

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 tumoricidal 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. Fortunately, 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 B₁₂ 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

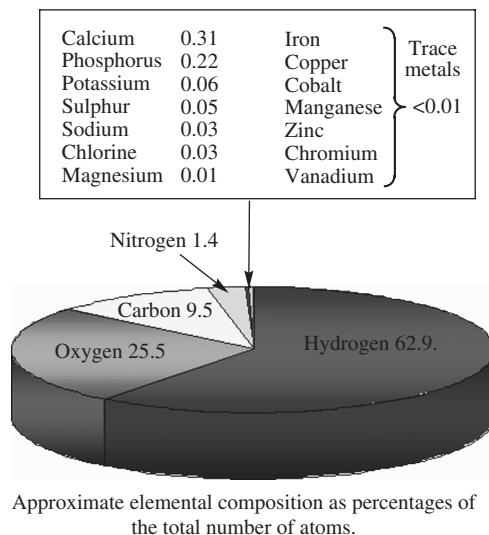


Figure 1 *The elemental composition of a typical human*

primary constituents of bone, together with oxygen and some hydrogen. A particular characteristic of metals in aqueous media, contributing to their biological importance, is that they carry a positive charge. This distinguishes them from most organic species which, even when uncharged, tend to be more negative in character often attracting positively charged species in solution.

The metals present in the human body can be crudely divided into two types, bulk metals and trace metals. These two types share some chemical similarities but the trace metals introduce additional chemical characteristics beyond those displayed by the bulk metals sodium, potassium, magnesium and calcium. The bulk metals are present in relatively larger amounts compared to the trace metals (Figure 1) and have various biological rôles. Apart from its structural function in bone calcium, together with sodium and potassium, is involved in signal transmission through nerves. Calcium is also important in triggering actions, *e.g.* in muscles, while magnesium is found in some phosphohydrolase and phosphotransferase enzymes. Sodium and calcium are important extra-cellular bulk metals while potassium and magnesium are the major cellular metals. As a group, the bulk metals share broadly similar chemical properties but differ in the sizes and charges of the forms in which they exist in aqueous media. These differences are reflected in the properties of the metals so that sodium, for example, can be discriminated from potassium, which is larger in size, and from calcium which has a higher charge. The bulk metals are chemically promiscuous and generally do not form long-term associations with any particular entity, such as a protein. Rather they will usually move between hosts being quite rapidly exchanged. Compared to the trace metals their chemical reactivity is more limited and they remain in the same positively charged state throughout their time in the body.

In contrast with bulk metals, the trace metals show more varied chemical reactivity and, with the exception of zinc, can change the magnitude of their positive charge under the right conditions. The trace metals are usually found incorporated in a biological host entity such as a protein with which they will have a comparatively long-term relationship. Taken together the trace metals iron, zinc, copper, nickel, chromium, manganese, molybdenum, cobalt and vanadium barely constitute 0.01% by mass of the human body (Table 1). Despite this they are essential elements and any deficiency can have serious adverse consequences for health. Trace metals are involved in a wide variety of biochemical processes including the transport and storage of dioxygen, the dissolution of carbon dioxide in blood, the extraction of energy from food-stuffs, the breakdown of proteins, the removal of harmful species such as superoxide and many other chemical transformations. They can also have structural functions such as controlling the folding of proteins. While sharing some characteristics with the bulk metals as a result of their positive charges, the trace metals also possess additional chemical capabilities enabling them to participate in a wider range of chemical processes. For example, zinc is present in the enzyme carbonic anhydrase to catalyse the conversion of gaseous

