Review

Vanadium: Biological, Environmental, and Engineering Aspects

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Academic Editor: Maxim L. Kuznetsov

Special Issue: [Coordination Chemistry and Metal Complexes](#)

Advances in Chemical Research

2020, volume 2, issue 1

doi:10.21926/acr.2001002

Received: December 18, 2019

Accepted: December 31, 2019

Published: January 8, 2020

Abstract

Vanadium is an element that is widely distributed in Earth's crust as well as in sea-water and ground-water reservoirs. Therefore, it exerts a great influence on the issues related to life and environment. Vanadium is utilized by several marine organisms. For example, there are vanadate-dependent haloperoxidases in algae and several bacteria, e.g., *Azotobacter*, use it for nitrogen fixation and bacterial reduction involves the conversion of vanadate to oxidovanadium (IV). The similarity between vanadate and phosphate imparts a physiological functional role to vanadate (V), and consequently, several aspects of medicinal potential to vanadate and vanadium coordination compounds, such as their use in the treatment of diabetes, cancer, and cardiovascular problems, which may be explained in conjunction with vanadate/phosphate antagonism. Similar considerations apply to the efficacy of vanadium compounds in the treatment of HIV and [tropical] diseases caused by bacteria and protozoa. In addition to this biological efficacy, vanadium plays an increasingly recognized role in industrial processes, such as steel production, oxidation catalysis, and vanadium-based energy storage (batteries) and solar cells.

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Keywords

Vanadate; environmental significance; haloperoxidases; nitrogenase; diabetes; tropical diseases; bacterial deployment; industrial use; batteries

1. Introduction

With an overall abundance of 0.019%, vanadium is the 22nd most abundant element in Earth's crust, where it exists in the form of seventy minerals, and in the oxidation states of +III, +IV, and +V. This element is also present in shales and crude oil, for example, in the form of oxidovanadium (IV) porphyrins or bound to the thiophenogenic compounds. In seawater [1a], vanadate (essentially, H_2VO_4^-) is present at an average molarity of 30 nM (next to molybdate, the second most abundant metal in seawater), and serves as a partially essential energy source for marine organisms, such as macroalgae (seaweeds), sea squirts, and fan worms. Moreover, the utilization of vanadate in the conversion of halide to hypohalous acid by, inter alia, seaweeds (such as *Ascophyllum*), and the concomitant release of the halide species and/or singlet oxygen into the atmosphere, generate consequences for the atmospheric chemistry. In certain mineral water springs, vanadium concentrations may reach a value of 50 μM , while the mean vanadate concentrations in freshwater are much lower [1b]. The global omnipresence of vanadium [1c] accounts for its generally non-specific presence in living organisms as well. A few on-shore organisms, such as certain lichens and the mushrooms belonging to genus *Amanita*, contain a functionally active vanadium compound named amavadin. Several bacterial species exploit the redox equilibrium between V^{V} (commonly in the form of H_2VO_4^- or VO^{3+}) and V^{IV} (as VO^{2+}). It is noteworthy in the context of bacterial activity that vanadium nitrogenase in *Azotobacter* is responsible for the conversion of aerial N_2 into NH_4^+ . Whether vanadium is essential for humans [and other mammals], in low concentrations, as an antagonist and consequently as the regulator for the phosphatases, has not yet been assessed conclusively. In this context, vanadium compounds have attracted considerable attention regarding their potential medicinal applications [2a]. Besides the afore-stated biological functions, vanadium has been used traditionally as an additive in steel (ferro-vanadium), as an oxidation catalyst (V_2O_5 in the production of sulfuric acid), and more recently, in the production of high-capacity flow batteries which are based on lithium vanadate. Recently, a few reviews on the role of vanadium in natural as well as in medicinal and industrial processes have been published in the literature [2b, c-4].

2. Biological Aspects

In this section, the following aspects would be addressed: the role of vanadium (a) in enzymes (haloperoxidases, nitrogenases), (b) the role of vanadium in ascidians and fan worms, (c) microbial use of vanadium and its transformation, (d) its physiological aspects (the phosphate/vanadate antagonism), including potential medicinal applications. Several reviews concerning these aspects have been published previously [5-7].

