

Preface to Volume 13

Interrelations Between Essential Metal Ions and Human Diseases

Most of the 13 metals and 3 metalloids and their ions, which are covered in this volume, have been proven to be essential for humans. Indeed, it is an old wisdom that metal ions are indispensable for life. The main group metals, i.e., sodium, potassium, magnesium, and calcium, belong to the so-called bulk elements, and they occur in humans (70 kg) between about 20 g (Mg) and 1000 g (Ca) [H. Sigel, A. Sigel, H. G. Seiler, in *Handbook on Metals in Clinical and Analytical Chemistry*, Eds H. G. Seiler, A. Sigel, H. Sigel, Dekker, New York, 1994, pp. 1–12]. The remaining 9 metals are transition elements, including zinc, and they all occur at trace levels, though iron and zinc dominate in humans with about 4 and 2.5 g, respectively. All the other metals, as well as the three metalloids (silicon, arsenic, selenium), occur only at ultra-trace levels, e.g., manganese and cobalt with about 12 and 1 mg, respectively. They comprise the essential elements manganese, cobalt, copper, molybdenum, and selenium; chromium, vanadium, nickel, silicon, and arsenic have been *proposed* as being essential in the second half of the last century. However, it turned out that their essentiality is difficult to establish because, if at all, they are certainly needed only in ultra-trace amounts, and because of their prevalence in the environment from natural and anthropomorphic sources, it has been difficult to prove whether or not there is a requirement for them, though the likelihood for vanadium and silicon as being essential appears to be high.

The introductory Chapter 1 presents an overview of the topic, metal ions and infectious diseases, as seen from the clinic. The dilemma is that next to the bulk elements, also the trace elements are required by both, humans and bacterial pathogens. Since these metal ions are both necessary for life, but toxic in excess, metal homeostasis is tightly controlled by both bacteria and humans. Thus, pathogens utilize a variety of strategies to sense, acquire, store, and export metal ions in/from the vertebrate host.

The bulk elements **sodium**, **potassium**, **magnesium**, and **calcium** are dealt with in Chapters 2 to 4. All these elements are essential for human health and the chapters summarize their basic physiological actions. For example, a proper cellular Mg^{2+} homeostasis is in all instances compulsory; deficiency or overload gives rise to diseases, and these are described. Interestingly, evolution has thoroughly exploited the chemical properties of Ca^{2+} , i.e., its fast ligand-exchange rate and its reversible binding to sites with an irregular geometry, and selected it as a carrier of cellular signals.

The next chapters focus on the roles of the transition elements beginning in Chapter 5 with **vanadium**: Since vanadate can be considered a close blueprint of phosphate with respect to its built-up, it likely takes over a regulatory function in metabolic processes depending on phosphate; e.g., phosphatases can be inhibited and kinases activated, but its essentiality for humans has not been proven. Yet in 1982/83 the discovery of vanadate-dependent bromoperoxidase in the marine macroalga *Ascophyllum nodosum* established that some forms of life need it. At common concentrations it is non-toxic for humans and this opens up a wide playground for pharmacological applications. Similarly, is **chromium** essential, pharmacologically relevant or toxic? At present chromium cannot be considered as an essential element because (i) nutritional data demonstrating chromium deficiency and improvement in symptoms from chromium supplementation are lacking, and (ii) no biomolecules have convincingly been demonstrated to bind chromium and to have an essential function in the body.

Manganese, covered in Chapter 7, is important for human health. Though it is absolutely necessary for development, metabolism, and the antioxidant system, excessive exposure or intake may lead to manganism, a neurodegenerative disorder that causes dopaminergic neuronal death and parkinson-like symptoms. The effects of **iron** deficiency or overload are covered in great detail in Chapter 8. Iron is a redox-active metal which is abundant in the Earth's crust. It has played a key role in the evolution of living systems and as such it is an essential element in a wide range of biological phenomena, being critical for the function of an enormous array of enzymes, energy transduction mechanisms, and oxygen carriers. Since the redox nature of iron renders the metal toxic in excess, all biological organisms carefully control iron levels. For example, low body iron levels are related to anemia, whereas systemic iron overload results from, e.g., hyperabsorption, and can be treated by iron-chelation therapy. Furthermore, iron chelators have been widely investigated for the treatment of cancer, tuberculosis, and malaria.