Table 1 *Trace metals in humans*

<i>Metal</i>	<i>Mass^a (mg)</i>	<i>Daily intake^b (mg day⁻¹)</i>	<i>Examples of some biological rôles</i>
Iron	4200	12 (male) 15 (female)	Dioxygen storage and transport, cytochromes enzymes – oxidases, reductases, hydrogenases
Zinc	2300	15	Structural control in proteins, enzymes involved in the chemical addition of water, alcohol dehydrogenase
Copper	72	2	Dioxygen storage and transport, electron transfer proteins
Nickel	15	–	Enzymes – urease, hydrogenases
Chromium	14	0.05–0.2	May be essential in mammalian glucose metabolism
Manganese	12	2	Enzymes – phosphatase, mitochondrial superoxide dismutase
Molybdenum	5	0.075–0.25	Enzymes – reductases, hydroxylases, nitrogenases
Cobalt	3	3(as vitamin B ₁₂)	Enzymes – as vitamin B ₁₂ coenzyme
Vanadium	0.11	–	Enzymes – nitrogenases, haloperoxidases

^a Approximate amount in 70 kg average adult human

^b Recommended adult daily intake requirement.

carbon dioxide to dissolved carbonic acid, while iron is present in hemoglobin and myoglobin to reversibly bind dioxygen. Iron is also found in systems, which add oxygen to organic substrates or transfer energy between biological components in metabolic energy transfer chains. Cobalt, in the form of vitamin B₁₂ coenzyme, is used to carry out chemical transformations associated with structural changes in carbon-compounds, and copper is present in some superoxide dismutase enzymes to convert superoxide to dioxygen and peroxide. In each case the metal brings its own distinctive properties to the task and these are exploited by the biochemical system in which the metal participates.

Living organisms require efficient systems for managing metals. The bulk metals tend to be quite freely mobile but selective means of transporting them across cell membranes are necessary to maintain a delicate electrolyte balance and for nerve cells to function efficiently. Trace metals may be transported and stored by proteins. In particular iron is transported by transferrin and stored in ferritin while copper can be transported and stored in ceruloplasmin. Metals are also stored in the proteins, *e.g.* cytochromes or enzymes, within which they express their biological function. Some clinical applications of the chemistry of metals are concerned with the management of metals in the body. Metal containing pharmaceutical formulations can be used to treat deficiencies of a particular metal, *e.g.* iron for anaemia or cobalt as vitamin B₁₂ for pernicious anaemia. Conversely the chemistry of metals may be exploited in treating problems arising from an excess of a metal in tissues, *e.g.* copper in Wilson disease or iron overload in patients receiving repeated blood transfusions. One approach to the treatment of iron overload exploits a natural microbial iron-sequestering agent. Since iron in the environment is generally found in a rather insoluble and inaccessible form, some micro-organisms excrete agents known as siderophores which strongly bind iron and facilitate its absorption into the micro-organism. Agents of this type can be adapted to bind iron in the body and promote its excretion providing an example of the application of bioinorganic chemical knowledge in a clinical application.

Beyond clinical applications which relate to the natural utilisation of trace metals, others exploit quite unnatural and non-physiological features of metal chemistry. As examples the toxicity of platinum complexes is managed and targeted in treatments involving anticancer drugs such as cisplatin while, in diagnostic medicine, the differing biodistributions of various technetium complexes can be exploited in imaging applications.

1.3 Metallopharmaceuticals

1.3.1 General Requirements

Metals may not seem an obvious choice as components of pharmaceuticals and it is a common perception that metal compounds are toxic, unstable and generally not well suited for pharmaceutical applications. Certainly in some historic uses of metal compounds, the treatment may have been as dangerous as

the disease and early beneficial applications exploited the microbiocidal properties of metals such as mercury, arsenic and bismuth. Pharmaceuticals are more usually expected to be organic carbon based compounds, *e.g.* aspirin or penicillin, these being relatively unreactive chemically, often uncharged and amenable to structural variation to optimise their medicinal properties. However, over the past 30 years the particular chemical reactivities of metals, their magnetic and nuclear properties and the structural variety of their compounds, have become important in a variety of medical applications. Although not exactly Erlich's 'magic bullet', the organ specific uptake of technetium radio-pharmaceuticals and the highly specific nature of the binding of cisplatin to DNA demonstrate the potential of this class of compound in specific medicinal applications.

