diets. Because vanadium can not fulfill all current criteria for essentiality, its nutritional importance for higher animals is being questioned even though some recent convincing circumstantial evidence for essentiality has appeared. In 1963, Schroeder and coworkers (*11*) stated "no other trace metal has so long had so many supposed biological activities without having been proved to be essential;" that statement still could be made today.

Criteria Used to Establish Essentiality

In the 1960s and 1970s, criteria (*14-18*) were developed to establish essentiality of mineral elements that could not be fed low enough to cause death or to interrupt the life cycle; they usually included the following: 1) The element must react with biological material or form chelates. 2) The element must be ubiquitous in sea water and earth's crust. In other words, it had to be present during the evolution of organisms so it could be incorporated when essential functions developed which required the element. 3) The element must be present in significant quantity in animals. 4) The element should be toxic to animals only at relatively high intakes in comparison to nutritional intakes. 5) Homeostatic mechanisms must exist for the element so that it is maintained in the body in a rather consistent amount during short term variations in intake. 6) Finally, and most importantly, a dietary deficiency must consistently and adversely change a biological function from optimal, and this change is preventable or reversible by physiological amounts of the element.

In the 1980s and 1990s, establishing essentiality on the basis of these criteria was questioned when a large number of elements was suggested to be essential because of some small change in a physiological or biochemical variable. It seemed possible that many of these changes were not necessarily the result of a suboptimal function, but perhaps a consequence of a toxicological or pharmacological action. In this context, pharmacological was defined as the ability of a dietary intake of a

substance to alleviate a condition other than the nutritional deficiency of that substance, or to alter a biochemical function or biological structure in a therapeutic manner (*19*).

Today, if dietary deprivation of an element can not be shown to cause death or interrupt the life cycle, a defined biochemical function generally is required before an element is unequivocally accepted as essential.

Status of Vanadium Essentiality

Early Animal Deficiency Experiments. In the 1970s, it was widely believed that vanadium had fulfilled all the necessary criteria and thus should be considered nutritionally essential. However, in the vanadium deprivation studies of the 1970s, "controls" or supplemented animals were fed 0.5 to 3.0 μg V/g diet (*13*). Although these amounts are near those in natural diets which apparently contain about 1.0 μg V/g (*20*), those doses of vanadium in the form of highly available salts apparently are 10 to 50 times those normally found in purified or semipurified diets (*20*). Because vanadium is a relatively toxic and pharmacologically active element, it was difficult to determine whether the "deficiency signs" in early experiments obtained with diets, whose adequacy or balance in other nutrients could be questioned, were true deficiency signs or manifestations of a pharmacological action of vanadium.

For example, in 1971, Strasia (*21*) reported that rats fed less than 100 ng V/g diet exhibited slower growth, higher plasma and bone iron and higher hematocrits than controls fed 500 ng V/g diet. Williams (*22*), using a diet lower in casein and higher in iron and ascorbic acid, was not able to subsequently produce those deficiency signs in the same laboratory in which Strasia had worked. These contrasting findings suggest that, because vanadium can positively affect iron metabolism in rats fed inadequate iron under certain conditions (*23*), the plenteous vanadium supplement in the experiments of Strasia was pharmacologically beneficial for iron metabolism.

In 1971, Schwarz and Milne (*24*) reported that a vanadium supplement of 0.25 to 0.50 μg/g diet gave a positive growth response in suboptimally growing rats fed an amino acid based diet apparently deficient in riboflavin (*25*) and with an unknown vanadium content. On the other hand, Hopkins and Mohr (*26*) reported in 1971 that the only effect vanadium deprivation had in rats was impaired reproductive performance (decreased fertility and increased perinatal mortality) that became apparent only in the fourth generation; the diet they used contained luxuriant amounts of methionine and arginine and was probably deficient in cysteine. The inconsistency in findings and dietary concerns easily allows for the suggestion that vanadium possibly acted in a pharmacological manner in these studies.

Recent Animal Deficiency Experiments. The uncertainty about vanadium deficiency signs stimulated new efforts to produce deficiency signs in animals fed diets apparently containing adequate and balanced amount of all known nutrients. In nine experiments, Anke and coworkers (*27-30*) found that, when compared to controls fed in the first experiments 2 μg V/g diet and in the latest experiments 0.5 μg V/ g diet, goats fed less than 10 ng V/g diet had more difficulty in conceiving, exhibited a higher rate of spontaneous abortion, increased ratio of female to male kids born, and those animals that delivered offspring produced less milk. Between days 7 and 91 of life, 42% of kids from vanadium-deprived goats died with some deaths preceded by

convulsions; only 8% of kids from vanadium-supplemented goats died during this time. Vanadium-deficient goats had only 50% the life span of control goats. Also, deficient goats exhibited pain in the extremities, swollen forefoot tarsal joints, and skeletal deformations in the forelegs. Biochemical changes exhibited by the vanadium-deficient goats included decreased serum ß-lipoproteins, creatinine, isocitrate dehydrogenase, and lactate dehydrogenase, and increased serum glucose.

