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Newer Chelating Agents for *in Vivo* Toxic Metal Mobilization

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Newer Chelating Agents for *in Vivo* Toxic Metal Mobilization

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Studies directed towards the development of more effective chelating agents for the removal of toxic metals from the mammalian body have shown that a considerable number of properties, in addition to the stability constant, may be of critical importance. These additional properties include penetration into target organs, molecular weight, toxicity, ionic charge at physiological pH, chirality, degree of chain branching, rates of ligand substitution reactions of the toxic metal ion and rates of excretion and metabolism of the chelating agent. The way in which these properties may be manipulated is illustrated by an examination of recent developments of compounds for the *in vivo* mobilization of cadmium, iron and plutonium.

Key Words: *chelating agents, toxic metal mobilization, cadmium, iron, plutonium*

INTRODUCTION

The great majority of the work of bioinorganic chemists is concerned with the coordination chemistry of *essential* metal ions in

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living organisms, and the examination of aspects of the interactions of these *essential* metal ions with the rest of the enzyme, organelle or cell in which they are found. The present study, however, is concerned with the manipulation of the coordination environment of *toxic* metal ions *in vivo* in order to accelerate their excretion from the organism. These toxic metal ions may be either ions which are never utilized by the organism and are only capable of interference with normal metabolic processes or essential metal ions which have accumulated to toxic levels.

Thus chelating agents are used to remove a toxic metal from the body in two types of clinical problems. These arise as a result of:

1. Environmental and industrial exposures to toxic metals such as lead, mercury, cadmium, arsenic, and the like.
2. Metabolic diseases which result directly or indirectly in the accumulation of excessive amounts of an essential metal. A case of direct accumulation is found for copper in Wilson's Disease. Indirect accumulation is found for iron in most thalassemia patients, as the treatment of thalassemia involves the prolonged administration of blood transfusions with an accumulation of iron to toxic or lethal levels.

There may be significant differences in the organ distributions of the toxic metals in these two cases. Environmental and industrial exposures generally result from the inhalation or ingestion of the toxic metal and its deposition in, and absorption from, the lungs and the gastrointestinal tract. Pulmonary exposures usually result in some deposition in the lungs if the particles are fine enough, though larger particles are swept up the trachea and then swallowed. Following gastrointestinal absorption, the toxic metals concentrate, depending upon their organ preferences, in the liver, the kidneys, the pancreas, the bone or other organs. Where essential metals are accumulated as a result of metabolic disease, they tend to occur preferentially and initially in the organs most concerned with their metabolism, usually the liver or the kidney, though as the continuing accumulation proceeds, such metals move to most of the other organs. In both cases, we desire a chelating agent which goes preferentially to certain organs *in vivo*. In view of the growing industrial and commercial use of toxic metals and their increasing release into the atmosphere, the problem of developing

effective treatments for such exposure will assume growing importance in the future. The sheer magnitude of the problems that are faced in reprocessing nuclear fuels and in the dismantling of nuclear weapons insure that human exposures to uranium and the transuranium elements, such as plutonium, will not diminish in the near future.

In discussing chelating agent design it is necessary to remember that all chemical compounds are toxic; however, they differ primarily in the dose required to elicit a toxic response. In consequence, the toxicity of the chelating agent is an important factor in the ultimate determination of which chelating agents are used in the clinic. The goal of chelating agent treatment of metal intoxication is to transform a toxic metal bound to a constituent (usually a protein) of a living organism into a less toxic metal chelate complex which is readily excreted. It has long been known that the stability constant of a metal complex is a key factor in the determination of the toxicity of certain types of metal chelate complexes, with the toxicity decreasing as the stability constant increases.[1] The stability constant has also long been recognized as a key factor in the determination of the ability of the chelating agent to remove the metal from a living organism.[2,3] During recent years the methods of preparing chelating agents with greater stability constants and the delineation of the other factors which determine the effectiveness of a chelating agent as a toxic metal mobilizing agent have progressed to the point that such factors may be incorporated directly into chelating agent design to enhance the probability of obtaining agents which are more effective *in vivo* than previously known compounds.[4-7] The result has been the recent appearance of newer chelating agents which are significantly more effective or easier to administer in the control of intoxication by iron, plutonium, and cadmium in animal or human models. The manner in which these factors have been manipulated in these cases can be outlined in such a fashion as to facilitate their application to the development of more effective chelating agent antagonists for other toxic metals of interest. To present the experimental biological data on a comparable basis, chelating agents are discussed here on the basis of their effectiveness:

$$\text{Effectiveness} = \frac{[\text{Toxic metal remaining in treated animal or organ}]}{[\text{Toxic metal remaining in untreated animal or organ}]}.$$

