

Book Review

P. L. Carver (Guest Editor): *Essential Metals in Medicine*. Volume 19 of the *Metal Ions in Life Sciences* series, **A. Sigel, E. Freisinger, R. K. O. Sigel (Series Editors)**. Berlin/Boston: De Gruyter (2019). ISBN 978-3-11-052691-2, 412 pages, 220 Euro

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In the Preface to the book, the Guest Editor points out that many metals play a significant role in medicine, including not only those that are now recognized as essential (indispensable for human life) and for which a maintenance of metal ion homeostasis is required, but also a large group of elements that are used in diagnosis and therapy of diseases. In an introductory chapter, also by the Guest Editor, the contents is subdivided into aspects of (a) metal-related diseases, (b) metals as medicines, and (c) metal ion toxicity, indicating the broad scope of the subject.

An international group of specialized authors has been recruited for a set of chapters of the book that are dedicated to the most prominent essential metals in the transition metal series (mainly the 3d block). No main group metals (s and p-block), lanthanides or actinides, and metalloids have been included. No less than five chapters are dedicated to the role of iron covering the following topics where the titles speak for themselves. “*Iron chelation for iron overload in thalassemia*” by G. Crisponi, V. M. Nurchi and J. I. Lachowicz; “*Ironing out the brain*” by R. J. Ward and R. R. Crichton; “*Infections associated with iron administration*” by M. Nairz and G. Weiss; “*Iron oxide nanoparticle formulations for supplementation*” by A. B. Pai; “*Building a Trojan Horse: Siderophore drug conjugates for the treatment of infectious diseases*” by E. Giumienna-Kontecka and P. L. Carver. This series is followed by a chapter on the role of vanadium with the title “*Developing vanadium as an antidiabetic or anticancer drug: A clinical and historical perspective*” by D. C. Crans, L. Henry, G. Cardiff, and B. I. Posner. The role of chromium in medicine is reconsidered in a chapter presented by W. Maret with the title “*Chromium supplementation in human health, metabolic syndrom and diabetes*.” This is a particularly valuable contribution since it summarizes the limited present knowledge on the biological activity and often questioned essentiality of this metal, which is highly

toxic in its highest oxidation state [Cr(VI) in chromates] but is now widely used in complexes of its also common oxidation state Cr(III), e.g. as a trace element additive to vitamin pills for humans and in animal nutrition. By contrast, manganese is again an essential element as summarized in the chapter by K. M. Erikson and M. Aschner: “*Manganese: Its role in disease and health*”, which shows the abundance of this element in many domains of the human body and its role as a coenzyme for man biological processes requiring a regular supply. Though cobalt is also known to be essential, its role in clinical applications is limited and the element has been relatively ignored by the pharmaceutical industry. Only few families of complexes have been thoroughly studied regarding the role of the coordinating ligands employed in the formulations of manganese supplementations. For the chapter with the title “*Cobalt-Schiff-Base complexes: Preclinical research and potential therapeutic uses*” by E. A. Bajema, K. F. Roberts and T. J. Meade, a specific class of complexes has been chosen, for which the results of preclinical studies suggest antimicrobial, antiviral, anticancer, and amyloid- β inhibitor activities.

Copper has been well known to be an essential metal for several decades and its bioinorganic chemistry has been studied for many years to unravel its large variety of basic biological functions. One of the main research areas is currently the significance of copper homeostasis in Alzheimer’s disease, since post-mortem analyses of amyloid plaques have indicated an excessive accumulation of copper (less so for Zn and Fe) in the human brain, due to a “mis-metabolism of metal ions”. A large number of blood-brain-barrier permeable hydroxyquinoline-derived chelators have been applied as copper scavengers, and some of these were found to be copper-specific (over Zn and Fe). Surprisingly, this report on recent promising investigations has been included as part of a chapter with the title “*Small molecules: The past and future in drug innovation*” by A. Robert, F. Benoit-Vical, Y. Liu, and B. Meunier, which first addresses very general aspects of chemical drug development (which is good and informative reading) and more specifically the family of trioxaquinones as antimalarial hybrid molecules, but the role of metal ions in this context is not really obvious.

