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An Alternative Model for the Selection of Therapeutic Chelating Agents

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Abstract

An alternative model is presented for the selection of therapeutic chelating agents to enhance the mobilization and excretion of a toxic metal. The model is based on the *in vivo* patterns of absorption, distribution, reaction and excretion of the chelating agent, a typical toxic metal ion and complexes of the two. The model emphasizes the kinetic aspects of the processes involved and indicates how other processes may be incorporated such as redox reactions involving the chelating agent or metal. The identification of rate determining steps and methods for their manipulation are assumed to be of importance. The application of this model to specific metals is outlined.

Introduction

The models generally used in the discussion of therapeutic chelating agents are ones based upon a consideration of various equilibria [1]. The first such model was outlined by Schubert [2–4] and emphasized the necessity for the stability constant of a chelating agent with a given metal ion to be greater than that of the corresponding calcium complex if the metal ion were to be bound by the chelating agent in the calcium rich plasma. This model has subsequently been subjected to considerable refinement by Catsch *et al.* [5]. Perrin *et al.* [6, 7], Laurie *et al.* [8], and by May *et al.* [9–12, 43]. The ability of these models to screen promising chelating agents is quite impressive, though animal tests reveal that its predictions are not always verified. An examination of the situations in which it fails (*e.g.* 14) reveals a variety of causes for these failures. Most are related to the simplifications introduced in order to avoid a reliance on any type of data other than stability constants. Some of these have been discussed previously [13]. One of the main restrictions on the usual equilibrium models arises from their emphasis on low molecular weight complexes capable of urinary excretion, *e.g.* the Plasma Mobilization Index of May and Williams [10]. This emphasizes the importance of that fraction of the metal in the serum which is filtered out at the glomerulus and, hopefully, not reabsorbed in the proximal or distal tubules. It thus calculates the increase in the fraction of metal available for urinary excretion. When urinary excretion of the metal is of considerably less importance than biliary excretion, the model may well be ill in accord with *in vivo* experiments (*e.g.* in the case of Cd^{2+}). However, because of the numerous, and frequently impressive, successes of this equilibrium model, and its firm foundation in basic thermodynamic principles, it must be at least a part of any new model as a special case. The model outlined here is based primarily on the rate constants for the various processes involved in the mobilization, excretion and redistribution of a toxic metal ion in the presence of a chelating agent and emphasizes the importance of identifying the rate determining steps in the overall detoxification process. It encompasses the equilibrium model as a special case where certain processes are very rapid and all other complicating factors can be neglected. It must be emphasized that for a chelating agent to be effective in complexing and removing a toxic metal ion from the mammaliam body it must satisfy the requirements of the equilibrium theory *i.e.* the free energy change for the transfer of the metal ion to the chelating agent must be negative; it must be thermodynamically capable of removing the toxic metal ion from competing ligands *in vivo*. Whether the formation of the metal chelate and its subsequent metabolism lead to detoxification, however, is determined by rate processes.

Model

The model developed here is designed for chronic or acute intoxication. One of the common differences between acute and chronic intoxication is the relative amount of extracellular *vs.* intracellular toxic metal. For many types of toxic metals, acute intoxication is a situation in which a relatively large percentage of the toxic metal is in extracellular spaces in process of being transferred to intracellular sites. In typical chronic intoxication a large percentage of the metal is found in intracellular sites. Thus,