The majority of chelating agents that are commercially available have been developed for purposes other than the removal of toxic metal ions from the mammalian body. As a result, it should come as no surprise that their structures are not ones which would have been selected if this had been their main application. For example, sodium diethyldithiocarbamate is readily available and forms complexes with a large number of metal ions. The complexes formed are, however, frequently quite lipid soluble, with the result that they pass readily through the blood–brain barrier and increase the toxic metal content in the brain.[8,9] Chelating agents such as EDTA and DTPA have several ionized carboxylic acid groups at physiological pH values and cannot pass through cell membranes to any significant extent.[7,10] As a result, EDTA and DTPA are very effective in removing many metal ions from the serum, but relatively ineffective in removing metals from intracellular sites[11–13] unless the intracellular and extracellular compartments re-equilibrate very rapidly. They are thus quite unable to remove cadmium from intracellular sites, although their stability constants with cadmium indicate that *at equilibrium* such cadmium should be removed. Long before such an equilibrium is attained, the EDTA or DTPA has been almost completely excreted in the urine.[14]

The path that a chelating agent must take *in vivo* if it is to be capable of removing toxic metal ions from an intracellular site is shown in Fig. 1. Here the chelating agent can be put into the extracellular fluid via an intravenous injection or in some cases by oral administration. Its passage through the cellular membrane is dependent upon the availability of appropriate routes via the lipid portion of the membrane itself, or channels, receptors or pumps in the membrane that are normally used by the cell for other purposes. If the metal is concentrated within an intracellular organelle, the chelating agent must also penetrate the membrane that surrounds this. For those organs which have a plentiful blood supply, such as the liver or the kidney, the delivery of a chelating agent to the site of the toxic metal is relatively easy. For some organs, such as the lungs or the bone, the removal of toxic metals by chelating agent treatments is a more difficult process.

The earliest attempts to develop chelating agent antagonists were for lead intoxication[15]; these utilized sodium citrate, because it forms a stable lead complex at physiological pH (7.4) and because

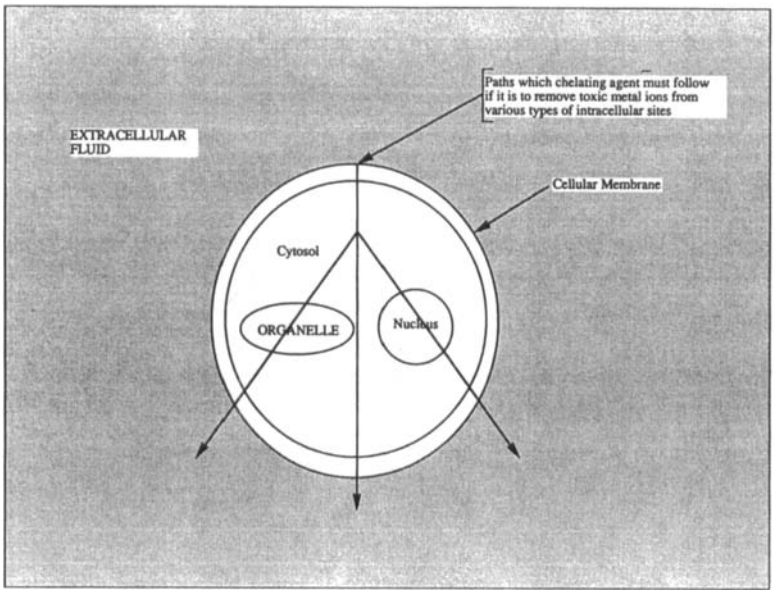


FIGURE 1 Path of a chelating agent that removes a toxic metal from the interior of a cell.