One of the further chapters (by J. Lopez, D. Ramchandany and L. Vahdat) is dedicated to “*Copper depletion as a therapeutic strategy in cancer*.” Unfortunately, despite promising preclinical data, the clinical experiences

(phase II) with various chelating Cu-selective agents have not yet supported this approach regarding inhibition of the evolution of cancer and metastatic spread. A large selection of organic and inorganic complexants were employed, such as prodrugs which are metabolized to give thiocarbamates as chelators for Cu(II), but no satisfactory overall performance has as yet been reached. The well-known therapeutic effect of tetrathiomolybdates may also be partly due to its assistance in copper depletion.

These chapters dedicated to a single element (Fe, V, Cr, Co, Cu) are complemented by articles orientated at the role of metals in specific therapeutic solutions for certain diseases, such as the chapter by D. Gambino and L. Otero on “*Metal compounds in the development of antiparasitic agents. Rational design from basic chemistry to the clinic.*” The focus here is on metal-based antiparasitic compounds and the metallomics in parasites responsible for malaria etc. The metals so far chosen for this work are those that have already proved useful in cancer therapy including therefore platinum group metal (Pt, Pd, Ru, Rh, Os, Ir) and oxovanadyl(II) [VO]²⁺ complexes. Ruthenium appears to be one of the more promising elements, for which a large variety of carriers (ligands) have been employed to accommodate both Ru(II) cations and organoruthenium(II) units (π -arene and cyclopentadienyl complexes) as coordination centers. Although the metallomics of some of these compounds has been studied in detail, none of the examples has entered clinical trials, except for Ferroquine which is a ferrocenyl derivative of the established antimalarial drug chloroquine. The title of the chapter therefore should be taken as an optimistic promise.

“*Chemical and clinical aspects of metal-containing antidotes for poisoning by cyanide*” (by S. G. Suman and J. M. Gretarsdottir), is another specific topic presented in a final chapter of the book. The metal-based antidotes are designed to intercept the cyanide anion by complexation

before it can reach its target (lethal non-competitive inhibition of cytochrome c oxidase). Next to metal-free antidotes like nitrites and thiosulfate (which are slow and lead to serious side-effects), the dicobalt(II) ethylenediaminetetraacetate tetrahydrate $\text{Co}_2(\text{EDTA})(\text{H}_2\text{O})_4$ and hydroxocobalamine (an analogue of vitamin B₁₂) are quick and efficient cyanide scavengers upon intravenous application. Aqueous solutions of thiomolybdate and thiosulfate serve as sulfur sources to convert cyanide to thiocyanide (and sulfite) and appear to have also a high benefit-to-risk ratio. In this context it should be kept in mind that (hydrogen)cyanide (like NO) is an endogenous molecule with functions not yet fully disclosed.

As described above, the book is a rather heterogeneous collection of reviews and cannot claim to be a comprehensive coverage of the subject announced in the title, as many essential metals are missing. Nevertheless, each review is a valuable account of the current status of its subject. Most chapters are well illustrated with multi-color Schemes and Figures. Useful glossaries that help the reader in deciphering the plethora of abbreviations are provided, and in all cases there is a large library of references that give access a wealth of literature. There are exceptions, like chapters 6 and 9, where the authors offer very little assistance to identify the chemical composition of the formulations and stick to trademarks, short-cut nomenclature and acronyms, or seeking refuge at Paracelsus (“it’s the dosage...”) or in statements like “absence of evidence is not evidence of absence” (for chromium) and: “The biological activity of essential compounds is often not optimal” (?). This book will find a divided readership split into two major groups with a scientific background in bioinorganic chemistry on the one hand, and pharmacology, toxicology and (pre)clinical medicine on the other. For both one or the other of the chapters will be a treasure mine of knowledge to dig deeper.