Studies with Wistar-Kyoto rats indicated that vanadium affects thyroid metabolism, and thus glucose and lipid metabolism (*32*). Vanadium deficiency increased thyroid weight and thyroid weight/body weight ratio in rats. Moreover, as dietary iodine was increased from 0.05 to 0.33 to 25 μg/g, thyroid peroxidase activity decreased with the decrease more marked in vanadium-supplemented (1 μg V/g diet) than in vanadium-deprived (2 ng V/g diet) rats. The greatest difference between the vanadium-deprived and -supplemented rats occurred when dietary iodine was the lowest. Also as dietary iodine increased, plasma glucose increased in the vanadium-deprived rats but decreased in the vanadium-supplemented rats. As a result, plasma glucose differences between vanadium-deprived and -supplemented rats were most apparent when dietary iodine was low or high; there was essentially no difference when iodine was normal. That vanadium nutriture affects thyroid, glucose and lipid metabolism was confirmed by a three-way 2x2x2 factorially arranged experiment in my laboratory (*32*). In this experiment the variables were deficient and adequate dietary vanadium, or about 2 ng and 500 ng/g diet; low and luxuriant dietary iodine, or about 50 ng and 25 μg/g diet; and type of rat, either the diabetes-prone or diabetes-resistant BB/Wor rat. Each treatment group contained 8 rats that were fed their appropriate casein-ground corn-corn oil based diet for 90 days.

Surprisingly, only five of the diabetes-prone rats developed diabetes which was expected to occur in most all by the end of the experiment. Although these five rats were given implants to supply insulin, with most variables examined, their values were far removed from the values of the rats that did not develop diabetes; thus, the diabetic rats were not included in the comparisons shown in Tables I and II. As found in the earlier experiment with Wistar-Kyoto rats, dietary vanadium markedly affected the response of BB/Wor rats to changing dietary iodine. As shown in Table I, increasing dietary iodine decreased thyroid weight, but the decrease was affected by dietary vanadium. Thyroid weight was slightly higher in the vanadium-deprived than -supplemented rats when dietary iodine was low, but when dietary iodine was high, vanadium-deficient thyroids were 20 to 30% smaller than those from the vanadium-supplemented rats.

The concentration of thyroid hormones found in plasma was also affected by an interaction between vanadium and iodine. When rats were fed a low iodine diet, thyroxine concentrations were much less in vanadium-supplemented than -deprived rats. Increasing dietary iodine markedly increased the thyroxine concentrations in the vanadium-supplemented rats but had very little effect on the concentrations in the vanadium-deprived rats. As a result, the response to a change in dietary vanadium was greatest when dietary iodine was low. The findings with triiodothyronine concentrations were quite different than those of the thyroxine findings. When dietary iodine was low, the plasma triiodothyronine was higher in vanadium-supplemented than -deprived rats. Iodine supplementation decreased the triiodothyronine concentration in vanadium-supplemented rats, but increased it in the vanadium-deprived rats; this effect was most marked in the diabetes-resistant rats. Once again,

Table I. Effect of Dietary Vanadium and Iodine on Thyroid Weight, Plasma Thyroxine and Plasma Triiodothyronine in Diabetes-Prone and -Resistant BB/Wor Rats

Dietary[a]		Rat	Thyroid	Plasma	Plasma
V, μg/g	I, μg/g	Type[b]	Weight, mg	Thyroxine, μg/100 ml	Triiodothyronine, ng/100 ml
0.0	0	P	29.6 ± 3.3[c]	5.06 ± 0.98	27.4 ± 7.4
0.5	0	P	26.3 ± 3.7	2.81 ± 0.23	35.1 ± 2.9
0.0	0	R	44.9 ± 6.4	4.78 ± 0.45	31.3 ± 7.9
0.5	0	R	40.3 ± 3.9	2.93 ± 0.43	41.5 ± 6.9
0.0	25	P	10.3 ± 5.9	5.05 ± 0.49	33.1 ± 8.7
0.5	25	P	15.0 ± 6.8	5.65 ± 0.55	32.4 ± 7.7
0.0	25	R	14.6 ± 5.9	5.61 ± 0.40	36.5 ± 6.7
0.5	25	R	17.6 ± 4.7	5.79 ± 0.36	34.4 ± 7.1