its administration enhances the fecal and urinary excretion of lead. After the development of BAL and EDTA (see Fig. 2), chelating agents were available which formed much more stable complexes with the lead ion and were much more effective in increasing the excretion of lead. These compounds were applied to the treatment of lead intoxication in humans.[16,17] The study of related problems in removing radioactive elements from the mammalian body led to the formulation of a model showing the relationship between the anticipated degree of effectiveness of the chelating agent as an antidote and the stability constants for the toxic metal and metals in the serum.[2,3] Subsequent studies extended this approach to the point where a large number of equilibria which occurred in the serum and affected the complexation of the chelating agent with the toxic metal were considered.[18–20] This type of model was shown to have certain shortcomings in treating experimental data on animals by Catsch and his co-workers,[21] although it is still necessary as a guide to sort out what is possible thermodynamically from

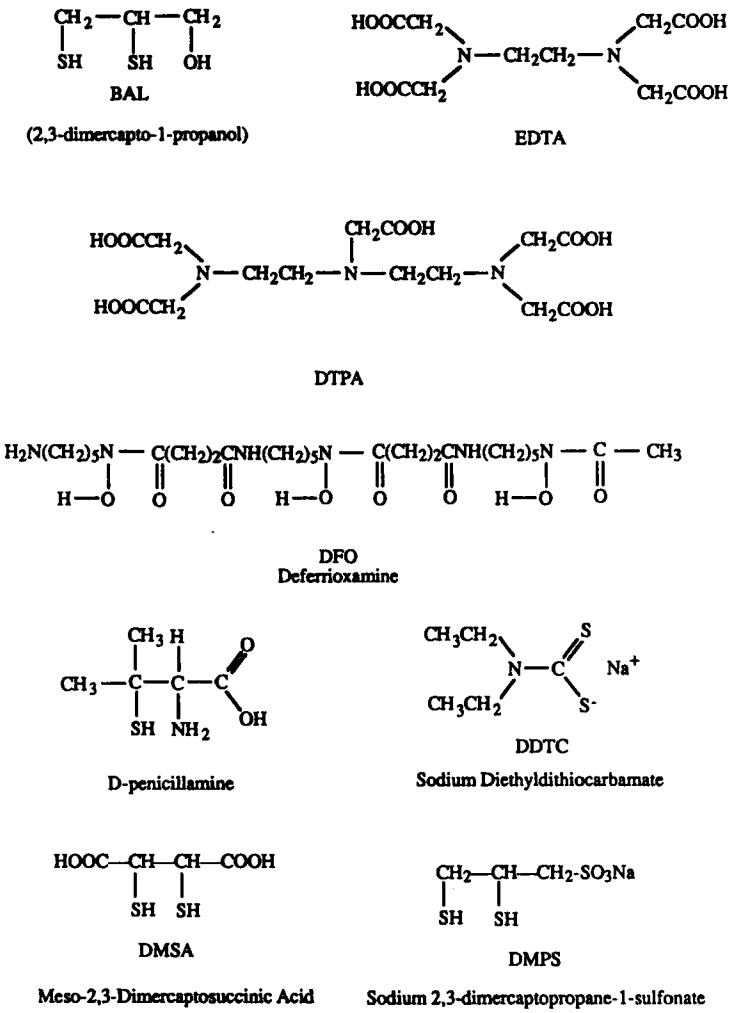


FIGURE 2 Structures of chelating agents that are effective *in vivo* antagonists for some toxic metals and have been used in the clinic for this purpose.

what is not. During the last decade, efforts to develop more effective chelating agents for removing various toxic metals from the mammalian body have shown that a considerable number of factors may influence the behavior of such compounds *in vivo*. While the

importance of the stability constant and the toxicity of the chelating agents have been recognized for many decades, factors related to the ability of the chelating agent to penetrate cellular membranes and which govern its organ distribution have been recently shown to be important considerations in the determination of the effectiveness of such compounds in animal tests.

With these comments as a background it is possible to enumerate *some* of the properties of the chelating agent that govern its relative effectiveness in removing a toxic metal from a cell or more complex organism. These can be enumerated as follows[6]: (1) the effective stability constant for the toxic metal, (2) penetration into the target organs, (3) molecular weight, (4) toxicity, (5) ionic charge at physiological pH, (6) chirality, (7) degree of chain branching, (8) rates of removal of the toxic metal ion from its *in vivo* binding sites, and (9) the rates of excretion and metabolism of the chelating agent. Each of these can have a considerable influence on the effectiveness of a particular chelating agent *in vivo*. Here the newer chelating agents developed during the last decade, which are effective in animal studies, are given special emphasis, although only one of these has been used in preliminary clinical studies.