In order to be useful in medicine, chemical compounds need to meet a variety of criteria. The most obvious requirement is that they must exhibit a medically beneficial effect with minimal toxic side effects. The relative benefit of a drug compared to its toxicity can be expressed in terms of its therapeutic index. This can be defined as the ratio of the dose required to kill 50% of test animals (LD_{50}) to the dose required to produce an effective therapeutic response in 50% of test animals (ED_{50}), *i.e.* Therapeutic Index = LD_{50}/ED_{50} . A high therapeutic index is clearly desirable, indicating that a relatively large dose is required to produce a toxic effect compared to that required to produce the therapeutic effect. However, because LD_{50} values cannot be obtained using human subjects, the therapeutic index can only have limited value for comparing different test compounds as it cannot be based on wholly human data.

As the dose of a compound with some medically beneficial effect is increased, and its *in vivo* concentration in the subject rises, it may be expected that the therapeutic benefit will increase. However, at some point this benefit will start to be negated by toxic effects until the dosage becomes so high as to be positively detrimental to the patient (Figure 2). Thus there will be a particular concentration range, associated with a particular dosage regime, which maintains the desired therapeutic effect. (A similar argument could be applied to foodstuffs. As an example carrots, a source of vitamin A, will produce a beneficial effect in normal dietary amounts. However, excessive consumption can lead to chronic or acute toxic effects, particularly in the liver where vitamin A accumulates. Those with liver damage, *e.g.* from over consumption of alcohol, are especially at risk). Typically the concentration of a drug will rise after administration then fall again as the compound is processed in the body and excreted. The timescale over which this process takes place, and any tendency for the drug to accumulate, will affect the dose regime necessary to maintain concentrations within the optimal therapeutic range.

A pharmaceutically useful compound must have an appropriate bioavailability and biodistribution, allowing it to pass through barriers such as cell membranes which lie between the outside world and the site of action (Figure 3). The rates of absorption, distribution, metabolism and elimination of a drug determine its pharmacokinetics. Parenteral drugs enter the bloodstream directly, typically by intravenous injection, but oral drugs must be absorbed

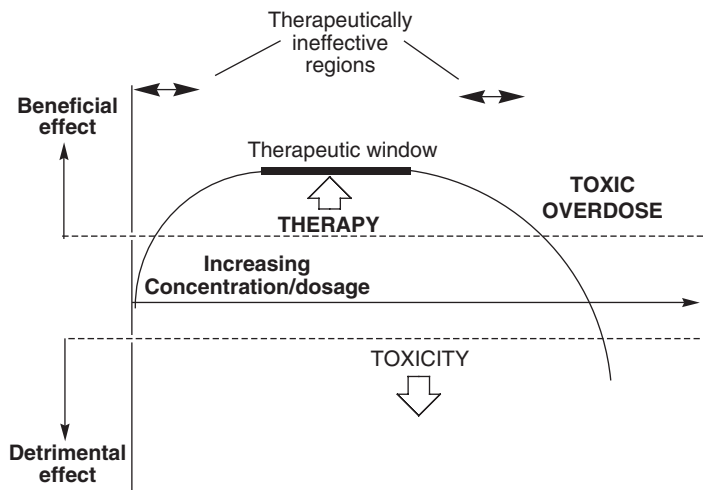


Figure 2 *The effect of increasing pharmaceutical dosage, or concentration in vivo, on benefit to the patient. Initially the beneficial effect increases with increasing concentration but at high doses, toxic effects predominate. Dosage regimes need to be adjusted to keep concentrations within the therapeutic window*