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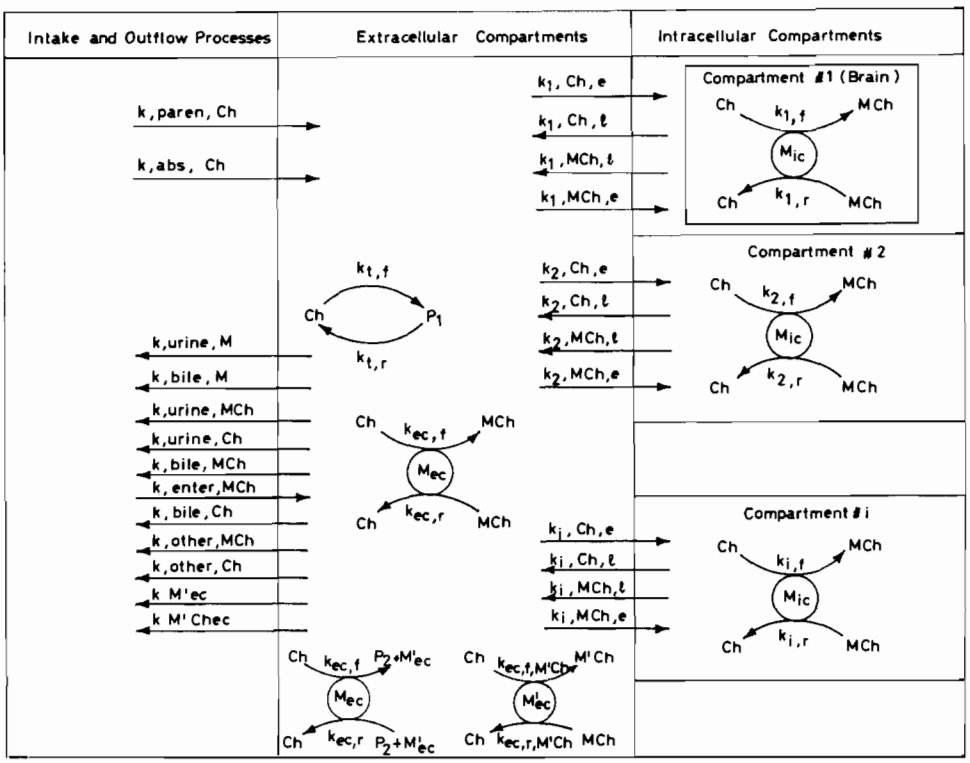

Fig. 1. Outline of the alternative model. Here the rates of processes involved in the mobilization, transport and excretion of the metal are indicated.

TABLE I. Symbols Used in Fig. 1.

Ch	= chelating agents (may form only a single bond if toxic metal is Hg^{2+}, Au(I), Ag^{+} or other ion of analogous stereochemistry)
P_1	= metabolic product formed from chelating agent
P_2	= redox product formed by reaction of chelating agent and metal species
M_{ic}	= intracellular metal, generally present as a complex
M'_{ic}	= intracellular metal in a different oxidation state than M_{ic}
M_{ec}	= extracellular metal, generally present as a complex to serum constituents such as albumin, glutathione, *etc.*
M'_{ec}	= extracellular metal in a different oxidation state than M_{ec}
k	= rate constant
$k_{i,Ch,e}$	= rate constant for entry of chelating agent into intracellular compartment i
$k_{i,Ch,l}$	= rate constant for passage of chelating agent out of intracellular compartment i
$k_{i,MCh,l}$	= rate constant for passage of metal chelate complex (MCh) out of intracellular compartment i
$k_{i,MCh,e}$	= rate constant for entry of metal chelate complex (MCh) into intracellular compartment i
$k_{i,f}$	= rate constant for reaction between chelating agent and M_{ic} to form metal chelate complex (MCh)
$k_{i,r}$	= rate of transformation of metal chelate complex into intracellular metal and chelating agent in compartment i
$k_{paren,Ch}$	= rate constant for introduction of chelating agent via parental injection
$k_{abs,Ch}$	= rate constant for absorption of chelating agent from gastrointestinal tract
$k_{urine,X}$	= rate constant of excretion of X into urine
k_{bile} X	= rate constant of excretion of X into bile
$k_{e,f}$	= rate constant of electron exchange between Ch and $M_{ic,i}$
$k_{e,r}$	= rate constant of electron exchange between P_2 and $M'_{ic,i}$
$k_{ec',f}$	= rate constant for formation of M'Ch from M' and Ch in extracellular compartment
$k_{r,M'Ch}$	= rate constant for release of Ch from M'Ch
$k_{ec,f}$	= rate constant for forward redox process involving extracellular metal
$k_{ec,r}$	= rate constant for reverse redox process involving extracellular metal
$k_{enter,MCh}$	= rate constant for absorption of MCh from gastrointestinal tract

