Vanadium in Mammalian Physiology and Nutrition

Forrest H. Nielsen

USDA, ARS, Grand Forks Human Nutrition Research Center, 2420 2nd Avenue North, P.O. Box 9034, University Station, Grand Forks, ND 58202-9034, USA

1. BRIEF INTRODUCTION AND HISTORY 544

2. METABOLISM 545
   2.1. Absorption 545
      2.1.1. Amounts Absorbed 545
      2.1.2. Factors Affecting Absorption 547
      2.1.3. Mechanisms Involved in Absorption 547
   2.2. Transport and Retention 549
      2.2.1. Form in Blood and Organs 549
      2.2.2. Amounts in Organs and Fluids 551
      2.2.3. Factors Affecting Retention 551
   2.3. Excretion 553
      2.3.1. Sites and Mechanisms of Excretion 553
      2.3.2. Forms Excreted 554

3. ESSENTIALITY 555

543
1. BRIEF INTRODUCTION AND HISTORY

In 1876, Priestley and Gamgee [1] reported on the toxicity of sodium vanadate in frogs, pigeons, guinea pigs, rabbits, dogs, and cats. Two other reports appeared shortly thereafter in which the toxic action of vanadium on heart muscle contraction [2] and in liver resulting in fatty degeneration [3] were described. But following these studies, interest in the biological actions of vanadium essentially lay dormant until the turn of the nineteenth century, when various French physicians used vanadium as a panacea for a number of human disorders [4]. Since that time to the present, vanadium has been brought to the fore numerous times as an element of possible pharmacological or nutritional importance. Through the years, enthusiasm has risen and fallen for the possible use of vanadium as a pharmaceutical for treating syphilis [5], reducing serum cholesterol [6,7] and preventing caries [8]. Recently, vanadium has been receiving much attention because of its insulin-mimetic properties (see Chap. 17).

Research examining the hypothesis that vanadium plays a physio-
logical role or is an essential nutrient in higher animals also can be characterized as having periods of convincement followed by periods of much skepticism. In 1931 it was found that vanadium as a supplement with an incompletely effective dose of iron was superior to copper in alleviating anemia caused by feeding a milk diet to rats [9]; vanadium also improved growth [10]. 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 [11] suggested that vanadium may be nutritionally important for animals because it stimulated the mineralization of bones and teeth in rats and guinea pigs. However, almost 20 years later, Schroeder et al. [12] 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 [13] stated “we are secure in the concept that vanadium is an essential nutrient.” However, 11 years later, a review appeared [14] that presented a convincing argument that the evidence for the nutritional essentiality of vanadium was still inconclusive. This review indicated that the findings accepted as evidence for vanadium essentially were mostly manifestations of high vanadium supplements which induced pharmacological changes in animals fed unbalanced diets. Some substantive evidence for vanadium essentiality has appeared since 1987 and is described in the following. Nonetheless, still today, because a defined biochemical function for vanadium in higher animals has not been described, vanadium is not unequivocally accepted as an essential nutrient for higher animals. It seems as if the statement made by Schroeder et al. [12] in 1963 still holds true today, i.e., “no other trace metal has so long had so many supposed biological activities without having been proved to be essential.”

2. METABOLISM

2.1. Absorption

2.1.1. Amounts Absorbed

In 1917, Proescher et al. [5] fed a healthy young man a relatively high dose of vanadium, or 12.5 mg of sodium tetravanadate. They found, by
using a potassium permanganate titration method, that 12.4% of the
dose was voided in the urine and 87.6% passed through the feces. More
recent research indicates that 8–10% of absorbed vanadium is excreted
through the bile [15–17]. Thus, this first study of vanadium absorption
suggested that about 15% of a large single bolus of vanadium is ab-
sorbed. Some studies in which rats were given relatively high doses of
vanadium also indicated that vanadium absorption can exceed 10%.
Wiegmann et al. [17] recovered in the feces only 69.1% of a 5-μmol dose
of Na₃VO₄ containing the tracer ⁴⁸V gavaged into fasted rats; recovery
from the feces increased to 85.7% if a suspension of Al(OH)₃ was
administered simultaneously with the vanadium. Bogden et al. [18]
used the balance method to determine that rats absorbed about 40%,
and excreted about 59% in the feces, of vanadium ingested as sodium
metavanadate supplemented at 5 or 25 μg/g to a casein-sucrose-
dextrin–based diet.

Most studies indicate that the amount of ingested vanadium ab-
sorbed in higher animals is much lower than 10%, and probably is
normally near 1–3% with usual intakes in the presence of natural-type
foods. For example, based on the very low concentrations of vanadium,
generally less than 0.8 μg/L, found in urine [19], in comparison with the
estimated daily intake of 10–30 μg [19,20], and the high fecal content of
vanadium [19], less than 5% of vanadium ingested is normally absorbed.
Two research groups found that the administration of tartrate salts of
vanadium with meals to humans resulted in quite variable amounts of
vanadium in the urine, and thus variable absorption. Curran et al. [21]
calculated that about 0.1–1.0% of vanadium in 100 mg of the very
soluble diammonium ox tartratovanadate fed daily for 6 weeks to five
normal, healthy men, aged 23–26 years and consuming identical diets,
was absorbed. Dimond et al. [22] obtained similar findings with five
females and one male, aged 30–55 years. When these patients were fed
25–125 mg of ammonium vanadyl tartrate daily for a minimum of 6
weeks, urinary vanadium ranged from 25 to 1514 μg/24 hr; these
amounts suggest an absorption of less than 1%.