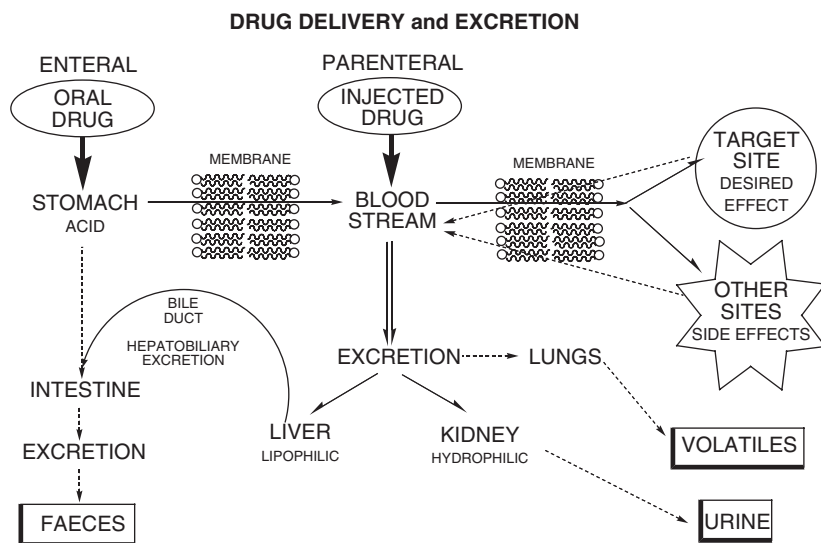


Figure 3 *A diagram summarising the intake, distribution and excretion routes of a pharmaceutical*

through the gut (Figure 3). Consequently, oral drugs must be able to withstand the acidic conditions in the stomach and pass through the gut wall to enter the bloodstream in a suitable form. This presents further challenges in the design of oral drugs compared to parenteral drugs. Since uncharged compounds are

generally absorbed through membranes more readily than charged compounds, neutral compounds, or those which become neutral under acidic conditions, tend to be more promising candidates for the formulation of oral drugs.

To be effective a drug will need to be sufficiently stable *in vivo* that it is not degraded by biological processes before having had chance to exert its effect. It will also need to reside in the body long enough to exert its effect but not so long as to irreversibly accumulate to the extent that unacceptable toxic effects start to arise. Sometimes drugs are administered in a form which is not the therapeutically active agent. Rather they are precursors which will be converted to the active form by metabolic processes *in vivo*. Such compounds are known as prodrugs and must show suitable pharmacokinetics before and after their conversion to the active form.

The primary means of distributing a drug around the body will be *via* the bloodstream. Here pharmaceutical compounds can encounter a variety of challenges. Firstly, the compound will need to retain sufficient solubility in the aqueous saline environment of the blood. Secondly, interactions with the proteins and other species present in blood need to be considered. This is particularly important for metal containing drugs since proteins may compete to bind the metal and so influence its biodistribution and properties. In some cases this may be a desirable effect, in others it may not. As an example, radioactive gallium is easily converted to an insoluble form in water and so is injected as its citrate which is more stable. In the blood the iron transport protein transferrin competes with citrate for the gallium and transfers it to other sites where it is deposited. In other cases binding to serum proteins in the blood may lead to an unwanted distribution of the metal, so it may be necessary to inject it in a form resistant to competitive binding by serum proteins. A further challenge is provided by natural metabolic processes for affecting the breakdown of chemicals in the body. In the case of metal containing drugs, this process can sometimes release the metal and allow it to be converted to a form which may accumulate in the body. This issue needs to be considered in the design and formulation of a metallopharmaceutical agent. The elimination and excretion of a drug and its metabolic products can usually take place through the liver or kidneys. Water soluble, hydrophilic, compounds are generally excreted in urine *via* the kidneys (Figure 3). Here the process of glomerular filtration eliminates simple salts and small molecules while tubular secretion deals with larger molecules such as proteins, some of which may be reabsorbed. Fatty, lipophilic, compounds tend to be processed through the liver and bile duct (hepatobiliary system) passing into the gut for reabsorption or excretion in faeces.