2.1 Vanadium-Dependent Enzymes

Vanadate-dependent haloperoxidase (VHPO) enzymes have been isolated from marine algae (in particular, *Ascophyllum nodosum*; Figure 1, right) and from hyphomycetes fungi such as the mold *Curvularia inaequalis*; these enzymes may also be present in certain cyanobacteria [7]. Haloperoxidases catalyze the two-electron oxidation of halides (iodide and bromide in particular, although chloride and pseudohalides such as thiocyanate may also serve as substrates for this reaction) to hypohalous acids or hypohalites, in the presence of a peroxide (hydrogen peroxide), as depicted in Figure 1 and eq. (1a) regarding the formation of hypobromous acid/hypobromite. These hypohalites are strong oxidizing agents which are probably involved in the protective anti-parasitic mechanisms in algae. The hypohalous acids HOX may further produce, in a symproportionation reaction, free halogens X_2 [eq. (1b)], which when released in the air, undergo photolytic splitting to form halogen radicals. These halogen radicals, in turn, contribute to the annihilation of the ozone layer [eq. (1c)]. Therefore, a climatological impact should be considered in the areas with excessive algal bloom due to over-fertilization [5].

Figure 1 Left: The conceivable mechanism for the formation of hypohalous acid (shown here for HOBr) at the active center of a bromoperoxidase, based on an earlier report [8]. Right: The marine brown alga *Ascophyllum nodosum* is the “pioneer” in the establishment of the biological function of vanadium as the central and active constituent of vanadate-dependent bromoperoxidases [9].

The second enzyme of substantial importance in regard to life is a nitrogenase containing vanadium in its active center in place of the more commonly present molybdenum (Mo).

Vanadium-dependent nitrogenase (VNase) has been isolated from the nitrogen-fixing [$\text{N}_2 \rightarrow \text{NH}_4^+$; eq. (2)] aerobic bacterium *Azotobacter vinelandii* [10], and in times of Mo deficiency, from the bacteria that would otherwise employ molybdenum, for example, *Rhodobacter capsulatus*. Several other bacterial strains and cyanobacterial symbionts belonging to the family Nostocaceae also exhibit the presence of a vanadium-dependent nitrogenase. The ammonium ions formed as a result of the action of nitrogenase are subsequently employed in the biosynthesis of amino acids, and consequently, proteins. In its resting state, VNase has a $\{\text{VFe}_7\text{S}_9\}$ cluster at its center, which is linked to the protein through cysteine, histidine, and homocitrate (the latter two are directly coordinate-bonded to vanadium). In contrast to the molybdenum analog of the enzyme, VNase is able to effectively reduce carbon monoxide and carbon dioxide to hydrocarbons [eq. (3) and (4)] [11]. VNase is also involved in the catalytic reduction of ethene to ethane [eq. (5)]. Furthermore, HCN may be subjected to enzymatically driven reduction reaction [12]; for example, in the reaction represented by eq. (6). A recently reported structure for the active center of the iron–vanadium cofactor [containing, in its turn-over state, a $\{\text{VFe}_7\text{S}_8\text{OH}\}$ core] is depicted in Figure 2.

Figure 2 The cofactor of vanadium nitrogenase in its turnover state, according to the earlier work [13]. The light atom ligand (in blue) is represented here by OH; this group is in hydrogen bonding contact with histidine and glutamine from the protein matrix.

2.2 Vanadium in Ascidians and Fan Worms

The marine organisms that utilize vanadium are the ascidians and the polychaete fan worms, although the use of vanadium and its potential benefit for these organisms has not been reported with valid evidence so far. Since the environmental occurrence of vanadium in the form of hydrogenvanadate (V) and oxidovanadium (IV) and (V) is toxic to a certain extent, the accumulation of vanadium by certain organisms may reflect its use as an anti-predator agent. Polychaeta fan worms uptake vanadium in the branchial crown, and it has been proposed by previous studies that VO^{2+} is bound by, and consequently suppresses, a nucleoside diphosphate kinase [14], which is consistent with the otherwise well-established fact that vanadate and/or