Effective Stability Constants

It is obvious that if the effective stability constant for the toxic metal is not sufficiently great, the chelating agent cannot compete with the endogenous chelate structures for the toxic metal ion, nor can the toxic metal ion compete effectively with endogenous metal ions (such as Ca^{2+} and Zn^{2+}) for the donor sites of the chelating agent. As a general rule, it is advantageous to optimize the effective stability constant, provided that this does not require structural changes which interfere with one of the necessary steps in the overall process. The optimization of the effective stability constant is frequently accomplished via the introduction of additional donor groups.[4,5] When these are charged, such as $-CH_2COO^-$, the addition of increasing numbers of such groups soon results in a structure which cannot penetrate cellular membranes to any significant extent.[22]

The procedures for devising structures of enhanced stability constants have been examined in considerable detail.[4,5,7,23-25] Ex-

amples which clearly demonstrate these procedures can be seen in several families of structures which have been developed for the mobilization of plutonium. The key requirement is the design of a structure which will more effectively form a set of donor atoms that completely envelops the toxic metal ion of interest. The studies of Raymond on compounds for the mobilization of plutonium show this process as it develops from a group of compounds with the ability to sequester iron *in vivo*: the siderophores which are used by microorganisms to extract needed iron from their environments.[26-28] This is an effective method because the path of plutonium in the mammalian body is very similar to that of iron.

Penetration into Target Organs

The alterations of molecular structure that have been used to enhance the penetration of the chelating agent into target organs are usually such as to enhance the hydrophobic nature of the molecule as a whole. This is a way to raise the partition coefficient of the structure, which is the equilibrium constant for the process:

$$\text{Chelating Agent (water)} \rightleftharpoons \text{Chelating Agent (octanol)},$$

$$\text{Partition Coefficient} = \frac{[\text{Chelating Agent (octanol)}]}{[\text{Chelating Agent (water)}]} = P.$$

Because P covers such a wide range, it is customary to tabulate log P. By increasing P, one can generally facilitate the transfer of a structure across the lipid portions of cellular membranes; octanol exhibits some of the same solvent characteristics as the lipid portion of the cellular membrane. Changes that increase P often increase the toxicity of the structure also. The partition coefficient is important because it determines the ability of the chelating agent to cross the *lipid* portion of the cellular membranes. The partition coefficient generally decreases as the charge becomes more negative. If the partition coefficient is quite large and the chelating agent is very lipophilic, it will also usually be found to be more toxic than chelating agents which are amphipathic.

The techniques that have been used to obtain compounds that are successively more effective in their penetration of target organs

can be seen in the development of compounds designed to be more effective than DTPA for removing plutonium from intracellular sites,[29,30] in a series of successively more effective dithiocarbamates for the removal of cadmium from its aged deposits in the kidney and the liver,[31] and in the development of compounds which can be administered orally for enhancing the excretion of iron.[7,10]

Molecular Weight

It is well established that molecules with molecular weights above a certain range are preferentially removed from the circulation by the liver and excreted in the bile.[32] An increase in the molecular weight of the chelating agent will favor this process, especially for molecules that have neither high ionic charges nor a purely lipophilic structure. Thus an increase in the molecular weight of a chelating agent which does not alter the general ability of the donor groups to chelate the toxic metal under consideration will lead to a compound with an enhanced ability to remove this toxic metal from the liver.[31] Such changes can lead to preferential uptake by the liver, which then becomes a preferred route of excretion of both the chelating agent and its metal complexes.

Toxicity

The toxicity of a chelating agent can generally be modified by structural changes which enhance its water solubility as such changes mirror the normal detoxification processes which occur in the mammal, such as glucuronidation, sulfate ester formation, and oxidation processes which generate more polar species.[33]

Ionic Charge at Physiological pH

Chelating agents that bear a charge of -2 or a charge even more negative, such as EDTA, DTPA, or DMSA (Fig. 2), are not able to pass through cellular membranes to an appreciable extent. Chelating agents bearing a single negative charge, such as DMPS (Fig. 2) may be able to use one of the special routes, such as the organic anion transport system of the kidneys.[34,35] As a result, most chelating agents with ionic charges more negative than -1 are not able to remove toxic metal ions from intracellular sites. This is a

not uncommon cause for the limited effectiveness *in vivo* of a chelating agent designed to have a high stability constant via the incorporation of several groups which ionize to form anions at physiological pH values.