1.3.2 Structure-Activity Relationships

Understanding the relationship between the molecular structure, and properties, of a chemical compound and its biological activity can provide an important tool to aid the design of new pharmaceuticals. Unfortunately, the

complicated nature of the interactions between chemical compounds and biological systems does not make it easy to devise accurate quantitative structure-activity relationships. However, by collecting data on the behaviour of a large number of closely related compounds it may sometimes be possible to develop a general understanding of the importance of different structural features in the molecule. In some cases more quantitative correlations can be developed between a parameter describing a particular property of the compound and a particular biological effect.

One example of a parameter which has been used in this way is provided by a partition coefficient describing the distribution of a compound between water and a selected oily liquid which does not mix with water. The partition coefficient provides a numerical value reflecting the relative preference of a compound for oily organic regions, such as membranes, compared to aqueous media, such as blood serum. The numerical value may be correlated with a chosen pharmacological parameter such as the minimum concentration required to induce a particular physiological response. Data from a large number of experiments can be used to define the relationship between the partition coefficient and the physiological response. Once the form of this relationship has been established, the chemical structure of new trial compounds can be designed so as to optimise the partition coefficient without modifying other structural features essential for biological activity. In this way the search for new active compounds can be focused on those most likely to prove effective.

Usually drugs will need to interact with a site in the body which has a specific chemical structure so that the size and shape of a molecule are important design features. The presence of specific chemical groups at particular locations in the molecule can also be important as can the polarisability of parts of the molecule. Modern computational methods offer a powerful tool for modelling the properties of compounds and their compatibility with potential binding sites. Together with structure-activity relationships, such computer modelling can facilitate the design of new active compounds offering significant economies in the costly process of drug development. This approach is now well established for organic compounds but the inclusion of metals creates some additional complications when it comes to the design of new metallopharmaceuticals.

Where a metal is fully contained within an organic host, modification of the host structure to optimise biological distribution and activity might follow precedents set with non-metal containing drugs. However, often the properties or reactivity of metal will be an important feature of a metallopharmaceutical. In such cases the host structure containing the metal must not be modified in a way which might impair the ability of the metal to perform its function. Thus, although modelling and structure-activity relationships can be applied to metallopharmaceuticals, it is necessary to introduce additional considerations relating to the rôle of the metal and the nature of its interaction with the host structure in which it is contained. Some examples of the importance of structure in determining the efficacy of specific metallopharmaceuticals can be found in Chapters 3 and 4.

1.3.3 Clinical Trials

The evaluation of new compounds for clinical use involves several stages. There will be a discovery or design phase in which a serendipitous discovery, or a new example of a class of compound known to, or thought likely to, have medicinal properties, is evaluated. If sufficiently promising results are obtained, and acceptable toxicity levels established, the drug may proceed into clinical trials. These can be divided into four phases as follows:

- PHASE I Small groups of healthy volunteers receive the drug so that assessments can be made of its absorption, biodistribution, pharmacokinetics, accumulation, side effects and dosage. Initially the trial will start with smaller doses than needed for therapeutic effects to check for adverse reactions. If the drug is shown to be safe in humans the trial may proceed to Phase II.
- PHASE II Small groups of patients suffering from the ailment to be treated receive the drug to establish its effectiveness. The optimum dosage regime and any adverse reactions are assessed.
- PHASE III A large number of patients with the ailment are evaluated in double blind trials involving the new drug, comparison treatments and placebos to establish the efficacy of the new drug and obtain safety data to support applications for its licensing and approval for clinical use.
- PHASE IV Monitoring of patients treated with the drug continues following approval and throughout general clinical use in order to further optimise procedures and check for previously undetected side effects.

This whole process can take many years. As an example US FDA approval for the clinical use of cisplatin was granted in 1978, some 14 years after the serendipitous discovery that platinum compounds suppressed cell division and 7 years after the start of Phase I clinical trials.