oxidovanadium (IV) interact with, and thereby regulate, the phosphatases and kinases [see also, Section 2 (d)]. Ascidians (sea squirts) uptake vanadium in the form of vanadate (V) H_2VO_4^- , which is subsequently reduced to VO^{2+} in two successive steps, and finally to vanadium (III) after binding to the lysine residues of vanabin (a vanadium-binding metallo-protein); the reaction is represented by eq. (7) [15a]. The reductant in the second step is cysteinylmethionine (CysMet). Interestingly, bacterium *Pseudomonas isanchencovi*, which was originally isolated from the tunicates, is also capable of reducing vanadate (V) to oxidovanadium (IV) [Section 2 (c)] and vanadium (III) [15b]. Vanadium accumulation in ascidians results in the activation of glucose-6-phosphate dehydrogenase, an enzyme that catalyzes the interconversion between *D*-glucose-6-phosphate and 6-phospho-*D*-glucono-1,5-lactone [eq. (8)]. The degree of vanadium accumulation in ascidians may reach up to 10^7 -fold the vanadate concentration in the seawater. The uptake of vanadate also occurs in several bacterial strains [16], as would be described in the section ahead.

2.3 Microbial Usage of Vanadium

In this section, the utilization of inorganic vanadium by bacteria, predominantly in the redox processes, would be briefly addressed. The relevance of vanadium as a vital constituent of the nitrogenase enzyme in nitrogen-fixing bacteria, such as *Azotobacter*, has already been described in section 2 (a), and the bacterium potentially relevant for the reduction of vanadate in fan worm has been stated in section 2 (b), while the role of vanadium in the potential treatment of diseases of bacterial origin would be described in section 2 (d).

Certain bacteria which thrive in the soil, groundwater reservoirs, and wells, a group usually confined to the colloids, may use vanadium, generally in the form of dihydrogenvanadate (H_2VO_4^-), as an energizer, through the redox conversion of vanadium (V) (commonly H_2VO_4^-) and vanadium (IV) (usually in the form of VO^{2+}) [17]. Such a process is of relevance in the context of detoxification of the industrial waste (waters) in conjunction with, for example, the production of vanadium-steel and sulfuric acid (in the presence of V_2O_5 as a catalyst). Well-investigated scenarios of bacterial vanadate reduction (and therefore, detoxification of vanadate) have suggested the presence of a periplasmic reductase as an initiator. Such vanadate reduction is conducted by, inter alia, the widely distributed dissimilatory metal-reducing bacteria *Shewanella oneidensis* and *Shewanella loihica*, belonging to the group of facultative anaerobic proteobacteria [18, 19, 20]. Formic acid, lactate, and/or citrate are employed as electron sources [see eq. (9)] for the oxidation of formic acid. The reduction product is VO^{2+} , which is responsible for the blue coloration in the reaction medium, or the insoluble $\text{VO}(\text{OH})_2$, which essentially remains attached to the cellular surface.

In addition to *Shewanella*, the soil bacterium *Geobacter metallireducens*, which is present in the subsurface soil, is able to effectively convert vanadate into oxidovanadium (IV), usually by employing acetate as the electron source [21]. Alternatively, lactate may serve as an efficient electron donor. A simplified scheme for the trans-membrane transport of the reduction equivalents (electrons) to the extracellular space and the bioavailability of the reducing equivalents for the reduction of soluble vanadate (V) to insoluble oxidovanadium (IV) are illustrated in Figure 3. The primary electron donor is lactate, which is located in the inner membrane and oxidized under the catalysis of lactate dehydrogenase to form pyruvate. The electrons are subsequently transferred across the periplasm by the cytochrome-c type hemoproteins CymA and MetrC through a changeover between the ferric and ferrous oxidation states of the central iron ion, and are delivered across the outer membrane to the extracellular space, where the reduction of soluble vanadate to insoluble oxidovanadium (IV) hydroxide finally occurs.

Figure 3 Electron transfer pathway (simplified) across a bacterial cell membrane, following earlier reports [22] and [23].

Geobacter metallireducens is capable of converting V^{V} into V^{IV} in concentrations of up to 5 mM [24]. The bioreduction of vanadate in contaminated groundwater is conducted efficiently by using autohydrogenotrophic bacteria such as *Clostridium* and *Rhodocyclus* [25] [eq. (10)]. These bacteria deliver the reduction equivalents (electrons) to vanadate by employing molecular hydrogen ($\text{H}_2 \rightarrow 2\text{H}^+ + 2\text{e}^-$).