Chirality

The chirality of a chelating agent *may* have a profound effect on the *in vivo* behavior of the chelating agent. A case in point is penicillamine (Fig. 2), a chelating agent used to enhance the excretion of copper in the treatment of Wilson's Disease.[36] This compound occurs in the form of optical isomers, generally called the D and L forms. The L-form is much more toxic than the D-form, and for this reason the pure D-form is used in the treatment of Wilson's Disease to enhance the urinary excretion of copper. The L-form is an antimetabolite and interferes in the normal processes by which vitamin B_6 functions. L-penicillamine does this by forming an unreactive Schiff base with vitamin B_6. Such differences between optical isomers are not always so pronounced. Thus the DL and the *meso*-forms of 2,3-dimercaptosuccinic acid differ in toxicity (LD50 values of 10.84 mmol/kg and 13.73 mmol/kg, ip, in the mouse) but are of essentially equal effectiveness as arsenite antidotes.[37] The optically active forms of 2,3-dimercaptopropanol (BAL) have been prepared,[38] but their biological properties have not apparently been characterized.

Degree of Chain Branching

Chain-branching is also known to affect the relative ability of isomeric chelating agents to mobilize a toxic metal, e.g., cadmium,[39] but the number of examples which have been characterized is too small to permit of any broad generalities at this time.

Rates of Removal of the Toxic Metal Ion from Its in Vivo Binding Sites

Instances where experimental animal data indicate that a chelating agent with a high stability constant is less effective in removing a toxic metal than a related chelating agent with a lower stability constant are not unknown. One of the clearest cases is that re-

ported by Borthwick and his collaborators[40,41] who examined the behavior of some macrocycles as copper mobilization agents. In these cases, the macrocycle with the highest stability constant for copper was found to be quite ineffective in enhancing the excretion of copper. This limitation may not apply to some of the compounds recently synthesized which encapsulate the metal ion and form extremely stable complexes with copper.[42]

Rates of Excretion and Metabolism of the Chelating Agent

Most chelating agents are removed from the mammalian body by excretion or altered by metabolic processes. For water-soluble compounds such as EDTA and DTPA, the rate of excretion is fairly rapid for the majority of the substance injected, and this means that the complexation reactions must occur rapidly *in vivo* if the compound is to remove a substantial portion of a toxic metal.[14]

The manner in which these enumerated factors affect the behavior of chelating agents *in vivo* can best be appreciated by a more detailed consideration of recent developments in the search for more effective antagonists for three metal ions, where the operation of these factors can be seen. These toxic ions are cadmium, iron and plutonium.

CHELATING AGENTS FOR CADMIUM MOBILIZATION

The development of chelating agents capable of removing cadmium from its aged intracellular deposits in the kidneys and the liver during the past decade illustrates the manipulation of several of the factors governing such effectiveness other than the stability constant. As with many problems in medicinal chemistry, the starting point was two compounds which had some of the desired properties. Thus, they were capable of removing cadmium from some organs, but generally produced an undesirable redistribution of the cadmium to other organs. These two compounds were 2,3-dimercaptopropanol (BAL) and sodium diethyldithiocarbamate (DDTC) (Fig. 2). From these two compounds, other related struc-

tures have been developed which were more effective and/or less toxic than the original compounds themselves.

This is most clearly seen in a series of dithiocarbamates of increasing effectiveness which have been prepared and characterized in the removal of cadmium *in vivo*. The structures of these are shown in Fig. 3. Data on the relative effectiveness are shown in Table I. As can be seen there has been a clear trend towards the development of compounds which are effective at lower total dosages.[6,31,39] Note that a given dosage is more effective in removing cadmium from the rat than from the mouse.