Cobalt and its role in human health and disease is primarily defined by the functioning of cobalamin (vitamin B_{12}); it is dealt with in Chapter 9. Cobalamin acts in humans as a cofactor for methylmalonyl-coenzyme A mutase and methionine synthase, both enzymes being important for health. Especially the dysfunction of methionine synthase causes disruption of many cellular processes and leads to disease. In contrast, so far no **nickel**-containing enzyme or cofactor is known in higher animals. However, nickel has been included in the group of "possibly essential elements" for animals and humans already in the 1970s and its importance for plants, bacteria, archaea, and unicellular eukaryotes is well documented. In this context

Helicobacter pylori, a gram-negative bacterium, may be mentioned. This pathogen colonizes the human gut, giving rise to acute and chronic gastric pathologies, including peptic ulcer, and possibly also to gastric carcinomas and lymphomas. The toxic effects of nickel can produce serious respiratory, cardiovascular, and kidney diseases; they also alter the immune response giving rise to dermatitis, etc.

Copper, the metal of Chapter 11, represents in humans the 3rd most abundant transition metal; it is essential but it can also harm cells due to its potential to catalyze the generation of toxic reactive oxygen species. Therefore, the transport of copper and the cellular copper content are tightly regulated. Nutritional copper deficiency gives rise to anemia, to neuropathies, to impaired immune responses, etc. Genetic copper deficiency leads to Menkes disease and distal hereditary peripheral neuropathy. Genetic copper overload causes Wilson's disease and infantile cirrhosis. Ingestion of high doses of copper gives rise to nausea, vomiting, headache, diarrhea, hemolytic anemia, gastrointestinal hemorrhage, liver as well as kidney failure and finally death may occur. Furthermore, alterations of copper homeostasis have been associated with neurodegenerative diseases such as prion diseases, Alzheimer's disease, Parkinson's disease or Huntington's disease, etc., but the exact role of copper in these important neurological disorders remains unclear.

Zinc is dealt with in Chapter 12: The total amount of zinc in a human (70 kg) is 2 to 3 g, i.e., there is nearly as much zinc as there is iron. Also the cellular Zn^{2+} concentrations are rather high, that is, nearly as high as those of major metabolites like ATP. The vast knowledge of the physiological functions of zinc in at least 3000 proteins and the recent recognition of fundamental regulatory functions of Zn^{2+} ions released from cells or within cells links this nutritionally essential metal ion to numerous human diseases. It is not only the right amount of zinc in the diet that maintains health, at least as important is the proper functioning of the dozens of proteins that control cellular zinc homeostasis and regulate its intracellular traffic. Zinc and its role in organ pathophysiology as well as in genetic, metabolic, chronic, and infectious diseases are covered.

The essential trace element **molybdenum**, treated in Chapter 13, plays a crucial role in human health and disease. Remarkably, it is the only metal of the 2nd transition row (4d) of the periodic table with a biological role for humans. Four mammalian Mo-dependent enzymes are known, all of them harboring a pterin-based molybdenum cofactor (Moco) in their active site. In the focus are the individual pathways and the clinical and cellular consequences of their dysfunction. In all these enzymes molybdenum catalyzes oxygen transfer reactions from or to substrates using water as oxygen donor or acceptor, whereby it shuttles between the oxidation states +IV and +VI. Especially important are the functions and deficiencies of xanthine dehydrogenase and sulfite oxidase. The underlying molecular basis of Moco deficiency, possible treatment options, and links to other diseases including neuropsychiatric disorders are discussed.

The metalloid **silicon** is the second most abundant element in the Earth's crust behind oxygen and has many industrial applications including its use as an additive in the feed and beverage industry. Chapter 14 discusses the possible biological potential of the metalloid, which is bioavailable as orthosilicic acid, and its potential

beneficial effects on human health. Asbestos, its fibrous crystalline form, is a health hazard promoting asbestosis and leading to significant impairment of lung function and an increased cancer risk. Specific biochemical or physiological functions of silicon, if any, are largely unknown, although generally thought to exist.

Can the toxic metalloid **arsenic** sustain life? Clearly, the biochemical and physiological properties of arsenic are invariably linked with the toxicity of this element. The aim of Chapter 15 is (i) to summarize the evidence for beneficial or sustaining roles of arsenic in living organisms, including its substitution for phosphorus, and (ii) to summarize its Janus-faced role in both causing and treating human disease. Arsenic oxide, deadly at high doses, is also an approved and effective drug for the treatment of acute promyelocytic leukemia. The well known toxicity of this element and its ability to cause diseases, including cancer of the skin, lung, bladder, liver, and kidney, make it a health hazard. So far it has not been recognized as being essential for humans because it has been difficult to establish whether or not there is a requirement for arsenic at ultra-trace levels considering its prevalence in the environment from natural and anthropomorphic sources. In contrast, **selenium** is established as an essential micronutrient for mammals, but it is also proven to be toxic in excess, leading to selenosis. Selenium exerts its biological functions through selenoproteins which contain selenocysteine. In fact, 25 selenoproteins are encoded in the human genome; most of their known functions are involved in redox systems and signaling pathways.

Overall, this volume offers a wealth of information about human health and the interrelations between essential, or possibly essential, metals or metalloids.

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