2.4 Vanadium and Human Physiology; Medicinal Applications

The average daily intake of vanadium in humans is about 2 mg. The intake is essentially in the form of vanadate H_2VO_4^- present in the water, oxidovanadium (V) and (IV) present in nutrients, and V_2O_5 in the air available for breathing. This amount of ingested vanadium is clearly below the tolerable level of 10 mg. Vanadium ingested via water and food may be resorbed in the form of

vanadate, which enters the blood circulation. However, most of this vanadium is generally converted to $\text{VO}(\text{OH})_2$ in the gastro-intestinal tract, and finally removed from the body along with the feces. Inhaled vanadium compounds, such as vanadium oxides in the industrial or the otherwise polluted areas, enter the bloodstream, where they are converted to H_2VO_4^- in case of vanadium (V) or in case of VO^{2+} , are bound to the iron sites of transferrin [26a], and to a lesser extent, also to serum albumin. The transferrin complex may enter the cells and release the oxido vanadium ion, which then becomes involved, at least in part, in various secondary reactions with different intracellular compounds. In the form of vanadate, vanadium may enter the cells through the phosphate channels. Specific vanadium coordination compounds which have been either introduced intravenously or generated in the blood serum from vanadate and the serum constituents (such as transport molecules and the molecules recognized by the cell membrane receptors), directly enter the cells, including the blood cells [26b]. In addition, the oxido vanadium (IV) cation VO^{2+} may competitively intervene the Mg^{2+} transport pathways [27]. In the bone tissue, vanadate is able to partially replace phosphate; VO^{2+} becomes efficiently incorporated into the hydroxyapatite matrix of the bones, where it is able to make a coordinate bond with triphosphate in the apatite structure of the bone [28a]. In the context of toxic effects and the medicinal applications, vanadate–phosphate antagonism is of particular interest. The anions occurring at physiological conditions are HPO_4^{2-} and H_2VO_4^- . These anions, although comparable in size, are distinct in their ability to increase their coordination sphere when interacting with the substrates in the physiological broth [28b]. While the vanadium center in vanadate readily increases its coordination environment by establishing a covalent bond with a donor atom (O, N, or S) of the substrate, usually resulting in the formation of a *stable* penta-coordinated (distorted) trigonal bipyramid, such a structural arrangement is achieved just intermittently in the case of phosphate.

The medicinal applications of vanadium are rooted either through the *in vivo* formation of vanadate applied in the form of a coordination compound or in the direct interaction between the coordination center and/or the coordination sphere of the vanadium species applied in a medicinal context. Here, “direct interaction” refers to any of the following: a physiological interference of the original, a physiologically altered coordination compound (as in the case of diabetes, cancer, and cardiac dysrhythmia), or toxicity against the parasites, bacteria, and viruses. So far, not even a single vanadium compound of potential medicinal use has been accredited by the pharmaceutical industry. The only compound to reach the clinical trial phase I and II was the anti-diabetic maltolato-vanadium complex $\text{VO}(\text{mal})_2$ [29], although it had to be abandoned owing to the associated renal problems with several of the probands. The following subsections would be dealing with the diseases originating from viruses, bacteria, and fungi, as well as with health problems caused by parasites (protozoa, amoebae, and flagellates).

Table 1 provides an overview of the vanadium compounds that have been successfully applied (*in vitro* and/or *in vivo* with test animals) in the treatment of selected diseases caused by bacteria, viruses, and parasites. A recent overview concerning the same has been reported previously as well [30].

Table 1 Selected vanadium compounds that have been applied in the treatment of diseases caused by viruses, bacteria, and protozoa.

Disease	Responsible Organism	Symptoms ^{a)} (selection)	Compound(s) in Figure 4	Ref.
Tuberculosis	<i>Mycobacterium tuberculosis</i>	Bloody sputum, chronic cough	1, 2	[31], [32]
Pneumonia (of bacterial origin)	<i>Pseudomonas aeruginosa</i> um)	Cough with phlegm, difficult breathing, nausea	3	[33]
Diarrheal diseases	<i>Giardia intestinalis</i> (a protozoa)	Diarrhea	Nicotinamidium decavanadate	[34]
AIDS/HIV	Human immune deficiency virus	Failure of the immune system	4	[35]
Leishmaniasis	<i>Leishmania sp.</i> (a flagellate) ^{b)}	Skin ulcers, anaemia, damage of spleen and liver	5	[36]
Sleeping sickness ^{c)} ; Chagas disease ^{d)}	<i>Trypanosoma cruzi</i> ; <i>T. brucei</i> (flagellates)	Pains, itching; sensory disturbance	6	[37], [38]

^{a)} Other than fever. ^{b)} Spread by sand flies. ^{c)} Also known as trypanosomiasis; spread by the Tsetse Fly. ^{d)} Spread by Kissing Bugs.