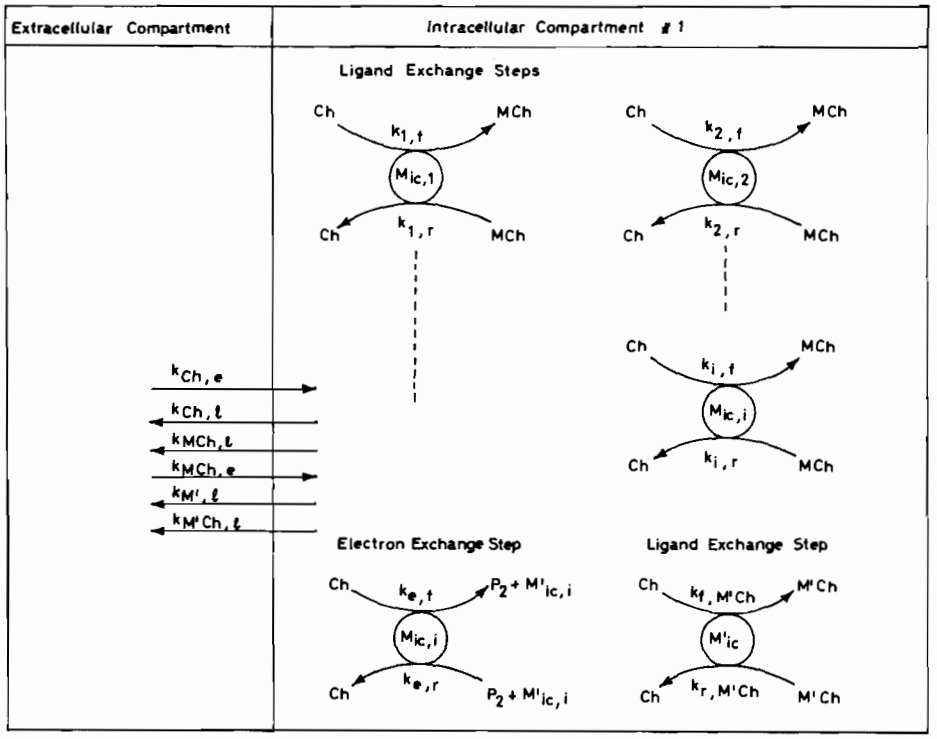

Fig. 2. The symbols used here have the same pattern of meanings as those used in Fig. 1. The purpose of this figure is to emphasize that the distribution of intracellular metal ions is over a variety of types of sites, each characterized by its own pattern of kinetic behavior.

for the removal of metals from the chronically intoxicated organism, the ability of the chelating agent to cross the cellular membrane is often absolutely essential for effectiveness. For acute intoxication, chelating agents capable of acting in the extracellular spaces are often quite effective. The exceptions to this situation include acute intoxication by those species which rapidly penetrate cellular membranes and the blood/brain barrier *e.g.* $Ni(CO)_4$, CH_3HgCl, and $Pb(C_2H_5)_4$: *i.e.* just those species whose treatment schemes and/or prognosis differs significantly from those for intoxication by typical *ionic* metal species.

The model is presented in Fig. 1 which summarizes the major possible pathways for the introduction of the chelating agent, its possible reactions in the extracellular compartment, the processes by which it can be absorbed into or excreted from intracellular compartments, its reactions with intracellularly deposited metal, and the routes by which the metal-chelate complexes can be formed and transferred from one compartment to another and the excretory processes involving the chelating agents and the metal chelate. For each process there is a characteristic rate constant and these are listed in Fig. 1 at the appropriate interface.

The model itself is simplified in many respects. One such simplification is the assumption that the extracellular and intracellular metal is present in only one form. A typical acceptor species, such as a metal ion, will be distributed among its preferred donor sites on many of the intracellular constituents in which such donor sites occur [9–12, 43]. This behavior also reveals itself in the fact that a given toxic metal will generally deactivate a considerable number of intracellular enzymatic systems in which these donor groups occur. A more generalized representation of the intracellular space is shown in Fig. 2. It is also feasible that more than one metal complex might be present. This possibility has not been considered in Fig. 1. With the concentrations of chelating agents generally used *in vivo*, the relative amounts of higher complexes need not be small [10]. The nature of the complex is given as, MCh, but this again may be an oversimplification, especially for those metal ions that readily form stable mixed or polynuclear species. Figure 2 shows one compartment in a case in which several metal chelate complexes are formed in which the metal ions is in different oxidation states.

This model directs our attention to the evaluation of the factors which affect the value of:

$$-\left[\frac{dM}{dt}\right]_{organism}$$

For chronic intoxication it is a reasonable approximation to take the pretreatment value of (dM/dt) organism as zero or a very small positive number (*i.e.* a steady state) and to consider the effects of various factors of this magnitude of this rate.