CHELATING AGENTS FOR IRON MOBILIZATION

Chelating agents for the removal of iron from the human body assume special importance in the treatment of certain disorders of hemoglobin synthesis. The most thoroughly studied of these disorders is thalassemia, a hereditary condition in which the hemoglobin normally produced by the individual is rather ineffective as an oxygen carrier. The usual treatment of thalassemia is by the administration of a series of blood transfusions containing normal hemoglobin from unaffected individuals. Since the half-life of red blood cells is of the order of three to four months, such transfusions must be repeated at intervals. The iron in the transfused blood accumulates as the red blood cells age and are destroyed; ultimately a patient receiving such a treatment will die from chronic iron intoxication. The most obvious way to prevent this is via the administration of an iron chelating agent which will remove the iron at the same rate at which it accumulates from the transfusions. The iron-specific chelating deferrioxamine (Fig. 2), which is a siderophore (naturally occurring iron binding agent) synthesized by a microorganism to obtain iron from iron-poor environments, has been used in clinically effective procedures for prolonging the lives of such individuals. These procedures involve the repeated subcutaneous administration of deferrioxamine at a dosage that achieves a state in which the rate of iron accumulation is greatly reduced. The procedures are quite cumbersome, and it is accepted that an orally administered chelating agent would lead to much better patient compliance.[23–25]

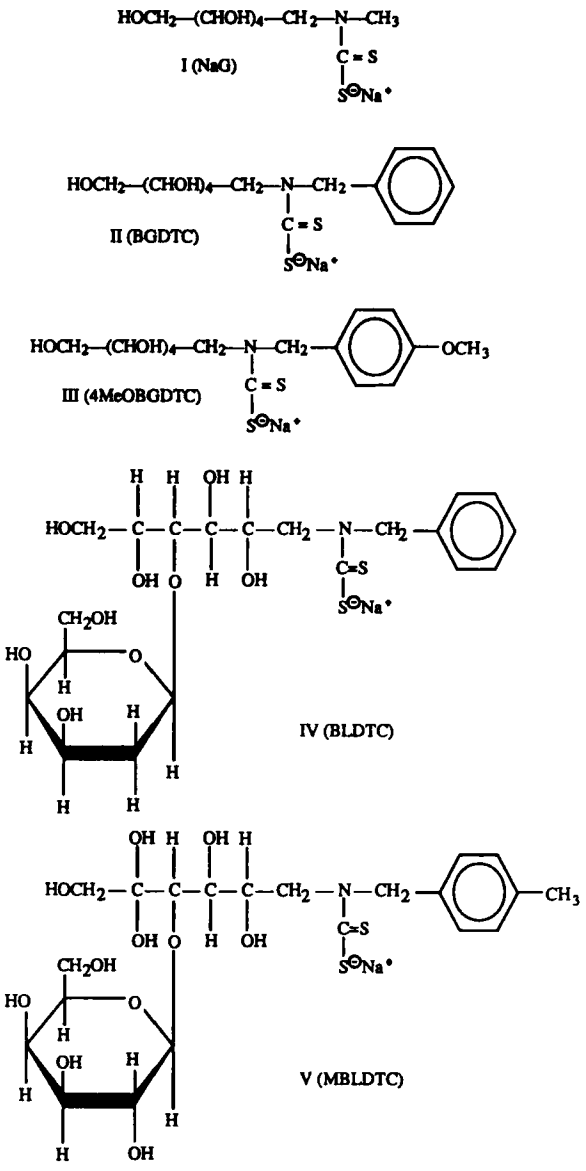


FIGURE 3 Structures of dithiocarbamates of increasing effectiveness (in the series from compound I to compound V) in the removal of aged cadmium deposits from the liver in animal models.

TABLE I

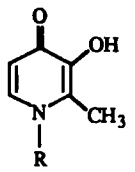
Comparative reduction of renal and kidney levels by dithiocarbamates[6,31,39]

Compound	Species	Dosage	Kidney Cd (% Control)	Liver Cd (% Control)
I (NaG)	mouse	4.4 mmol/kg × 9	46	97
II (BGDTC)	rat	0.4 mmol/kg × 7	52	28
II (BGDTC)	mouse	0.4 mmol/kg × 7	99	96
II (BGDTC)	mouse	1.0 mmol/kg × 5	57	74
III (MeOBGDTC)	mouse	1.0 mmol/kg × 5	19	39
III (MeOBGDTC)	mouse	0.4 mmol/kg × 5	68	75
IV (BGDTC)	mouse	0.4 mmol/kg × 5	39	38
V (MeBLDTC)	mouse	0.4 mmol/kg × 5	39	20

The Roman numerals used to designate these compounds are the same as those used in Fig. 3, where the structures of these compounds may be found. Note that it is easier to remove cadmium from the rat than from the mouse and also that the fraction of cadmium remaining after treatment is dependent upon the dosage of chelating agent used.