Figure 4 Vanadium complexes that have been shown to be active in the treatment of infectious diseases (cf. Table 1). Ligands: 1, a thiosemicarbazone derivative; 2, salicylglycine + 8-hydroxyquinoline; 3, cefuroxime; 4, cyclam; 5, salophen; 6, phendione.

Viral replication may also be *increased* in the presence of vanadium complexes. The anionic compound $[\text{VO}_2(\text{dipic-Cl})]^-$ (dipic = dipicolinate), in certain cases such as when applied in combination with the oncolytic (i.e., cancer killing) Rhabdovirus VSVD51, increases viral infection and viability, thereby invigorating the immune system. The initiating compound is probably an intermittently formed vanadate species, which is generated through the hydrolysis of the dipic complex [39]; vanadate on its own, however, is ineffective. In order to have a further general view regarding the nature of the active species, commonly vanadate and/or the ligand and its secondary product(s) that are generated at physiological conditions, refer to the literature [40].

Vanadium compounds have also been successfully evaluated for the treatment of cancer, as reported in a previously published review [41]. Certain recent examples of such compounds have been presented in Figure 5. Complex 1, containing the flavonoid chrysin, has been reported to suppress the growth of osteosarcomas without any side-effects, in xenograft mice bearing a human osteosarcoma cell line [42a], apparently because the product formed as a result of the hydrolytic decomposition and oxidation in the physiological broth, i.e., “ $\text{VO}(\text{OH})_3$ ”, is incorporated into the bone structure (see also, above). In a similar manner, bone cancer was reported to have been treated successfully with Metvan ($[\text{VO}(\text{Me}_2\text{phen})_2\text{SO}_4]$, where phen = phenanthroline and Me = CH_3) [42b]. Compound 2 has been reported to exhibit anti-proliferative activity against various cancer cell lines. It binds strongly to the DNA (presumably after the loss of at least one of the ligands), generates reactive oxygen species (peroxide and superoxide), and causes damage to the mitochondrial membrane [43]. The target for Compound 3 is the breast cancer cells of MCF-7 (“Michigan cancer foundation”) and A549 (pulmonary alveolus). Compound 3 induces apoptosis and inhibits the cell cycles, probably through the generation of intracellular reactive oxygen species, particularly superoxide O_2^- [44].

Figure 5 Selected vanadium complexes for the potential treatment of cancer. 1: A chrysin complex for the treatment of osteosarcomas [42a]; 2: a catecholate complex carrying a bis(indolyl) substituent at the catechol moiety, active against various cancer cell lines [43]; 3: a peroxido complex containing an ethylenediamine-diacetate ligand [44].

An additional prominent field in the context of the role of vanadium in health issues is the one concerning diabetes mellitus. As stated earlier, the most significant undertakings in this field concern the clinical tests conducted more than a decade ago, pioneered by Orvig and Thomson [29]. An early report (1899) concerning the usage of vanadate in this regard [45], and the discovery that (i) vanadate as an effective competitor of phosphate in regard to transport, via ATPase, across the cell walls [46a] and that (ii) vanadate inhibits the ribonucleases [46b], served as the crucial basis for the development of vanadium-based compounds for the treatment of

diabetes (through a decrease in the blood glucose levels). Since then, various vanadium compounds have been introduced (for a recent review, see [47]), a selection of which has been presented in Figure 6. Most of the insulin-mimetic tests have been conducted with streptozotocin (STZ) or alloxan-induced test animals (commonly, rats or mice), and along with a reduction in the blood glucose levels both in the case of diabetes type I and diabetes type II, a lowering of the lipid levels has also been observed. STZ, a nitrosoureido glycopyranose, is toxic for the *b* cells (responsible for insulin production) located in the Langerhans islets in the pancreas.

