9: Metals in Medicine

Metal ions are required for many critical functions in humans. Scarcity of some metal ions can lead to disease. Well-known examples include pernicious anemia resulting from iron deficiency, growth retardation arising from insufficient dietary zinc, and heart disease in infants owing to copper deficiency. The ability to recognize, to understand at the molecular level, and to treat diseases caused by inadequate metal-ion function constitutes an important aspect of medicinal bioinorganic chemistry.

Metal ions can also induce toxicity in humans, classic examples being heavy-metal poisons such as mercury and lead. Even essential metal ions can be toxic when present in excess; iron is a common household poison in the United States as a result of accidental ingestion, usually by children, of the dietary supplement ferrous sulfate. Understanding the biochemistry and molecular biology of natural detoxification mechanisms, and designing and applying ion-specific chelating agents to treat metal overloads, are two components of a second major aspect of the new science that is evolving at the interface of bioinorganic chemistry and medicine.

Less well known than the fact that metal ions are required in biology is their role as pharmaceuticals. Two major drugs based on metals that have no known natural biological function, Pt (cisplatin) and Au (auranofin), are widely used for the treatment of genitourinary and head and neck tumors and of rheumatoid arthritis, respectively. In addition, compounds of radioactive metal ions such as ^{99m}Tc and complexes of paramagnetic metals such as Gd(III) are now in widespread use as imaging agents for the diagnosis of disease. Many patients admitted overnight to a hospital in the U.S. will receive an injection of a ^{99m}Tc compound for radiodiagnostic purposes. Yet, despite the obvious success of metal complexes as diagnostic and chemotherapeutic agents, few pharmaceutical or chemical companies have serious in-house research programs that address these important bioinorganic aspects of medicine.

cis-diamminedichloroplatinum(II) (cisplatin, or *cis*-DDP)

2,3,4,5-tetra-O-acetyl-1-1-β-D-thioglucose(triethylphosphine)gold(I) (auranofin)

This chapter introduces three broad aspects of metals in medicine: nutritional requirements and diseases related thereto; the toxic effects of metals; and the use of metals for diagnosis and chemotherapy. Each area is discussed in survey form, with attention drawn to those problems for which substantial chemical information exists. Since there is only a primitive understanding at the molecular level of the underlying biochemical mechanisms for most of the topics, this field is an important frontier area of bioinorganic chemistry. The major focus of this chapter is on the platinum anticancer drug cisplatin, which is presented as a case study exemplifying the scope of the problem, the array of methodologies employed, and the progress that can be made in understanding the molecular basis of a single, if spectacular, metal complex used in medicine today.

II. Metal Deficiency and Disease[1]

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C. Causes and Consequences of Zinc Deficiency[4-6]

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E. Design of New Inorganic Anticancer Drugs
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3. Second- and Third-generation Platinum Anticancer Drugs
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VI. Restrospective

The topics discussed in this chapter are helping to expand bioinorganic chemistry from a subject that arose chiefly from spectroscopic analysis of metal centers in proteins, because they were uniquely convenient functional groups, to a discipline where fundamental knowledge about metal functions and the application of metals as diagnostic and chemotherapeutic agents are making important contributions to medicine. As the case study of cisplatin is intended to demonstrate, progress in understanding how metals function in chemotherapy can be made only by the combined efforts of many disciplines, including synthetic and physical inorganic and organic chemistry, molecular and cell biology, immunology, pharmacology, toxicology, and clinical medicine. Although we have not yet reached the day where chemotherapeutic agents can be rationally designed from knowledge of a molecular mechanism, such a concept does not seem that farfetched. If nothing else, knowledge of fundamental bioinorganic processes related to metal-macromolecule interactions will continue to grow enormously through efforts to achieve this ultimate goal.

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Contributors and Attributions

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Thumbnail: Cisplatin, $PtCl_2(NH_3)_2$ A platinum atom with four ligands. Image used with permission (Public Domain; Benjah-bmm27).