1.4 The Special Properties of Metals

1.4.1 Comparison with Organic and Biological Compounds

In aqueous solutions metals differ from organic compounds in a number of important respects. In organic compounds carbon-carbon bonds are generally rather stable and provide the robust skeleton, which gives parts of biological molecules their shape and stability. Where there is a need for carbon containing units, such as amino acids in proteins, to be connected and disconnected, carbon-nitrogen or carbon-oxygen bonds are usually used to form the linkages. Although bonds of this type are stable, compared to carbon-carbon bonds they can be more easily broken or formed through the addition or

elimination of water. This can be done under biochemical control allowing proteins, for example, to be broken down and reassembled with comparative ease. Metals are often quite reactive towards changing the atoms they are bonded to in aqueous media. However, rates of reaction can vary substantially between different metals and between different compounds of the same metal. This offers a wide range of chemical behaviour. Sometimes it is useful to have metal compounds, which are inert and do not readily convert to other forms. Sometimes it is important for the metal compound to be sufficiently reactive to allow the metal to be exchanged and incorporated into specific biological systems. Controlling the reactivity of the metal compound is one way of controlling which biological system can have access to the metal.

The interactions between charged metal atoms and other species in solution are somewhat different from those involved in the interactions between organic biological compounds. Two biological compounds may enter into quite complicated interactions through mutual recognition and binding between several complementary sites in the two different species (Figure 4). The interactions between enzymes and their substrates or the complementary strands of DNA in a DNA duplex offer examples of this type of behaviour. The individual linkages may not be particularly strong compared to conventional chemical bonds, but can act in concert to give quite strong overall binding interactions. Unlike organic compounds, metals typically show what is known as ‘Lewis acid’ behaviour, that is they bind to atoms such as oxygen in water or nitrogen in ammonia. This allows them to spontaneously assemble groups of atoms around them to form a ‘metal complex’. They can also bind to certain oxygen, nitrogen or sulfur atoms in proteins and other biochemical species. In this way they can influence the structures of organic substrates to which they become attached (Figure 5). They can also form reactive centres within biological species to which they have become bound. Metals bound within enzymes may act to

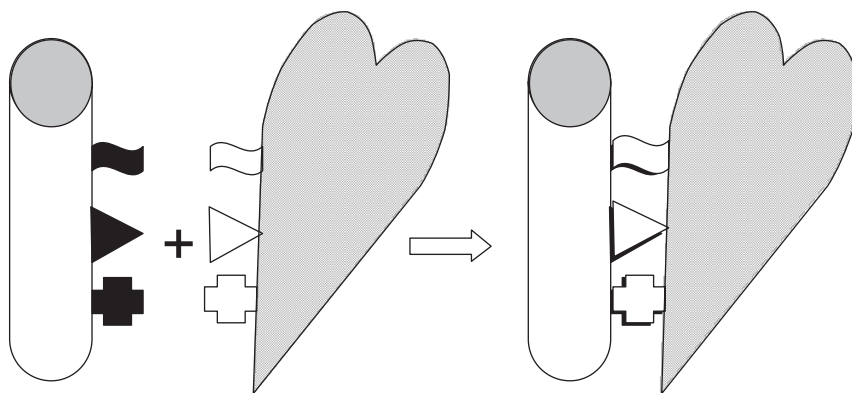


Figure 4 A schematic representation of two biological molecules with complementary binding sites recognising each other and combining to form a “complex”. Examples might be an enzyme and its substrate or the two strands of a DNA double helix