A vanadium coordination compound, once applied intravenously, [partially] degrades to form vanadate H_2VO_4^- , which then enters the cell and binds to the cysteinate residue of the protein-tyrosine phosphatase (PTP), thereby inhibiting PTP [48]. This inhibition, in turn, prevents the *dephosphorylation* of a tyrosine-phosphate residue linked to the intracellular site of the insulin receptor. As a consequence, the receptor is activated and the signaling pathway for glucose uptake is either maintained or restored.

Figure 6 Some vanadium coordination compounds that have been shown to counteract diabetes mellitus. For compounds 1 to 5, cf. refs. [49] (1), [50] (2), [51] (3), [29b] (4), and [52] (5).

3. Engineering Aspects

The application of vanadium for industrial or engineering purposes encompasses three main areas: (1) the vanadium compounds involved in catalysis, (2) vanadium-based batteries, and (3) vanadium in steel production (for example, chromium–vanadium steel, in which the vanadium content is approximately 0.1%, which increases the forgeability of the steel). In regard to the medicinal applications of vanadium (such as the implants with particularly high biocompatibility), the vanadium alloy Ti–6Al–4V having a vanadium content of approximately 4% is of particular interest [53].

A review concerning the catalytic applications of vanadium was published recently [54]. Vanadium oxides with the general formula of VO_x , where *x* ranges from 2 (V^{IV} , VO_2) to 2.5 (V^{V} ,

V₂O₅), are employed either directly or along with supports such as clay [55]. A well-documented and industrially applied practical example of this is the generation of sulfuric acid from sulfur dioxide. Also noteworthy is the oxidative conversion of methanol into formaldehyde in the presence of FeVO₄ as the catalyst [56a] [eq. (11)]. In the context of the ability of vanadium oxides acting as oxidation catalysts [56b], the antifouling (i.e., destruction [disinfection] through oxidative halogenation) properties of V₂O₅ nanowires deserve mention [57]. Low-valent vanadium oxides have been demonstrated to catalyze the hydrogenation of carbon monoxide [58a] and the reduction of nitrogen oxide [58b] [eq. (12) and (13), respectively]. In addition, the vanadium-catalyzed reduction of NO is of interest in the context of detoxification of the exhaust gases from automobiles and trucks. Another example of the [potential] importance of vanadium for the biologically relevant [drug] molecules is the enantio-selective oxidation of [aromatic] sulfides/thioethers to form sulfoxides [59]. Silica-supported vanadium oxides, V_xO₇–silica, have been employed as catalysts in the oxidative detoxification of the remains of organic sulfur compounds, such as dibenzothiophene, present in the crude oil and diesel fuels, through conversion into sulfones, which may be removed with acetonitrile. The oxidant employed in this reaction is *t*-BuOOH [60].

Possibly the most prominent example of the employment of vanadium in catalytically conducted processes is its usage in the form of vanadium pentoxide for the production of sulfuric acid [61], the reaction for which is presented in eq. (14).

Another application-oriented, and therefore, industrial aspect of the employment of vanadium is its usage in the energy storage/redox-flow batteries [61–63] and in solar cells [64]. Figure 7 presents the examples of (a) a flow battery based on a cathode consisting of lithium–oxidovanadium phosphate (LiVO(PO₄)) and a VO₂ anode, (b) a vanadium-only battery, and (c) a dye-sensitized solar cell with a vanadium coordination compound as the electrolyte and the redox mediator ($\text{VO}^{\text{IV}}\text{L} \rightleftharpoons \text{VO}^{\text{V}}\text{L} + \text{e}^-$). Principally, the other oxidation states of vanadium (i.e., V^{III} and V^{II}) could also play a role in vanadium-based batteries, thereby providing high energy densities, and may also be utilized in the storage batteries where the electron flow between V^{2+/3+} and/or VO^{2+/3+} is deployed.

Figure 7 (a) and (b): Schematic views of a lithium-vanadium (left) [61] and a vanadium-only battery (centre); red = catholyte, blue = anolyte. (c): A dye-sensitized solar cell based on $V^{IV/V}OL$ [64]; L is the diamidodiphenolato ligand $TFSI = [F_3C-SO_2-N-SO_2-CF_3]^-$ coordinated to Li^+ .

Author Contributions

Dr. Dieter Rehder did all the work.

Competing Interests

The author has declared that no competing interests exist.

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