Significant effects, Thyroid weight: Iodine, $P<0.0001$; Vanadium x Iodine, $P<0.006$; Diabetes-type, $P<0.0001$; Iodine x Diabetes-type, $P<0.0001$.
Significant effects, Thyroxine: Vanadium, $P<0.0001$; Iodine, $P<0.0001$; Vanadium x Iodine, $P<0.0001$.
Significant effects, Triiodothyronine: Vanadium x Iodine, $P<0.008$; Diabetes-type, $P<0.04$.
[a]Amount of vanadium and iodine supplemented to the diet.
[b]P = diabetes-prone; R = diabetes-resistant.
[c]Mean ± SD

Table II. Effect of Dietary Vanadium and Iodine on Pancreatic Amylase and Serum Lactate Dehydrogenase Activity in Diabetes-Prone and -Resistant BB/Wor Rats

Dietary[a]		Rat	Pancreatic	Serum Lactate
V, μg/g	I, μg/g	Type[b]	Amylase, U/mg Protein	Dehydrogenase, U/L
0.0	0	P	114 ± 14[c]	964 ± 100
0.5	0	P	102 ± 12	910 ± 101
0.0	0	R	119 ± 12	1060 ± 92
0.5	0	R	74 ± 7	902 ± 174
0.0	25	P	114 ± 15	924 ± 119
0.5	25	P	81 ± 12	977 ± 110
0.0	25	R	105 ± 8	927 ± 154
0.5	25	R	78 ± 11	1106 ± 169

Significant effects, pancreatic amylase: Vanadium, $P<0.0001$; Iodine, $P<0.02$; Diabetes-type, $P<0.008$; Vanadium x Diabetes-type, $P<0.04$; Vanadium x Iodine x Diabetes-type, $P<0.004$.
Significant effects, lactate dehydrogenase: Vanadium x Iodine, $P<0.004$.
[a]Amount of vanadium and iodine supplemented to the diet.
[b]P = diabetes-prone; R = diabetes-resistant.
[c]Mean ± SD

the greatest response to dietary vanadium occurred when dietary iodine was low.

Evidence that dietary vanadium can affect glucose or carbohydrate metabolism is presented in Table II. The activity of pancreatic amylase, which catalyzes the first step in the digestion of dietary starch to glucose, was lower in vanadium-supplemented than -deprived rats. This difference was much greater in the diabetes-resistant than diabetes-prone rat when dietary iodine was low; when dietary iodine was high, this difference was not as apparent between the types of rats. An interaction between iodine and vanadium also affected the activity of serum lactate dehydrogenase, the last enzyme in the glycolytic pathway. When dietary iodine was increased, lactate dehydrogenase activity decreased in the vanadium-deficient rats, while it increased the vanadium-supplemented rats. As a result, when dietary iodine was low, lactate dehydrogenase activity was lower in vanadium-supplemented than -deficient rats, but when dietary iodine was luxuriant, just the opposite occurred.

The use of deficient and excessive amounts of iodine in this experiment might be questioned. This was done because it was thought that the need for vanadium would be very low under normal conditions if its key role in animals involved thyroid metabolism. Thus it would be difficult to obtain a response in experimental animals because current technology results in diets that probably should be considered marginally low in vanadium. It was felt that the response to the marginally low diets would be increased if the need for vanadium was increased, for example, high iodine in the diet; or if there was some interference with the utilization of vanadium, for example, low iodine. The basis for this practice is the formula:

Pathological effects = stress x organic vulnerability (*33*).

Pathological effects are not likely to be seen if the vanadium deficiency or organic vulnerability is not multiplied by some significant stressor. Similarly, an organism probably can handle a specific stressor easily if there is no organic vulnerability or in this case, adequate vanadium. However, the multiplication of a subnormal intake of vanadium times the presence of a stressor affected by vanadium most likely would lead to pathological consequences. This approach apparently was successful because in the Wistar-Kyoto and BB/Wor rat experiments, vanadium responsive variables generally were more markedly affected by vanadium deficiency when dietary iodine was deficient or excessive; there was not much difference when the animals were fed a normal amount of iodine.

The finding that vanadium status affects thyroid metabolism which involves the halide iodine is intriguing. The functional role defined for vanadium in some algae, lichens, and fungi is that of an integral part of some haloperoxidases (*34*), or involved in halide metabolism. Thus, it seems possible that vanadium has an essential function in the metabolism or oxidation of halides in higher animals.

In summary, although vanadium at present is not unequivocally accepted as essential, accumulating circumstantial evidence strongly suggests that it is. This evidence includes the finding of dietary responses to vanadium in higher animals that are difficult to attribute to pharmacological action only, and the finding of biochemical roles for vanadium in lower forms of life.