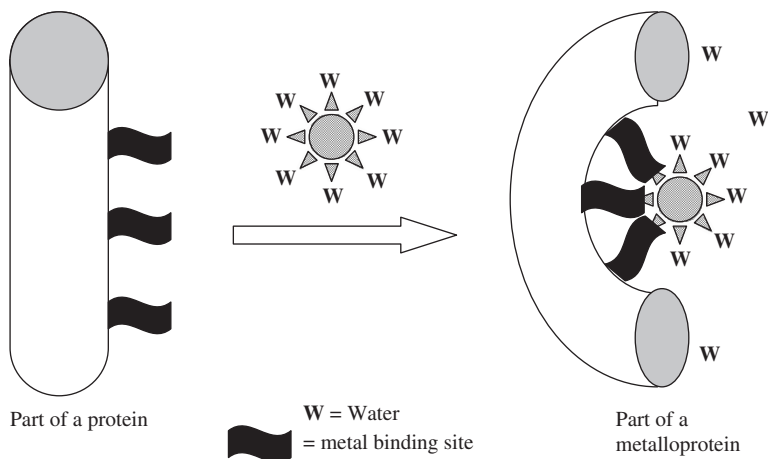


Figure 5 *A schematic representation of an aquated metal ion interacting with part of a biological substrate, such as a protein, to release some water and make the protein fold. This may just have a purely structural effect, or the metal may become a reactive centre within the biological molecule*

polarise a substrate to promote a particular reaction. An example is provided by zinc in carboxypeptidase acting as a centre catalysing protein degradation through the addition of water. Some metals can also change their charge and so act as electron transfer agents. This behaviour is found with iron in the cytochromes involved in mitochondrial electron transfer chains. Copper is also used as an electron carrier, for example in catalysing the conversion of superoxide to dioxygen and peroxide. Metals can also bind and activate small molecules such as dioxygen or nitric oxide in a much simpler and more reversible manner than would be possible using organic molecules. The use of iron centres to transport dioxygen in hemoglobin provides one obvious example.

Beyond the particular chemical features which metals bring to living systems and pharmaceuticals, they offer other attributes important for medical applications. Metals can form stable magnetic materials of a type becoming important in Magnetic Resonance Imaging applications. Organic compounds with magnetic properties tend to be very reactive and unstable *in vivo*. In addition the magnetism they can create is very limited compared to metals such as iron, manganese or gadolinium. Stabilising suitable forms of magnetic metals for use in magnetic resonance imaging applications presents a particular chemical challenge in (i) maintaining suitable magnetic behaviour (ii) controlling their biodistribution and (iii) preventing unwanted accumulation of the metal, for example in the liver. Radioactivity is another phenomenon with significant medical applications and a number of metallic elements are available in radioactive forms suitable for clinical use. In order to exploit this radioactivity it is again important to incorporate the metal in a compound with biodistribution and pharmacokinetic behaviour suitable for the clinical application. This

requires careful selection of the form in which the metal is administered and this, in turn, requires a good understanding of the chemistry of the metals involved.

1.4.2 Coordination Chemistry

The metallic elements used in medicine have characteristic features crucial to their particular application and not shared with organic compounds. In order to understand why a particular metal should be chosen for a particular medical application it is necessary to appreciate the properties and chemistry of the metals concerned. The branch of chemistry most closely concerned with the behaviour of metals under conditions relevant to living systems is known as coordination chemistry. This encompasses the chemistry of metals in aqueous media and their interactions with materials such as those encountered within living organisms or used in the formulation of metallopharmaceuticals. The origins of coordination chemistry as a distinct branch of chemistry date back to the beginning of the 20th century and are marked by the award of a Nobel prize to Alfred Werner in 1913. Among other achievements, Werner established the structure of the compound now known as cisplatin and used in cancer therapy.

To understand why metal atoms form compounds with particular structures and reactivities, it is necessary to have some appreciation of atomic structure and of chemical bonding models which go beyond those applicable to lighter elements such as carbon. The Crystal Field Theory proposed by Bethe in 1929 offered a starting point, although this was not developed into a generally used bonding model for coordination compounds until the 1950s. More elaborate theoretical models of bonding in metal compounds have since been developed but the Crystal Field Theory model continues to offer a relatively simple and accessible insight into the chemistry and magnetic properties of many metals. Chapter 2 attempts to provide a concise introduction to coordination chemistry. Those with prior experience of the chemistry of metals may wish to skip part or all of this chapter. Those with a limited chemistry background will hopefully find it a useful introduction to coordination chemistry, which underpins the subsequent chapters on diagnosis and therapy, and a platform for further reading on the chemistry of metals.