Some animal studies also support the concept that vanadium
absorption by the gastrointestinal tract is quite low. Conklin et al. [23]
found that, based on the uptake of ⁴⁸V in 40 μg of vanadium in the form
of V₂O₅ administered by gavage to rats, 2.6% of the dose was absorbed.
Sheep consuming a natural-type diet providing 1.9 mg V/day, or supple-
mented with ammonium metavanadate to supply 38 or 153 mg V/day, were estimated to have absorbed 0.13–0.75% (mean of 0.34%) of the ingested vanadium [24].

2.1.2. Factors Affecting Absorption

The variable urinary excretion findings described in the preceding section indicate that the absorption of vanadium can be modified by a number of different factors. Except for the Al(OH)₃ finding mentioned above, the direct determination of changes in vanadium absorption caused by various factors has received very little attention. However, indirect evidence that certain factors affect the absorption of vanadium has resulted from two other types of studies, i.e., a factor may be modifying vanadium absorption if it modifies vanadium toxicity, or tissue retention or accumulation. Table 1 lists a number of such factors.

Dietary vanadium probably occurs mainly as VO²⁺ (vanadyl, V⁴⁺) or as HVO₄²⁻ (vanadate, V⁵⁺). Most ingested vanadium probably is transformed in the acidic milieu of the stomach to VO²⁺ and remains in this form as it passes into the duodenum and when excreted in the feces [39]. However, vanadate is absorbed three to five times more effectively than vanadyl. Thus, the effect of other dietary components on the form of vanadium in the stomach and the speed at which it is transformed into vanadyl probably markedly affect the percentage of ingested vanadium absorbed. Moreover, the extent of binding, especially the cationic form of vanadium, to macromolecules such as complex carbohydrates and proteins apparently has a profound effect on vanadium absorption (see Table 1).

2.1.3. Mechanisms Involved in Absorption

Very little is known about the mechanisms involved in the absorption of vanadium in the cationic or VO²⁺ form, which apparently is the most prevalent form in the duodenum. In vitro studies suggest that anionic vanadium or HVO₄²⁻ can enter cells through phosphate or other anion transport systems [40]. Kinetic modeling of whole-body vanadium metabolism in sheep indicates that a significant amount of vanadium absorption occurs in the upper gastrointestinal tract [41].
<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum hydroxide</td>
<td>Retention of vanadium gavaged as $^{48}$V increased in feces and decreased in urine and tissues when administered with Al(OH)$_3$.</td>
<td>17</td>
</tr>
</tbody>
</table>
| Ascorbic acid        | Ascorbic acid alleviated growth retardation and bone vanadium retention in growing chicks caused by high dietary vanadium.  
|                      | Ascorbic acid alleviated the reduction in egg quality and production, and in body weight caused by high vanadium in the diet of laying hens. | 25,26|
| Carbohydrate form    | Replacing grain with sucrose in the diet of laying hens intensified the depression in egg quality and production, and body weight induced by high dietary vanadium.  
| (simple vs. complex)  | Lactose addition to the diet exacerbated vanadium toxicity signs of growth depression and mortality in growing chicks. | 27,28|
| Chloride             | Increasing the dietary supplement of NaCl from 0.5% to 2.0% ameliorated vanadate toxicity as assessed by growth rate and inconsistently decreased tissue accumulation of vanadium when its intake was high; the effect was found to reside in the chloride ion. | 29,30|
| Chromium             | Chromium reduced mortality, growth depression, and the uncoupling of oxidative phosphorylation caused by high dietary vanadium in growing chicks. | 28,31|
| Copper               | Chromium reduced bone vanadium content.                                | 32   |
|                      | High dietary copper alleviated the growth-retarding effect of vanadate for chicks but did not affect the femur concentration of vanadium. | 33   |
TABLE 1
Continued

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDTA</td>
<td>EDTA prevented vanadium toxicity in chicks assessed by growth depression and mortality, and decreased the amount of $^{48}$V from a tracer dose found in tissues.</td>
<td>31,34</td>
</tr>
<tr>
<td>Form or oxidation state</td>
<td>The tissue retention of vanadium was higher in rats fed 50 $\mu$g V/g diet as sodium orthovanadate than in rats fed 50 $\mu$g V/g diet as vanadyl sulfate.</td>
<td>35</td>
</tr>
<tr>
<td>Iron</td>
<td>Vanadium toxicity as assessed by chick growth was more severe with iron deficiency; however, $^{48}$V absorption was not affected by dietary iron. Iron-deficient animals retained more vanadium in the blood and liver, and less in bone.</td>
<td>36</td>
</tr>
<tr>
<td>Protein intake</td>
<td>Increasing dietary protein from 10% to 30% reduced mortality and growth retardation in chicks caused by vanadium toxicity.</td>
<td>37</td>
</tr>
<tr>
<td>Protein source</td>
<td>Replacement of soybean meal by cottonseed meal reduced the effects of high dietary vanadium in laying hens, including elevated tissue vanadium concentrations, reduced egg quality and production, and decreased body weight; replacement of soybean meal with herring fish meal intensified the effects of vanadium toxicity.</td>
<td>27,38</td>
</tr>
</tbody>
</table>