The search for compounds which are superior iron mobilizing agents, especially when given orally, has been quite intense during the last fifteen years.[43] The structures of the naturally occurring, iron-binding siderophores have played an important role in the development of new chelating agents to remove iron from iron-overloaded individuals.[23-26,44-46] The work of Hider, Kontoghiorghes and their collaborators had led to the development of 3-hydroxypyridin-4-ones as *orally* administered chelating agents to enhance the mobilization of iron in individuals with transfusional iron-overload.[7,10] The basic structure of these compounds, currently among the most promising of the numerous iron chelating agents developed over the past fifteen years, is shown in Fig. 4.

A study using a series of 3-hydroxypyridin-4-ones has been reported in which the manipulation of chelating agent polarity was examined. In this case, a compound of optimal effectiveness is found (Fig. 4) with an intermediate value of the partition coefficient.[47,48] Related studies demonstrated that the use of analogous compounds with greater values of the stability constant for the iron complex yields a more effective compound for the mobilization of iron.[7,10] Hider and his co-workers demonstrated that the access of the chelating agent to the iron of ferritin was dependent upon the size and polarity of the chelating agent, as this iron is encapsulated



R = CH_3-, CH_3CH_2- etc.

Order of effectiveness in releasing iron from hepatocytes in culture [57]:

$CH_3<CH_2CH_3<(CH_2)_2CH_3>CH(CH_3)_2>(CH_2)_3CH_3>(CH_2)_4CH_3$

FIGURE 4 Structure of the 3-hydroxypyridin-4-ones. The sequence of effectiveness given at the bottom of the figure is consistent with an optimum activity for an R group of intermediate hydrophobicity.

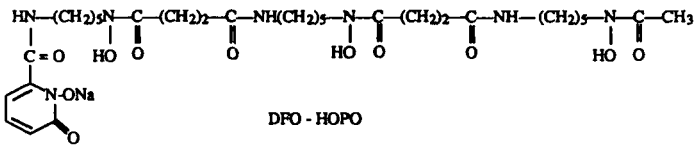
within a protein core with pores whose size limits the size of a chelate molecule which can gain access to the iron within the protein core.[10] One of the results of this size limitation is that the chelating agents with the highest stability constants are not necessarily the most effective in removing iron from such sites. This is consistent with earlier observations that the ability of a chelating agent to mobilize iron *in vivo* can be significantly enhanced in the presence of certain small molecules.[49] The current studies on the use of oral 3-hydroxypyridin-4-ones to mobilize iron in thalassemia patients with high iron burdens is of special promise as a treatment which may be significantly superior to that currently in use.[48,50]

CHELATING AGENTS FOR PLUTONIUM MOBILIZATION

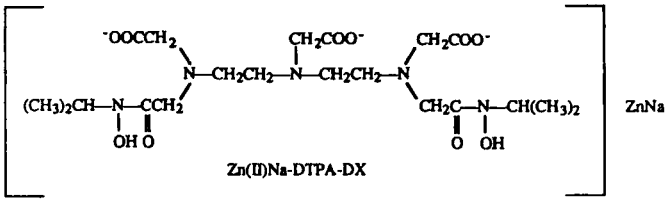
The widespread usage of plutonium has made the toxicology of this transuranium element important. Earlier studies had shown, first, that EDTA could be used to mobilize freshly injected plutonium(IV), and then, later, that DTPA (Fig. 2) was the most effective of previously known chelating agents for the removal of plutonium after exposure.[51,52] It was realized that DTPA had some serious shortcomings: it was not very selective; it could not pass

through cellular membranes to mobilize intracellular deposits of plutonium; and it acted very slowly. Attempts to utilize more hydrophobic derivatives of DTPA were only slightly more successful.[29,30] The problem was then taken up by Raymond and his coworkers who formulated a different approach to this problem via the design of chelating agents which would coordinate to all eight of the coordination positions of the Pu^{4+} ion in a much more selective manner.[53]