The potential rate determining or rate limiting steps are of the following types:

(a) slow absorption of the chelating agent from the gastrointestinal tract following oral administration, (a rate determining step which does not occur for other methods of administration of the chelating agent), or destruction via digestive enzymes,

(b) rapid excretion of the chelating agent in the urine,

(c) rapid metabolism of the chelating agent in the extracellular compartment,

(d) slow reaction of the chelating agent and the bound metal in the extracellular compartment,

(e) slow transport of the chelating agent from the extracellular compartment to the various intracellular compartments,

(f) slow reaction of the chelating agent with the metal bound in the intracellular compartments,

(g) slow release of the metal chelate complex from the intracellular compartments subsequent to its formation,

(h) slow passage of MCh into the urine, or its reabsorption in the proximal or distal tubules of the kidney,

(i) slow passage of MCh into the bile,

(j) rapid reabsorption of MCh from the gastrointestinal tract,

(k) slow secretion of a metal chelate complex which is not rapidly excreted in the urine or the bile.

Of these possible rate determining steps, many have been postulated as of significance in one or more types of metal decorporation processes. Step (a) has been invoked to explain the poor ability of many iron binding chelating agents to reduce iron overload in individuals who have received continuing blood transfusions when these chelating agents are given orally [15]. Step (b) is probably the most common limiting factor in the action of water soluble chelating agents such as $Na_2CaEDTA$, which frequently are cleared into the urine from the serum by processes so rapid that their half life in the serum is of the order of 30 min or so. Step (d) is responsible for the fact that certain macrocycles with very high values for the stability constants of their copper complexes are unable to accelerate the excretion of copper [16]. Step (e) is responsible for the fact that many chelating agents which possess very high values for the stability constants of their complexes with cadmium are unable to mobilize cadmium subsequent to its incorporation in metallothionein inside cells [17]. Step (g) is presumably found with certain thiols which transport cadmium to the kidney but then release it in the kidney prior to passage into the urine [19]. Step (i) can be found in the case of certain mercury complexes which are reabsorbed rapidly from the gastointestinal tract [20].

To enhance the excretion of any given metal ion it is often very useful to know the rate determining steps in previous attempts which have failed. For many common chelators, $k_{i,Ch,e}$, the rate constant for the entry of the chelating agents into the intracellular compartments is quite low.

To a considerable extent, chelating agents which cannot readily enter cells are capable of mobilizing only that fraction of a metal ion which is in the extracellular space. In some cases, because of the ease with which a metal ion can move into or out of a cell, this limitation is not a serious one. With other metals, which tend to be immobilized in intracellular spaces as a result of chronic intoxication (*e.g.* Cd^{2+}, Fe^{3+}), a chelating agent which is unable to cross the cell membrane, even if it has a very high stability constant for its complex with a given metal, will not be useful in mobilizing that metal. At the present time a considerable number of serious problems involved in the mobilization of metal ions in cases of chronic intoxication are related to the lack of suitable chelating agents for the metal ion which are able to move through the cell membrane. These include Cd^{2+} and Fe^{3+} mentioned above, as well as radioactive lanthanides, beryllium(II), chromium(III), aluminium(III), lead(II) and a variety of insoluble compounds which are phagocytized in *e.g.* the lung, but then persist for years, in some cases causing cancer *e.g.* Ni_3S_2, chromates. ThO_2, etc.

An additional aspect which is ignored when one considers only stability constants is the possibility of reducing the toxicity of a species via a redox process. In general, the toxicity of the various species derived from a toxic element varies significantly as the oxidation state is altered. Thus vanadate can be reduced to the less toxic vanadyl ion [21] and selenite is detoxified in normal biological processes *in vivo* via transformation to some types of –Se– compound containing –2 selenium [22]. Reduction does not always lead to a decrease in toxicity as $Ni(CO)_4$ is more toxic than Ni^{2+} [23] and As^{III} is more toxic than As^{V} [24].

The model has the additional advantage that it delineates a wider variety of possible rate determining steps than merely ligand exchange of the toxic metal. For a reasonable number of toxic metals, biliary excretion is preferred to urinary excretion and the nature of the complexes excreted via the two routes probably differs significantly [25]. Urinary excretion is favored by low molecular weight, water-soluble complexes. Biliary excretion is favored by higher molecular weight complexes of very limited water solubility. Biliary excretion is very important in the metabolism of cadmium, copper and

manganese, for example [33].