2.2. Transport and Retention

2.2.1. Form in Blood and Organs

About 90% of the vanadium in blood is associated with the plasma fraction. Although it was once thought that extracellular vanadium existed mainly as vanadate [42], current thought is that the vanadyl
form is most prevalent in blood. If vanadate appears in blood, it apparently is quickly converted to vanadyl in the erythrocytes by glutathione [43,44], or in plasma by reductants such as ascorbate [45], catecholamines [46], and cysteine [47]. However, as a result of oxygen tension, vanadate still exists in blood. Vanadyl is bound and transported by transferrin and albumin [48]. Vanadate apparently is transported by transferrin only [48]. Chasteen et al. [39] estimated that at least 50% of vanadium in plasma is associated with transferrin [39]. Harris et al. [49] found that radiolabeled vanadium as either vanadyl or vanadate injected intravenously into adult beagle dogs required about 30 hr to reach the maximum degree of transferrin binding, which was about 77%. Low molecular weight species account for only 3% of the vanadium present in plasma [48]. Chasteen et al. [48] stated that “the actual distribution of vanadium between oxidation states and between transferrin and albumin will depend on kinetic factors such as concentration and identity of reductants in plasma, the fluctuation of oxygen tension between 40 and 100 torr for venous and arterial blood, respectively, and the flux of the metal in and out of cells.”

According to Chasteen et al. [50], vanadium is targeted to cells that are rich in iron where a significant amount of it as vanadyl is bound to ferritin, the iron storage protein. Evidence for this statement is that radiolabeled vanadium orally administered, injected intravenously (IV) or instilled intratracheally (IT) is retained in high amounts in liver and spleen [23,51–54]. Sabbioni and Marafante [55] found that one day after IV administration of $^{48}\text{VO}^{2+}$, 29% of $^{48}\text{V}$ incorporated in rat liver cytosol existed as a vanadium–low molecular weight complex (<5000 MW). By day 9, however, they found that the low molecular weight complex had disappeared and vanadium was present only as vanadium-ferritin (15%) and vanadium-transferrin (85%) in rat liver cytosol. Nine days after the administration of vanadium, partial purification of heart myoglobin, liver mitochondrial and microsomal cytochromes b, b$_5$, and c, and ferriporphyrin, and red blood cell hemoglobin showed no significant incorporation of $^{48}\text{V}$ into these proteins [56]. Although these findings indicate that only nonheme iron metalloproteins are involved in the metabolism of vanadium in vivo, it remains to be determined as to whether ferritin is a storage vehicle for vanadium, and whether vanadyl-transferrin can transfer vanadium to cells through the transferrin receptor.
Vanadium in milk of lactating rats injected with $^{48}$V was found mainly in the protein fraction associated with a transferrin-like protein, apparently lactoferrin [57]. Nursing pups absorbed a significant amount of the $^{48}$V in the milk; this suggests that a lactoferrin-vanadium complex is important in vanadium metabolism in the suckling rat pup.

Other organs that retain relatively high amounts of orally, IV, or IT administered vanadium are kidney, bone, and testis [23,51–54]. The high amount in kidney may reflect its being the site of vanadium excretion. Part of the retention of vanadium in bone is thought to occur because vanadate substitutes for phosphate in the hydroxyapatite crystal [58]. Bone also contains the iron-protein-rich marrow. Why testis retains relatively high amounts of vanadium and how it is bound are unclear.

2.2.2. Amounts in Organs and Fluids

Heydorn [59] reviewed analytical methods for the determination of vanadium in the low amounts found in tissues, blood, and urine. For this task, especially for human plasma and serum, methods using atomic emission spectrometry, particle-induced X-ray emission, flame atomic absorption spectrometry, and catalysis were found to be inadequate. Methods that apparently can determine vanadium accurately in low amounts are electrothermal atomic absorption spectrometry, neutron activation analysis with radiochemical separation, and neutron activation with preirradiation separation. Thus, early reports of the vanadium content of organs and fluids determined by unreliable and insensitive techniques should be disregarded, including that by Schröder et al. [12]. Recent analyses using reliable techniques indicate that very little vanadium is retained under normal conditions in the body; most tissues contain less than 10 ng V/g wet weight (Table 2). The total body burden of vanadium is about 100 μg.