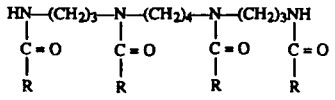
The studies by Raymond and his collaborators during the last decade have been directed toward the design of chelating agents capable of mobilizing plutonium (present as Pu^{4+}) from the mammalian body by utilizing those structural features needed to prepare chelating agents which would possess a degree of specificity for the actinides.[53] The development of the newer chelating agents for plutonium illustrates these design methods, which should be applicable to analogous situations with other toxic metal ions. Plutonium(IV) is a larger ion than iron(III) and can accommodate eight donor atoms. Chelating agents with seven, eight or more donor atoms were prepared by two routes: (1) via modification of known chelating agents and (2) via synthesis of derivatives in which catechol and hydroxypyridinone groups were positioned at appropriate sites on a polyamine chain to achieve eight-fold coordination with Pu^{4+}. Deferrioxamine (Fig. 2), an iron chelating agent with six donor atoms, was modified to give a new chelating agent with eight donor atoms, DFO-HOPO[27] (Fig. 5) and DTPA (Fig. 2) was modified to replace some of the carboxylate groups with hydroxamic acid groups in Zn(II)NaDTPA-DX[26] (Fig. 5). The second route is illustrated by the compounds LICAM-C,[54] LICAM-S[55] and LIHOPO[27] shown in Fig. 5. DFO-HOPO enhances the excretion of intravenously injected plutonium from the rat when it is administered intraperitoneally at a dosage of only 3 μmol/kg, and is more effective than either Zn(II)NaDTPA-DX or DTPA for this purpose.[28] LIHOPO was found to be somewhat superior to DFO-HOPO in mobilizing plutonium. All of these compounds, except Zn(II)NaDTPA-DX (given as the zinc complex), were found to be superior to DTPA (given as its calcium complex) in the mobilization of plutonium *in vivo*.[56]



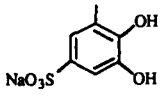
DFO - HOPO



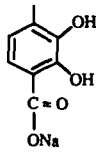
Zn(II)Na-DTPA-DX



3,4,3 LICAM(S), R =



3,4,3 LICAM(C), R =



3,4,3 LIHOPO, R =

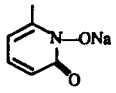


FIGURE 5 Structures of newer compounds effective in the mobilization of plutonium.

CONCLUSION

The approaches taken in the development of more effective chelating agents for the *in vivo* mobilization of cadmium, iron, and plutonium differ significantly. In the cadmium study, a clue was furnished by the ability of sodium diethyldithiocarbamate to act as an antagonist. In subsequent studies structural features were modified to alter the ability of the dithiocarbamates to pass through cellular membranes, but no effort was made to prepare compounds with larger effective stability constants. The compounds currently most effective for cadmium mobilization in animal models are only bidentate chelating agents, so compounds of higher denticity may well replace these. In the development of orally effective chelating agents for iron, the naturally occurring iron chelating agents (siderophores) played a key role in suggesting the types of chelating functions which were most promising, with the development centering on simple molecules which show the desired properties. Studies of various 3-hydroxypyridin-4-ones to determine which one had the optimal balance of hydrophobic/hydrophilic properties and the development of analogs with higher stability constants both played an important role.[7,10] With iron we again see a situation in which a compound which is only a bidentate chelating agent in clinical trials. Here it competes effectively against multidentate compounds (at present) because it is easily prepared and its modest toxicity allows it to be administered orally at a sufficiently high dosage. In the case of plutonium the development of rather specific chelating agents with very high stability constants for plutonium and the manipulation of such structures to obtain compounds which are more effective and less toxic have led to new compounds which are unambiguously more effective than DTPA, the current standard for clinical applications.[52] The chelating agents described here have been tested primarily in animal models, except for the iron chelating agents, one of which has been tested extensively in the clinic.[50] The patterns used to develop such compounds illustrate the main factors which must be manipulated to obtain chelating agents of enhanced effectiveness; it seems very likely that they can also be used to develop more effective chelating agents for the mobilization of many other toxic metals from the mammalian body.

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