CHAPTER 1

Introduction

1.1 Metals in Medicine – A Historical Perspective

The use of particular metals, or their compounds, in medicinal preparations can be traced back for thousands of years. Copper sulfate and alums were among the many substances used by the ancient Egyptians to prepare potions, possibly because they had a sterilising effect on the concoction produced. In Arabia and China gold preparations appear to have been used by physicians as long ago as 2500 BC and, more recently, mercury was used to treat syphilis during the European epidemic of the late 15th and early 16th centuries. Aqueous suspensions of gold flakes known as Goldschlager or Geldwasser have also been used in medicinal preparations, although there is no proven medical value in the ingestion of metallic gold. Koch's observation of the bactericidal action of gold cyanide in 1890 offered a more scientific basis for the use of gold in pharmacy. However, gold compounds were subsequently found to be ineffective in the treatment of pulmonary tuberculosis. A more successful application followed in the 1930s when gold drugs were used to treat rheumatoid arthritis. In this case double-blind studies showed them to be effective for many, though not all, patients. Earlier, in 1909, Erlich had introduced the arsenic compound Salvarsan for treating syphilis. This was followed by another arsenic compound, mapharsen, and in 1921 bismuth compounds were also introduced and used in combination with mapharsen to treat syphilis. These pharmaceuticals, particularly those involving arsenic, could have severe side effects and no doubt this contributed to a common perception that metals are generally toxic and not well suited to use in pharmaceuticals.

In the second half of the 20th century, two elements in particular played a large part in arousing much greater interest in the medicinal use of metal compounds; one of these was platinum and the other technetium. In Michigan State University in 1964, Barnett Rosenberg was investigating the effect of electric fields on the growth of bacteria and made a quite serendipitous discovery that some platinum compounds could inhibit cell division. This observation led on to the development of the platinum compound cisplatin, which was approved by the US Food and Drug Administration (FDA) in 1978 for use in the treatment of ovarian and testicular cancer. Cisplatin had been known for over 100 years previously but its medicinal potential remained unrecognised until Rosenberg's investigations. Since then other second generation platinum drugs have followed, including compounds suitable for oral administration. The discovery of cisplatin has also stimulated research into a variety of other metal compounds with tumorocidal properties and the potential to become clinically useful anticancer drugs.

Beyond these innovations in therapy, the man-made element technetium began to make an important contribution to diagnostic medicine during the later part of the 20th century. Technetium was first identified by C. Perrier and E. Segrè in 1937, being found in molybdenum targets after bombardment with deuterium nuclei in a cyclotron. All forms of technetium are radioactive and one form in particular has nuclear properties which make it particularly suitable for use in diagnostic medicine. This form emits γ-rays which, when originating from a source within the body, pass through living tissues and can be detected externally. This allows an image to be created of the distribution of the technetium γ-ray source within the body. Fortuitously, technetium also has a rich and versatile chemistry allowing it to be incorporated into many different kinds of compound. This allows the use of chemical compounds with affinities for different specific organs or tissue types to selectively transport technetium to specific locations in the body. In this way images of diseased or damaged regions can be obtained without the need for invasive surgical examinations. Other radioactive elements can also be used in non-invasive diagnostic imaging procedures but technetium has become pre-eminent in this application.

The use of radioactive elements as components of drugs suitable for use in therapeutic medicine offers a rather greater technical challenge than that posed by diagnostic imaging applications. However, recently the chemistry of metals has even begun to bear fruit in this difficult arena. It is over 100 years since Paul Erlich envisioned the development of a 'magic bullet', a dye carrying a toxic heavy metal which would target disease causing agents while leaving healthy tissue unharmed. He had developed the technique of staining tissue types with dyes (1877–1890), shown that a dye could kill trypanosomes infecting blood (1907) and prepared the arsenic compound Salvarsan to kill syphilis spirochetes (1909). The 'magic bullet' idea was visionary extension of these developments but the means to properly realise it did not exist at that time. Radioactivity was still a newly discovered phenomenon at the end of the 19th century, although its potential for use in therapeutic medicine was recognised around 1911. Radium preparations were used to treat various ailments including tumors, *e.g.* when inserted in vials for cervical cancer treatment at the Holt Radium Institute in Manchester. It was almost half a century later (1953) before Korngold and Pressman showed that antibodies labelled with radioactive iodine could be localised in tumors in rats. The use of radioactive emissions to kill tumors, rather than using a chemical toxin, offered the advantage that the pharmaceutical did not have to be internalised by the cell to exert its toxic effect. However, the necessary tumor specific antibodies were difficult to obtain in any quantity, restricting the clinical viability of the approach. It was further quarter of a century before Köhler and Milstein (1975) fused B-cells producing antigen specific antibody with myeloma cells to form hybrid cells expressing antibodies specific to a single target. Even then the development of immortalised monoclonal antibody cell lines did not address the problems of loading sufficient antibody onto the target tissue within an acceptable timescale, and with sufficiently rapid clearance from non-target tissue. Further developments in immunology, including the ability to manipulate fragment antibodies to obtain improved rates of uptake, were necessary for the 'nuclear magic bullet' approach to become viable. Unsurprisingly the first approvals for the clinical use of radiolabelled antibodies, or their fragments, were for diagnostic imaging purposes involving relatively low radiation doses to tissues. However, finally in 2002 Zevalin® (Ibritumomab) received FDA approval for treating types of B-cell non-Hodgkin's lymphoma. This compound contains a monoclonal antibody labelled with radioactive yttrium and heralds the clinical application of what is known as radioimmunotherapy using a radioactive metallic element. It seems that, for one type of disease at least, Erlich's 'magic bullet' had finally arrived.

Current medical practice has access to a variety of metal containing pharmaceuticals. In addition to the continued use of gold drugs to treat rheumatoid arthritis, lithium is now used to treat depression, platinum to treat certain types of cancer, bismuth to treat stomach ulcers, vanadium to treat some cases of diabetes, iron to treat anaemia, iron compounds to control blood pressure, cobalt in vitamin B_{12} to treat pernicious anaemia and certain radioactive metals to alleviate the pain of bone cancer. Beyond these therapeutic uses metals have also become important in diagnostic medicine, particularly diagnostic imaging applications. In addition to technetium, radioactive forms of thallium, gallium and indium are also used routinely for diagnostic imaging purposes. Another important diagnostic imaging technique, developed more recently, uses what is known as magnetic resonance to produce images of internal organs by examining the water content of the tissues involved. Metals with magnetic properties, particularly gadolinium, are finding use as a means of enhancing some of the images produced by this method. In addition to these examples various other metal compounds, still in a preclinical research and development phase, show promise for clinical use in therapeutic and diagnostic applications.

1.2 Metals and Human Biochemistry

The special chemical properties of metals have long been exploited by biological systems and various metals are essential for human health. However, despite their biological importance, metals nonetheless constitute a rather small proportion of living organisms. The human body is mostly water and an elemental analysis of a typical individual (Figure 1) reveals that hydrogen, oxygen, carbon and nitrogen together account for just over 99% of the atoms present. Calcium and phosphorus make up much of the remainder being the