2.2.3. Factors Affecting Retention

There are reports that occupational exposure and several pathological conditions can affect the tissue retention of vanadium. Most of these reports must be accepted with wariness because the vanadium concentration values given, even for healthy, normal individuals, do not con-
<table>
<thead>
<tr>
<th>Fluid/organ</th>
<th>Vanadium (ng/g or mL)</th>
<th>Ref.</th>
<th>Fluid/organ</th>
<th>Vanadium (ng/g or mL)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amniotic fluid</td>
<td>12</td>
<td>60</td>
<td>Milk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile</td>
<td>1.0</td>
<td>19</td>
<td>Guatemala</td>
<td>0.21</td>
<td>67</td>
</tr>
<tr>
<td>Blood</td>
<td>0.058</td>
<td>61</td>
<td>Hungary</td>
<td>0.11</td>
<td>67</td>
</tr>
<tr>
<td>Bone</td>
<td>3.5</td>
<td>19</td>
<td>Nigeria</td>
<td>0.46</td>
<td>67</td>
</tr>
<tr>
<td>Brain</td>
<td>0.75</td>
<td>19</td>
<td>Philippines</td>
<td>0.69</td>
<td>67</td>
</tr>
<tr>
<td>Bronchus</td>
<td>60</td>
<td>62</td>
<td>Sweden</td>
<td>0.13</td>
<td>67</td>
</tr>
<tr>
<td>Fat, subcutaneous</td>
<td>0.72</td>
<td>19</td>
<td>Zaire</td>
<td>0.27</td>
<td>67</td>
</tr>
<tr>
<td>Fingernails</td>
<td></td>
<td></td>
<td>Placenta (dry wt)</td>
<td>8.3</td>
<td>68</td>
</tr>
<tr>
<td>Canada, India, USA</td>
<td>80</td>
<td>63</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>150</td>
<td>63</td>
<td>Red blood cells</td>
<td>0.026</td>
<td>69</td>
</tr>
<tr>
<td>Poland</td>
<td>110</td>
<td>63</td>
<td>Serum</td>
<td>0.031</td>
<td>69</td>
</tr>
<tr>
<td>Hair, scalp</td>
<td>40</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>64</td>
<td>Subpleura</td>
<td>58</td>
<td>62</td>
</tr>
<tr>
<td>Heart</td>
<td>1.1</td>
<td>19</td>
<td>Teeth</td>
<td>3.6</td>
<td>19</td>
</tr>
<tr>
<td>Kidney</td>
<td>3.0</td>
<td>19</td>
<td>Primary</td>
<td>4.3</td>
<td>70</td>
</tr>
<tr>
<td>Liver</td>
<td>7.0</td>
<td>65</td>
<td>Permanent</td>
<td>3.9</td>
<td>70</td>
</tr>
<tr>
<td>Lung</td>
<td>30 (median)</td>
<td>19</td>
<td>Thyroid</td>
<td>3.1</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>66</td>
<td>Trachea</td>
<td>38</td>
<td>62</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.54</td>
<td>19</td>
<td>Urine</td>
<td>0.24</td>
<td>71</td>
</tr>
</tbody>
</table>
form with those shown in Table 2 (usually greater by a factor of at least 10). Nonetheless comparisons are made between healthy normals and targeted groups. Thus, a relative difference probably can be accepted as evidence that vanadium retention has been modified. When compared to healthy or normal controls, the vanadium concentration was higher in the hair of welders [72], patients with chronic renal failure [73], and patients with manic-depressive illness [64,74,75] and lower in the hair of multiple sclerosis patients [76]. Elevated blood, serum, or plasma vanadium concentrations have been found in patients with chronic renal disease [77–79] and manic-depressive illness [74,75,80–83]. Kidneys taken at autopsy from patients in which the cause of death was related to pulmonary pathology were found to contain increased vanadium concentrations [84].

Based on animal studies, high dietary vanadium also increases the retention of vanadium by the body. In rats, on a wet weight basis, vanadium increased from 10 to 554 ng/g in liver, from 2 to 210 ng/mL in plasma, from 2 to 110 ng/mL in whole blood, and from 10 to 1812 ng/g in kidney cortex when dietary vanadium was increased from 0.1 to 25 μg/g [18]. In sheep, bone vanadium increased from 220 to 3320 ng/g ash weight when dietary vanadium was increased from 10 to 220 μg/g [85]. Bone apparently is a major sink for retained vanadium.

Vanadium retention may also be affected by age. Hair vanadium concentrations were found to increase in infants from birth to 6 months of age [86]. In rats between ages 21 and 115 days, the vanadium concentration decreased in kidney, liver, lung, and spleen, and increased in fat and bone [87].

2.3. Excretion

2.3.1. Sites and Mechanisms of Excretion

Most ingested vanadium is excreted via the feces; most of the vanadium is that which was unabsorbed. However, based on studies in which vanadium was administered parenterally, a significant amount of absorbed vanadium is reexcreted via the intestinal tract. Kent and McCance [16] recovered in 2 weeks about 10% of an IV dose of sodium tetravanadate in the feces of two human subjects. Hopkins and Tilton [15], using the radiotracer ⁴⁸V, found that rats excreted 8.6% of the dose
in the feces within 96 hr after being IV injected. Wiegmann et al. [17] obtained similar results with an intraperitoneal (IP) injection of vanadium containing $^{48}$V. Sabbioni and Marafante [51] found that about 10% of IV-injected 10 μg/g of $^{48}$V-labeled vanadium as ammonium metavanadate appeared in the feces. It was suggested, based on experiments with cannulated rats, that the bile contributes to the intestinal elimination of vanadium during the initial hours after absorption when high amounts of circulating vanadium are present, but upon binding to hepatic constituents, biliary excretion is limited [88]. However, Hansard et al. [54] found that the appearance of an IV dose of carrier-free $^{48}$V as dioxovanadium chloride in feces progressively increased over 6 days at which time 5.3% of the dose had appeared. This suggests that even when circulating vanadium is low a significant amount is excreted via the bile. Further evidence that bile is an important excretory route is the finding of about 1.0 ng V/g of human bile [19].