In addition to the formally recognized steps in this model, there is another limitation which is not formally incorporated. This is the limitation set by the toxicity of the chelating agent itself. This limitation is not infrequently the most important practical limitation in chelate therapy. All chelating agents are toxic and this toxicity must always be incorporated in the development of protocols for the removal of a given metal from the mammalian body. Very striking examples are the toxicity of compounds such as 1,2,3-trimercaptopropane, 1,2-dimercaptopropanoic acid, cyanide, and some catechol derivatives. The stability constants of these compounds with toxic metal ions are very high, but the toxicity of the compounds is so great that they cannot be given serious consideration for removal of toxic metals. Even for much less toxic chelating agents however, it is their inherent toxicity that sets the limits on the maximum feasible concentration of that chelating agent which can be achieved *in vivo* and this in turn limits the rates of all of the processes which are dependent on its concentration.

It is possible to reduce the toxicity of many chelating agents by administering them in a large volume of water and this will frequently increase the time over which high concentrations of the agent can be maintained. This will increase the amount of metal excreted in the urine, often by a very significant factor.

Rates of Metal Mobilization Reactions

The reactions in which chelating agents displace metal ions from *in vivo* sites in which they are bound to several types of donor sites can be expected to show at least some kinetic similarities to analogous reactions *in vitro*. A rate determining step usually involves the concentrations of both the chelating agent and the metal species. For convenience, the pH *in vivo* can be assumed to be essentially constant so one may write approximate rate laws for the mobilization process in the form [26]:

$$\frac{d[MCh]}{dt} = k[Ch]\,[MB]$$

where [MCh] is the concentration of the metal chelate complex, [Ch] is that of the chelating agent and [MB] is that of the metal bound to donor groups of the biological system. Whether these are extracellular, intracellular or a mixture of the two is dependent upon the metal involved and the time elapsed between introduction of the metal and that of the chelating agent. In fact, the metal is bound by a variety of sites so the initial rate of formation of MCh will be the sum of all of the processes of this type:

$$\frac{d[MCh]}{dt} = [Ch] \sum_{i=1}^{n} k_i [MB]_i$$

$$= [Ch]_{extra} \sum_{i=1}^{n} k_i [MB]_{i,extra}$$

$$+ [Ch]_{intr} \sum_{j=1}^{m} k_j [MB]_{j,intr}$$

where the subscripts extra and intra refer to extracellular and intracellular processes respectively.

This clearly emphasizes the distinction between intracellular and extracellular metal deposits and that their rate of mobilization may differ greatly. This distinction is especially important with those metals which have a very long normal half-life when bound to intracellular sites and in discussing the action of chelating agents which are limited to the extracellular compartments. For metals with a relatively short half-life when bound to intracellular sites, the depletion of the metal from extracellular sites can be envisaged as prompting a fairly rapid redistribution of metal from intracellular to extracellular sites.

Since most previous attempts to quantitate the action of therapeutic chelating agents are based on considerations involving equilibrium constants, they contain an implicit assumption that this redistribution of metal is quite rapid and that the reactions between Ch and the various MB are very fast and attain equilibrium in a time which is short in comparison with the time required for a significant change in [Ch]. The shortcomings of these previous treatments are noted in those cases where such reactions are slow. Difficulties also arise, when the distribution of chelating agent and of metal between the extracellular and the intracellular compartments differ significantly.

While equilibrium constants can tell us whether or not a process can be expected to be spontaneous, it does not necessarily furnish us with a guide to determine which occur at a usable rate. This information can be gained from *in vivo* studies or, estimated from various pieces of information on the coordination chemistry of the processes involved. It is also necessary to note that while equilibrium constants furnish us with the most convenient measure of the spontaneity of ligand and chelate exchange reactions, there are other less quantitative estimates which can provide an indispensable guide when the data on equilibrium constants are incomplete or missing completely. Here, one may find preferred donor atoms among the vast amount of information from preparative coordination chemistry which is presented in standard textbooks on inorganic chemistry [29], and the classifications of donor atoms

presented by Chatt *et al.* [30] or by Pearson [31]. Where stability constants are missing such data are indispensable as they also provide a key to the types of donor–acceptor exchange processes which will be found to be spontaneous for a given toxic metal. The classification of Pearson has the added advantage that it allows the relative rates of such processes to be estimated.

Use of the Model

In order to use the model presented here, information must be available or estimated about the following factors.

A. Whether the chelating agent is thermodynamically capable of displacing the metal from its *in vivo* binding sites. Information on this can be obtained either from stability constant data or preparative reactions or similar data.