Physiological metabolism of vanadium

As indicated earlier, one criterion often used to support essentiality for an element is the presence of homeostatic mechanisms to regulate its content in the body. There is

evidence that tissue concentrations of vanadium are homeostatically controlled through absorptive, excretory and storage mechanisms. Recent reviews (*35,36*) of vanadium metabolism found that most vanadium ingested as a component of food is unabsorbed and is excreted in the feces. Based on the very small concentrations of vanadium normally found in urine compared with the estimated daily intake and fecal content of vanadium, less than 5% of ingested vanadium is absorbed. Animal studies generally support the concept that vanadium is not readily absorbed from the diet. However, two studies with rats fed vanadium as the salt sodium vanadate indicate that vanadium absorption can exceed 10% with some forms of vanadium or under certain dietary conditions (*37,38*); this suggests caution in assuming that a low percentage of ingested vanadium always is absorbed from the gastrointestinal tract.

Vanadium absorption. Most vanadium that is absorbed is probably transformed in the stomach to the vanadyl ion and remains in this form as it passes into the duodenum (*39*). The mechanisms involved in the absorption of vanadium in the cationic or vanadyl form are unknown. In vitro studies suggest that vanadium in the anionic or vanadate form can enter cells through phosphate- or other anion-transport systems (*40*). Vanadate is absorbed 3 to 5 times more effectively than vanadyl (*41*). Apparently the different absorbability rates for vanadate and vanadyl, the effect of other dietary components on the binding and forms of vanadium in the stomach, and the rate at which vanadate is transformed into vanadyl markedly affect the percentage of ingested vanadium absorbed.

Vanadium transport. When vanadate appears in the blood, it is quickly converted into the vanadyl cation (*42-46*). However, as a result of oxygen tension, vanadate still exists in blood. Vanadyl, the most prevalent form of vanadium in blood, is bound and transported by transferrin and albumin (*47*). Vanadate is transported by transferrin only (*47*). Vanadyl also complexes with ferritin in plasma and body fluids (*48,49*). It remains to be determined whether vanadyl-transferrin can transfer vanadium into cells through the transferrin receptor or whether ferritin is a storage vehicle for vanadium. Vanadium is rapidly removed from plasma and is generally retained in tissues under normal conditions at concentrations less than 10 ng/g fresh weight (*35*). Bone apparently is a major sink for excessive retained vanadium.

Vanadium excretion. Excretion patterns after parenteral administration (*50-53*) indicate that urine is the major excretory route for absorbed vanadium. However, a significant portion of absorbed vanadium may be excreted through the bile. This is supported by findings that human bile contains measurable vanadium (about 1.0 ng/g) (*54*), and about 10% of an injected dose of an isotopic tracer of vanadium was found in the feces of humans (*50*) and rats (*52*).

Nutritional requirement for vanadium

If vanadium is essential for humans, its requirement most likely is small. The diets used in animal deprivation studies described above contained only 2 to 25 ng/g; these amounts usually did not have severe consequences; this indicates that the vanadium

deprivation with these intakes may have been marginal. Most diets supply humans with less than 30 μg daily; many diets supply near 15 μg daily (*35*). Vanadium deficiency signs have not been found in humans with these intakes. These observations suggest that a dietary intake of 10 μg daily probably meets any postulated vanadium requirement. Suggesting an upper safe nutritional intake for vanadium is difficult because humans apparently are more tolerant to high vanadium intakes than experimental animals such as rats, and there are only limited human toxicological data on which to base such a suggestion. As reviewed elsewhere (*35*), there are findings suggesting an intake of over 10 mg daily can result in toxicity signs. However, much lower amounts of vanadium were found to have pharmacological actions in humans which suggests that they may have toxic manifestations under certain conditions. Most mineral elements at intakes 100 times their nutritional requirement are toxic. This suggests that a safe daily intake for vanadium is under 1.0 mg per day and might be 100 μg or less.

As indicated above, the daily intake of vanadium is relatively low in comparison with known essential trace elements. Foods rich in vanadium (greater than 40 ng/g) include shellfish, mushrooms, parsley, dill seed, black pepper and some prepared foods (*55,56*). Cereals, liver and fish tend to have intermediate amounts of vanadium (5 to 40 ng/g) (*54, 56-58*). Beverages, fats and oils, fresh fruits, and fresh vegetables generally contain less than 5.0 ng V/g, and often less than 1.0 ng/g (*54, 56-58*).

Because of its uncertain nutritional essentiality status, the practical nutritional importance of vanadium remains to be determined. The identification of an essential biochemical function for vanadium in higher animals is needed to disentangle pharmacological from nutritional or physiological observations with this element. Determination of a defined function also will facilitate the determination of status assessment indicators as well as data- supported safe and adequate intakes for vanadium. Until a defined function is described, it is unlikely that vanadium will be unequivocally accepted as an essential nutrient for higher animals including humans.

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Vanadium Compounds
Chemistry, Biochemistry, and Therapeutic Applications
Alan S. Tracey and Debbie C. Crans, Editors
Published 1998 by the American Chemical Society