Based on studies in which vanadium is administered parenterally, urine is the major excretory route for absorbed vanadium. Kent and McCance [16] gave two men six IV injections of sodium tetravanadate totaling 18 and 24 mg of vanadium in one week; at the end of 2 weeks, 86% and 83%, respectively, of the vanadium was found in the urine. Hansard et al. [54] found that 57–70% of an IV administered tracer dose of $^{48}$V appeared in the urine of sheep in 6 days. IV or IP vanadium appeared somewhat slower in rats. At 96 hr after an IV injection of $^{48}$V in rats, 30–46% of the dose had been excreted in the urine [15,51]. Within five days after IP administration of $^{48}$V-labeled vanadate to rats, only 41% of the dose had appeared in the urine. However, Roshchin et al. [52] found that 66% of $^{48}$V injected intramuscularly (IM) as VOCl$_2$ was eliminated in the urine within 24 hr.

2.3.2. Forms Excreted

Both high and low molecular weight complexes have been found in urine. Sabbioni and Marafante [51] found that $^{48}$V in the urine was mainly associated with high molecular weight components 3 days after an IV injection of $^{48}$V. They suggested that one high molecular weight component binding vanadium was transferrin. On the other hand, Chasteen et al. [39] found that the majority of vanadium excreted in the
urine was as a low molecular weight VO^{2+} complex; this complex was not identified.

3. ESSENTIALITY

3.1. Signs of Deprivation

Between 1971 and 1974, four research groups described possible signs of vanadium deficiency. However, there was much inconsistency in the findings. Strasia [89] 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 [90], using a diet lower in casein and higher in iron and ascorbic acid, was not able to produce those deficiency signs in the same laboratory in which Strasia worked. Schwarz and Milne [91] reported that a vanadium supplement of 0.25–0.50 μg/g diet gave a positive growth response in suboptimally growing rats fed an amino acid–based diet probably deficient in riboflavin and with an unknown vanadium content. On the other hand, Hopkins and Mohr [13] reported that the only effect of vanadium deprivation in rats was impaired reproductive performance (decreased fertility and increased perinatal mortality) that became apparent only in the fourth generation; the diet used contained luxuriant amounts of methionine and was probably deficient in cysteine.

Deprivation studies with chicks also gave inconsistent findings. Hopkins and Mohr [13,92] found that vanadium-deprived chicks exhibited significantly depressed wing and tail feather development, depressed plasma cholesterol and triglycerides at age 28 days, and elevated plasma cholesterol at age 49 days. Nielsen and Ollerich [93,94] reported that vanadium deprivation depressed growth, elevated hematocrits and plasma cholesterol, and adversely affected bone development.

In the preceding vanadium deprivation studies, “controls” or supplemented animals were fed 0.5–3.0 μg V/g diet. Although these amounts are near those in natural diets which apparently contain about 1.0 μg V/g [95], those doses of highly available vanadium apparently are 10–50 times those normally found in purified or semipurified
diets [95]. As indicated elsewhere in this book, vanadium is a relatively
toxic and pharmacologically active element. As a result, it is difficult to
determine whether the "deficiency signs" in early experiments with
questionable diets were true deficiency signs, indirect changes caused
by an enhanced need for vanadium in some metabolic function, or
manifestations of a pharmacological action of vanadium. However, some
recent findings suggest that the early findings of impaired reproductive
performance, bone structure changes, and plasma cholesterol changes
may have been true vanadium deficiency signs.

The uncertainty about vanadium deficiency signs stimulated new
efforts in the 1980s to produce deficiency signs in animals fed diets
apparently containing adequate and balanced amounts of all known
nutrients; findings from these studies are described below. Vanadium
deficiency signs for humans have not been described.

3.1.1. Gross Signs

In nine experiments, Anke and coworkers [96–99] 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. Forty-two percent of kids
from vanadium-deprived goats died between days 7 and 91 of life 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 exhib-
ited pain in the extremities, swollen forefoot tarsal joints, and skeletal
deformations in the forelegs; some of these changes have been illus-
trated [96,99]. Uthus and Nielsen [100] reported that, when compared
to controls fed 1 µg V/g diet, vanadium deprivation (2 ng V/g diet)
increased thyroid weight and thyroid weight/body weight ratio and
tended to decrease growth of rats.

3.1.2. Biochemical Signs

Uthus and Nielsen [100] found that as dietary iodine increased from
0.05 to 0.33 to 25 µg/g, thyroid peroxidase activity decreased, and the
decrease was more marked (38.1 to 12.3 to 3.5 mGU/mg protein) in vanadium-supplemented (1 µg V/g diet) than in vanadium-deprived (2 ng V/g diet) rats (18.7 to 10.2 to 6.8 mGU/mg protein). Also, as dietary iodine increased, plasma glucose increased in the vanadium-deprived rats but decreased in the vanadium-supplemented rats. Vanadium deprivation also depressed red blood cell glucose-6-phosphate dehydrogenase and cecal total carbonic anhydrase [101].

Seaborn et al. [102] found that, when compared to guinea pigs fed less than 10 ng V/g diet, guinea pigs supplemented with 0.5 µg V/g diet exhibited decreased hepatic glycogen and bone copper, and increased hepatic lipids, fecal bile acids, plasma cortisol, and bone calcium and magnesium. Vanadium supplementation also increased HDL cholesterol [103]. An interaction between dietary vanadium and ascorbate affected several variables in guinea pigs. Vanadium supplementation increased plasma 3-hydroxy-3-methylglutaryl coenzyme A reductase activity, fecal cholesterol, and hepatic copper and iron in ascorbate-deficient, but decreased these variables in ascorbate-adequate, guinea pigs; just the opposite occurred with plasma cholesterol and bile acids in bile [102]. Anke et al. [96] reported that, when compared to goats fed less than 10 ng V/g diet, goats fed 2 µg V/g diet exhibited decreased serum β-lipoproteins, creatinine, isocitrate dehydrogenase, and lactate dehydrogenase, and increased serum glucose.