B. Whether the chelating agent can pass through cellular membranes readily or not. This determines the relative magnitude of $[Ch]_{extra}$ and $[Ch]_{intra}$. Data on this can usually be obtained from measurements of the octanol/water partition coefficient of the chelating agent or, much better, from *in vivo* distribution studies on the radiolabelled chelating agent [32].

C. Whether the major site of metal to be mobilized is intracellular or extracellular. Data on this can be obtained from published studies on the organ distribution of metals; such studies are available on most of the toxic metals of interest [33].

D. Whether the metal ion itself can pass readily from intracellular to extracellular sites or *vice versa.* This can be determined from studies on cell cultures [34].

E. The relative rates of attack on the bound metal of the various possible types of chelating agent which are capable of gaining access to the *in vivo* deposits of the metal. A lot of data of this type have been compiled [35] or can be estimated from the HSAB theory of Pearson [31].

One of the main potential uses of this model in its present form is to facilitate the selection of chelating agents for use for a given metal, especially when very few stability constants are known. If some stability constants are known, it may be possible to estimate the ones which are desired [27, 28]. However, the use of this model in situations in which essentially no reliable stability constants are available can nevertheless proceed via an initial examination of the preferred donor partners of the particular toxic ion under consideration [29–31]. This is then followed by a careful consideration of the currently available chelating agents of modest toxicity, which are sorted out to select the most promising members [37, 38]. *In vivo* testing of these can then be used to select the most promising donor group and this, in turn, can be the subject of a structure–activity study to select the optimum chelating agent [39]. Information on the *in vivo* distribution of most toxic metals is available from studies using radioactive isotopes [33] and this can be used to estimate the relative importance of intracellular deposits and their accessibility to various types of chelating agents. In addition, a survey of previous attempts at chelate therapy for the particular toxic ion may greatly facilitate the search for proper types of donor groups for *in vivo* studies even when such studies were unsuccessful or only partly successful. An example of its use can be seen in a recent intercomparison of chelate antidotes for gold(I) (whose compounds are used in the treatment of rheumatoid arthritis) [36]. The coordination preferences of gold(I) allowed the screening to be restricted to compounds containing sulfur donor atoms of one sort or another, considerations of compound toxicity further limited the number of compounds for study. Of the eight compounds examined in acute studies, two showed themselves to be excellent antidotes (2,3-dimercaptosuccenic acid and 2,3-dimercaptopropene-1-sulfonate) and two more to be reasonably effective (N-acetyl-D,L-penicillamine and N-acetyl-L-cysteine). While other compounds may later prove to be superior, these compounds do provide a level of performance against which that of other compounds may be compared.

For metals with similar coordination preferences it can be expected that they will react with a similar pattern of sensitive biological donor sites. Thus soft acceptor species can be anticipated to react with glutathione, cysteine, lipoic acid and biological molecules of all sorts containing -SH groups, including molecules such as metallothionein. One might thus expect that the toxicity of metal ions be related not only to softness parameters [40–42] but quite directly to stability constants of these ions with appropriate -SH donor groups. The reversal of such toxic effects then depends on the displacement of the toxic metals from such sites by species which bind them more firmly.

In so far as the selection of chelating agents is involved, it is useful to note that about 20 such compounds with six or seven different types of donor groups are already available and in use *in vivo* [46]. For reaction with a toxic metal bound *in vivo,* the first consideration is the selection of a chelating agent whose donor atoms are of the type favored by the toxic metal. The second consideration is the selection of chelating agents from this group of 20 which have the appropriate organ distribution *in vivo* to be able to gain access to the deposits of toxic metal. These two criteria will usually suffice to select the most promising few chelating agents for preliminary trials from

among the 20 or so compounds for which *in vivo* data are available.

The model given here is consistent with other approaches to chelating agent choice. The preparation of special compounds selective for a single metal ion in biological milieu is one these. This is difficult but not impossible. The types of complications which arise to frustrate many attempts of this sort include (I) the fairly rapid hydrolysis of specially prepared peptides [44], (II) the oxidation of many species after they pass the cellular membrane by powerful oxidizing enzymes such as cytochrome P-450 [45], (III) the very slow rate of reaction of macrocycles with some metals which are tightly bound in biological sites [16].

The advantages of a more effective model in this field include a reduced dependence on whole animal experiments and their replacement by the more rapid and easily carried out experiments with cell cultures, the ability to screen chelating agents for their ability to pass through cellular membranes as an important step in their preliminary evaluation, as well as reduced dependence on the availability of stability constants especially where these are completely inaccessible.

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