Preface

During the later part of the 20th century, pharmaceutical compounds containing metals began to play an increasingly important rôle in medicine. In particular, the discovery of platinum anticancer drugs and the appearance of organ specific diagnostic-imaging agents containing technetium were prominent developments that have stimulated further interest in so-called 'metallopharmaceuticals'. Today, the metallopharmaceuticals industry has a global market measured in billions of pounds and has well-established applications in both diagnostic and therapeutic medicine.

The aim of this book is to review the diagnostic and therapeutic applications of selected metallic elements and consider the chemistry underlying the formulation of metallopharmaceuticals. In order to do this it is necessary to assume some basic understanding of the chemical behaviour of metals and, in particular, their 'coordination chemistry'. A very brief introduction to coordination chemistry is also presented for the benefit of those unfamiliar with this aspect of chemistry. The level of presentation of this section is designed for a general but scientifically literate audience, some of whom may have only a rudimentary knowledge of chemistry. It is hoped the text will be helpful to pharmacists as well as to clinicians and medical researchers using metal containing drugs in a clinical environment. However, it is also hoped that the book might also serve as an introductory text of interest to chemistry students wishing to learn about an aspect of their subject within an applied context, rather than just as a subject in its own right.

The discussion of medicinal applications focuses on the coordination chemistry of what are known as the 'transitional elements', particularly vanadium, manganese, technetium, ruthenium rhodium, platinum, gold and gadolinium. Compounds containing metals of this type are the most amenable to manipulation through chemical design so that coordination chemistry plays a significant rôle in the development of metallopharmaceuticals involving these metals. The so-called 'main group' metals (*e.g.* gallium, indium, tin, lead, bismuth) are, for the most part, not included though some of their applications are mentioned. These elements offer less scope for the application of coordination chemistry in product development as their compounds typically break down quickly *in vivo* transferring the metal to biological binding agents and a fate largely beyond the chemist's direct control.

The first introductory chapter aims to set the scene with a brief historical review and a consideration of some general aspects of the use of chemical substances in medicine. The second chapter provides a concise description of

the basic chemical principles required for understanding the particular properties of transitional metal elements and which are exploited in medical applications. The chapter assumes relatively little chemical knowledge and those with prior University level chemical training may wish to skip most or all of this material. However, it is hoped that it will help those without a strong inorganic chemistry background to appreciate the origins and nature of the particular properties of metals that are so useful in biology and in medical applications. It could serve as a concise introduction to coordination chemistry within the context of applications in medicine for students on some chemistry courses.

Subsequent chapters examine the utilisation of the metallic elements in various medical contexts divided into chapters on Diagnosis and Therapy. In addition to describing what is happening in a clinical environment, these chapters seek to consider past and current research into metallodrugs and the lessons this provides for the future. Particularly important and well-established applications include diagnostic imaging through the use of radioactive or paramagnetic compounds and the treatment of cancer with metallodrugs based primarily on platinum compounds. The final chapter considers the design of new metallopharmaceuticals and some examples of the relationship between structure and activity. Serendipity is still important in the development of metallopharmaceuticals but, as more information emerges about the mechanism of action of metallopharmaceuticals, rational design is playing an increasingly important part.

In addition to established applications in medicine, the chemistry of metal compounds offers new opportunities for the diagnosis or treatment of disease. This potential for the future development of metallopharmaceutical agents has been recognised by major US medical research funding agencies and, in 2000, a conference entitled 'Metals in Medicine – Targets, Diagnostics and Therapeutics' was held on the National Institutes of Health (NIH) campus at Bethesda, Maryland. The meeting identified applications of metal compounds in magnetic resonance imaging, radiology and radiation therapy as expanding areas of activity. Research into therapeutic applications of metal complexes was thought to be relatively under-developed. One area identified as particularly ripe for research growth was metal metabolism, including studies of the mechanisms of metal homeostasis and the roles of metals in the regulation of cell function and cell–cell interaction. Finally, a need was identified for a set of basic principles to guide the development of new metallopharmaceuticals. At a chemical level at least, coordination chemistry provides a basis for the rational design of metal complexes. This will need to be combined with medicinal experience and an expanding knowledge of bioinorganic chemistry if such a set of guiding principles is to be developed. It is hoped this text will help stimulate wider interest in the potential of metal containing pharmaceuticals, encourage readers to explore more advanced texts and contribute to realising the opportunities metallopharmaceuticals present.

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