Unfortunately, the conclusiveness of the findings from the recent studies is somewhat diminished by the fact that the control diets, like those in the early vanadium essentiality studies, contained high amounts of highly available vanadium (0.5–2 µg/g); these amounts may have had unknown pharmacological effects in these studies. For example, findings similar to the biochemical findings with control goats fed 2 µg V/g diet reported by Anke et al. [96] were not mentioned in later reports in which control goats were fed 0.5 µg V/g diet [98,99]. Seaborn et al. [102] suggested that the increased plasma cortisol in guinea pigs supplemented with 0.5 µg V/g diet was evidence that this amount of dietary vanadium was a stressor, and thus it may have been exerting pharmacological or toxicological effects. Nonetheless, because the diets used apparently were complete and well balanced, the recent vanadium deprivation studies probably have found some true deficiency signs. It seems unlikely that the diets lacked any nutrient that would cause some of the marked deficiency signs (especially the bone changes) that
would be prevented by a pharmacological action of the small vanadium supplements used.

3.2. Possible Biochemical Functions

A defined biochemical function for vanadium in higher animals, and thus humans, has not been described. Recently, however, functional roles for vanadium have been defined for some algae, lichens, fungi, and bacteria; these include roles in haloperoxidase [104] and nitrogenase [105] enzymes, a compound called amavadin found in mushrooms [106], and a substance isolated from ascidian blood cells called vandobin [107]. These findings, along with the animal findings above, suggest that vanadium has an essential functional role in higher animals, including humans.

Numerous biochemical and physiological functions for vanadium have been suggested based upon its in vitro and pharmacological actions; these have been discussed in several reviews [108–112] and are too extensive to discuss in detail here. In vitro studies with cells and pharmacological studies with animals have shown that vanadium has insulin-mimetic properties; numerous stimulatory effects on cell proliferation and differentiation; effects on cell phosphorylation/dephosphorylation; inhibitory effects on the motility of sperm, cilia, and chromosomes; effects on glucose and ion transport across the plasma membrane; interfering effects on intracellular ionized calcium movement; and effects on oxidation-reduction processes. In vitro cell-free systems have shown that vanadium inhibits numerous ATPases, phosphatases, and phosphoryl transfer enzymes. Vanadium also stimulates the activity of numerous enzymes in vitro including NADPH/NADH oxidase. However, vanadium has not been found to be the specific activator or inhibitor of any enzyme in higher forms of life.

With the entanglement of pharmacological and nutritional observations, it is difficult to speculate on a possible function for vanadium. However, two promising sites for a functional role of vanadium is in thyroid and in bone (and/or connective tissue) metabolism.

The finding that some haloperoxidases in lower forms of life require vanadium for activity suggests a similar function in higher animals. The best known haloperoxidase in animals is thyroid perox-
idase. As described previously, an apparent vanadium deprivation affected the response of thyroid peroxidase activity to changing dietary iodine in addition to elevating thyroid weight. Other findings pointing toward a role for vanadium in thyroid hormone metabolism are that the thyroid apparently contains relatively high amounts of vanadium [113], thyroidectomy-parathyroidectomy increases tissue retention of vanadium [114], and thyroxine administration alleviates the retention of vanadium in pancreas, kidney, and bone caused by hypophysectomy [115].

The changes in bone structure in the vanadium deprivation studies found by Anke et al. [96–99] and Nielsen and Ollerich [93,94] suggest a role in bone or connective tissue metabolism. Also supporting such a role is the finding that the uptake of an IP-injected dose of $^{48}$V as vanadyl chloride by chick tibia occurred only in areas of calcification, i.e., secondary center of ossification, and calcifying cartilage and bone; the highest uptake occurred in newly calcified cartilage [116]; similar findings were obtained with fish [117]. Additionally, vanadium has been found to stimulate the mineralization of bones and teeth [11] and the repair of bones [118]. The possibility that vanadium affects bone through an effect on thyroid metabolism has been discussed [119]. Another possible mechanism is through vanadium affecting or acting like a growth factor. Vanadate can mimic growth factors such as epidermal growth factor, fibroblast growth factor, and insulin [120,121]. For example, orthovanadate stimulates bone cell proliferation and collagen synthesis in vitro [120,122]. Also, vanadate was shown to increase proteoglycan synthesis by stimulating the conversion of poorly differentiated chondrocyte cultures from a “fibroblastic” expression to a “chondrocytic” expression [123]. Low concentrations of vanadium were found to be required for optimal growth of fibroblasts in tissue culture [124]. Finally, the oral administration of 1.0–10.0 μmol V/100 g to rats as vanadium pentoxide was found to increase bone DNA content and alkaline phosphatase activity [125].

Recently, the peroxy form of vanadium [126–128] has been discussed as being responsible for many biological actions of vanadium including its insulin-mimetic action and haloperoxidase roles. Vanadate can interact with $O_2^-$ formed by NADPH oxidase to generate peroxyvanadyl [V(IV)$\cdot$OO]. Peroxyvanadyl can in turn remove hydrogen from NADPH to yield vanadyl hydroperoxide [V(IV)$\cdot$OOH] [126]. Vanadium(III)- and (V)-superoxide complexes also have been postulated
Perhaps a peroxovanadyl form of vanadium is important at the physiological or nutritional level.

4. TOXICITY

4.1. Signs of Toxicity in Animals

Reports describing toxicological aspects of vanadium are too extensive to discuss in detail here; several comprehensive reviews of vanadium toxicity have been published [1,4,5,130–133]. From their in-depth study of vanadium toxicity, Proescher et al. [5] concluded that vanadium is neurotoxic and a hemorrhagic-endotheliotoxic poison with nephrotoxic, hepatotoxic, and probably leukocytotoxic components. Thus, it is not surprising that a variety of toxicity signs have been described for animals and that they can vary among species and with dosage. Some of the more consistent signs include depressed growth, diarrhea, depressed food intake, and death.

4.2. Signs of Toxicity in Humans

4.2.1. Chronic

Vanadium is a relatively toxic element for humans. Signs of toxicity through occupational sources have been well described [130,131,133]. The threshold level for toxicity through ingestion apparently is near 10–20 mg/day or 10–20 μg/g of diet; this is supported by animal findings [110] and the following human findings. Schroeder et al. [12] fed 15 patients 4.5 and 9 mg V/day as diammonium oxyltartratovanadate for 6–16 months without apparent detrimental effect. Curran et al. [21] fed each of five subjects 13.5 mg/day in three divided doses as diammonium oxyltartratovanadate for 6 weeks; no sign of intolerance or toxicity was found. On the other hand, Somerville and Davis [134] gave each of 12 patients 13.5 mg V/day for 2 weeks and then 22.5 mg V/day for 5 months as diammonium vanadotartrate; five patients exhibited persistent upper abdominal pain, anorexia, nausea, and weight loss, and five patients exhibited green tongue. It should be noted that, according to Curran
and Burch [7], "the infamous green tongue which has been cited as an example of vanadium toxicity is merely a staining from mucosal contact with vanadium salts." Dimond et al. [22] gave ammonium vanadyl tartrate orally to six subjects for 6–10 weeks in amounts ranging from 4.5 to 18 mg V/day; green tongue, cramps, and diarrhea were observed at the larger doses.

Excessive in vivo amounts of vanadium have been suggested as a factor in manic-depressive illness [64,74–76]. In patients with this illness, elevated concentrations of vanadium have been found in plasma and hair. Improvement in the illness occurred with treatments that alleviate vanadium toxicity [74]. Recently, it has been suggested that chronic exposure to vanadium may result in hypertension [135,136].

4.2.2. Acute

Acute signs of vanadium toxicity in humans have been described by Proescher et al. [5]. They reported that in man, after an IV injection of 20 mg $V_2O_5$ as sodium tetravanadate, constriction of the throat, salivation, lacrimation, disappearance of pulse, free discharge of feces, vomiting, cessation of respiration, and a drop of 3$^\circ$ in temperature occurred.

5. ASSESSMENT OF STATUS

Because no function for vanadium in higher animals has been defined, a biochemical indicator of vanadium status does not exist. Blood, serum, and hair vanadium concentrations are possible indicators of vanadium status. Hair vanadium concentrations have been found to be elevated in patients with manic-depressive illness [64,74,75] and renal failure [73]. Elevated blood, serum, or plasma vanadium concentrations also were found in these patients [77–83]. Human whole-blood vanadium concentrations ranged from 0.024 to 0.226 (mean 0.056) ng/mL in nonexposed children near Prague, Czechoslovakia [61]. The range of concentrations in potentially exposed children near Prague were similar (0.018–0.239 ng/mL), but their mean value was higher (0.099 ng/mL) [61]. These findings suggest that vanadium concentrations in blood, serum, or hair
significantly above or below those given in Table 2 may indicate an abnormal vanadium status.

6. SAFE AND ADEQUATE INTAKES

Any human requirement for vanadium would likely be very small. The diets used in animal deprivation studies contained only 1–25 ng V/g; often these did not markedly affect the animals. Vanadium deficiency has not been identified in humans; yet, as indicated in Table 3, most diets supply less than 30 μg daily, with many near 15 μg daily. These observations suggest that a dietary intake of 10 μg daily probably meets any postulated vanadium requirement.

The preceding discussion of toxicity indicated that a daily intake of over 10 mg of vanadium produced overt signs of toxicity. However, much lower amounts of vanadium were found to pharmacologically affect animals and humans, which suggests that they may have toxic manifestations under certain situations. For example, Schroeder et al. [12] found that 4.5 mg V/day decreased serum cholesterol in humans. In the preceding discussion of essentiality it was suggested that doses of highly available vanadium 10–50 times those normally found in purified or semipurified diets were having pharmacological effects in animals. Extrapolating these factors to humans indicates that the daily intake of vanadium probably should not exceed 100 μg.

Suggesting a safe and adequate intake of vanadium with the above limited information is difficult. However, based on the preceding, the safe and adequate intake of vanadium probably will be found to be near 10–50 μg/day.

7. DIETARY INTAKES

As indicated by Table 3, the daily intake of vanadium is relatively low in comparison with other essential trace elements. Foods rich in vanadium (greater than 40 ng/g) include shellfish, mushrooms, parsley, dill seed, black pepper, and some prepared foods [142,143]. Cereals, liver, and fish tend to have intermediate amounts (5–40 ng V/g) [19,137,140,142].
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>16.7&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>61</td>
<td>United States, age/sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Britain</td>
<td>13&lt;sup&gt;b&lt;/sup&gt;</td>
<td>137</td>
<td>6–11 mo</td>
<td>6.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>30&lt;sup&gt;b&lt;/sup&gt;</td>
<td>138</td>
<td>2 yr</td>
<td>6.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>140</td>
</tr>
<tr>
<td>Iran</td>
<td>34.7&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>61</td>
<td>14–16 yr, F</td>
<td>7.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>140</td>
</tr>
<tr>
<td>Italy</td>
<td>17.7&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>61</td>
<td>14–16 yr, M</td>
<td>11.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>140</td>
</tr>
<tr>
<td>Japan</td>
<td>2.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>139</td>
<td>25–30 yr, F</td>
<td>8.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>140</td>
</tr>
<tr>
<td>Spain</td>
<td>11.8&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>61</td>
<td>25–30 yr, M</td>
<td>18.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>140</td>
</tr>
<tr>
<td>Thailand</td>
<td>10.0&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>61</td>
<td>60–65 yr, F</td>
<td>6.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>140</td>
</tr>
<tr>
<td>Turkey</td>
<td>21.9&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>61</td>
<td>60–65 yr, M</td>
<td>10.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>140</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td>United States, TPN solutions</td>
<td>29&lt;sup&gt;b&lt;/sup&gt;</td>
<td>141</td>
</tr>
<tr>
<td>Southeastern</td>
<td>15.5&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North-central</td>
<td>22.8&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeastern</td>
<td>20.9&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southern</td>
<td>16.4&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western</td>
<td>25.3&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North Dakota</td>
<td>20.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Median.

<sup>b</sup>Mean.

<sup>c</sup>Daily intake calculated from dry weight concentration and based on a consumption of about 0.5 kg of food/day dry weight.
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 [19,137,140,142].

8. CLINICAL SIGNIFICANCE OF VANADIUM

The clinical importance of vanadium is uncertain. Because neither a defined biochemical function nor signs of vanadium deficiency have been described for humans, any discussion of its possible nutritional importance seems inappropriate at this time.

Toxic effects from the intake of high amounts of vanadium in the diet are unlikely. Except for a few vanadium accumulator plants, only small amounts of vanadium are taken up by plants from the soil and deposited on the edible portion. Low plant uptake prevents the production of foods with high vanadium content even if local soil concentrations are high and soil contamination occurs because of combustion of petroleum and other naturally occurring hydrocarbons, such as asphaltite, which contain appreciable amounts of vanadium [144]. Although tissue vanadium can be elevated in livestock fed high-vanadium phosphates [110], vanadium toxicity occurs in the animal long before the vanadium content of the food products from those animals are of concern. Toxicity of vanadium usually occurs only as a result of industrial exposure to high amounts of airborne vanadium. However, because vanadium is so active pharmacologically, a beneficial pharmaceutical role for this element may be found. Also, nutritional supplements containing vanadium are now being marketed. Thus, the possibility of oral toxicity of vanadium in the future may not be remote.

The primary clinical research need for vanadium is the identification of an essential biochemical function in higher animals. This is necessary to disentangle pharmacological from nutritional or physiological observations in order to assess the clinical importance of vanadium. Determination of a defined function also will facilitate other research needs of vanadium in nutrition including the determination of status assessment indicators as well as safe and adequate intakes. Furthermore, until a defined function is described, it is unlikely that vanadium will be unequivocally accepted as an essential nutrient for higher animals.
ABBREVIATIONS AND DEFINITIONS

ATP adenosine 5’-triphosphate
EDTA ethylenediamine-N,N,N’,N’-tetraacetate
HDL cholesterol high-density lipoprotein—cholesterol
IM intramuscularly
IP intraperitoneally
IT intratracheally
IV intravenously
mGU milliguaiacol unit (amount of enzyme that gives a change of 1.0 absorbance unit per second with guaiacol as substrate divided by 1000)
NADH nicotinamide adenine dinucleotide (reduced)
NADPH nicotinamide adenine dinucleotide phosphate (reduced)
TPN total parenteral nutrition

Pharmacological action: The effect of a relatively high dietary intake of a substance that either alleviates an abnormality caused by something other than a nutritional deficiency of that substance or alters some biochemical function or biological structure in a manner that may be construed as beneficial.

REFERENCES

32. B. J. Stoecker and Y. C. Li, in *Trace Elements in Man and...*


89. C. A. Strasia, in Vanadium: Essentiality and Toxicity in the Laboratory Rat, PhD thesis, Purdue University, Lafayette, IN, 1971.


METAL IONS IN
BILOGICAL SYSTEMS

Edited by
Helmut Sigel
and Astrid Sigel
Institute of Inorganic Chemistry
University of Basel
CH-4056 Basel, Switzerland

VOLUME 31

Vanadium and Its Role in Life

Marcel Dekker, Inc. New York • Basel • Hong Kong

Copyright © 1995 by Marcel Dekker, Inc.