Interactions between drugs and chemicals in industrial societies.
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CHELATING AGENTS - NEW PERSPECTIVES

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The most important property of chelating agents when we think of them as "drugs modifying environmental toxicity" is their ability "to remove toxic metals from the body and to prevent, or at least reduce, the risk of acute or long term injury." It is in this field that for many years chelation therapy has played its narrowly defined but very important role. Recently several other uses of chelating agents in medicine have been proposed.

A short review of some of the fundamentals which led to the design of the agents currently in clinical use also shows us the prerequisites that have to be fullfilled for the development of new and better drugs and how difficult they are to meet.

What is a chelating agent? The greek word "chele" means crab claw and from this the term chelate is derived. In this sense a chelating agent is a substance which holds a metal with two (or more) "claws" or putting it in a more scientific way: a substance which is able to donate more than one electron pair to a metal so that the metal then forms part of one or more heterocyclic rings. A metal thus chelated no longer exhibits the characteristic chemical and biological reactions of the free metal ion. It reacts according to the properties of its partner the chelating agent. There are - at first sight - only few general reactions which determine the possibility that a chelating agent may mobilize a toxic metal:

1. Ligand exchange: The concentration of free heavy metal ions in the body is extremely small, therefore most metal ions will be bound to endogenous ligands, anions such as phosphate or natural chelating agents such as amino acids, proteins etc. Metal mobilization, therefore, will always involve ligand exchange

- either direct: $AM + L \rightleftarrows A + ML$ (1a)
- or after dissociation: $AM + L \rightleftarrows A + M + L \rightleftarrows A + ML$ (1b)
- or via a ternary complex: $AM + L \rightleftarrows AML \rightleftarrows A + ML$ (1c)

2. Metal exchange: Since the chelating agent will normally not react exclusively with the toxic metal in question but will also possess an affinity for endogenous metals a metal exchange will occur simultaneously with the ligand exchange:

$$LM' + M \rightleftarrows LM + M' \qquad (2)$$

Most of the endogenous metals, however, can be neglected in this respect either because of their extremely low concentration and/or of the high stability of their complexes with endogenous ligands or because they do not form stable chelates, like Mg^{++} or the alkali metals. The only metal which is of importance in

this respect is Ca^{++} which has a concentration of ca 10^{-3}M in blood plasma. Thus, only this metal and the competition of protons have to be considered in order to define the so called effective (or conditional) stability constant

$$E = \frac{K_{ML} \cdot D_L}{\alpha_L + (Ca^{2+}) \; K_{CaL}} \qquad (3)$$

as a first indicator of the possibility that a particular chelating agent will mobilize a given metal.

In equation (3) K_{ML} and K_{CaL} are the stability constants of the 1:1 metal or Ca - chelate; the concentration of (Ca) can be assumed to be 10^{-3}M; and α_L takes into account the competition of protons for any given pH value. The equation is of course only valid if the dosage D_L of the therapeutic chelating agent by far exceeds the concentration of the metal to be removed (1).

The conditional stability constant E is of course a simplifying formulation. For example it does not take into account the numerous endogenous ligands which compete with the chelate for the toxic metal, and other models have been developed, for example the computer simulation model of the "plasma mobilizing index" (PMI) which is defined as "the factor by which the size of the low molecular weight fraction of the target metal in biofluids is increased by the administration of the chelating agent" (2). Since this model takes into account thousands of complexing reactions it might be expected to be a better indicator for predicting potentially useful chelating agents.

TABLE I

EFFICACY OF CHELATING AGENTS

1. Based on the stability constants of the Cd complex

Predicted	CDTA > DTPA > EDTA
Found	DTPA > EDTA > CDTA

2. Based on the plasma mobilizing index

Predicted	BAL > DMPS > DTPA > EDTA
Found	DTPA > EDTA > DMPS > BAL

A comparison of experimental data with the data calculated or computed using the models described, however, shows that neither of them is able to predict correctly the relative effectiveness of chelating agents (Table I). The reason for this discrepancy is due not only to oversimplification in both models but also to the fact that they do not consider the biochemical and biological behaviour of both metal and chelating agent within the body, e.g. if the distri-

bution space of metal and ligand is not the same ligand exchange (1a - e) will be impaired. And even if both are in the same compartment the dissociation of the metal from its natural ligand may involve a kinetically slow step. In this case the rate at which the exchange reaction occurs can be slower than the excretion and/or catabolism of the chelating agent, and, therefore, no matter how high the effective stability constant may be, mobilization cannot take place.

These few considerations already indicate that the development of effective new chelators is a difficult task and presupposes a profound knowledge of the chemical and biological properties of toxic metals and chelators. Moreover, we must recognize that therapeutic chelating agents always will represent compromises as the requirements for an ideal chelator are, probably always, mutually exclusive.

TABLE II
THE IDEAL CHELATING AGENT

1.	Selectivity for toxic metal
2.	High affinity " " "
3.	No interference with essential metals
4.	Sharing compartment with toxic metal
5.	Non toxic
6.	Resistant to metabolic degradation
7.	Quickly excreted
8.	Conveniently (i.e. orally) administered
9.	Cheap

For instance a powerful drug competing effectively against natural internal ligands must possess several very strong electron donor sites. These groups will tend to make the compound polar, i.e. very often anionic. Therefore, the molecules will not pass readily through biological membranes which means that 1.) they will be poorly absorbed by the intestine (e.g. only about 5% of orally administered EDTA and DTPA are absorbed) and 2.) that they are confined to the extracellular space and thus cannot come into direct contact with an intracellularly deposited toxic metal. Thus in Table II property 2 will in most cases exclude property 4 and/or 8.

Let us now consider the chelators already in therapeutic use and ask whether improvements are really needed:

BAL (British Anti-Lewisite, dimercapto-propanol) developed more than 40 years ago and in clinical use for about 20 years is still the chelator of choice in many metal poisonings e.g. Pb, Cd, Hg, in spite of its many adverse side effects.

Most of these probably originate from the binding of essential metals or of biochemically important SH groups inside the cell, since BAL as a lipophilic compound can traverse the cell membrane. On the other hand this property is probably also responsible for its therapeutic efficacy especially in cases in which the toxic metal has already moved into the cell.

DMPS (Unithiol, dimercaptopropane sulphonate) was developed to replace BAL. It possesses an ionized side group which makes it water-soluble and far less toxic. It has similar chelating properties to BAL and is very effective in removing Hg from the mammalian body but since it is confined to the extracellular space it is not able to displace BAL in all respects.

The polyaminopolycarbonic acids: EDTA has been tested in almost every kind of metal poisoning but does not have enough selectivity to compete well enough with the many complexing molecules in a biological environment. In one instance, however, as the main antidote for lead poisoning, it can be called the drug of choice.

DTPA, the higher homologue of EDTA, shows higher affinity towards many metals than the latter. Especially in the decorporation of radionuclides DTPA has proven highly superior to EDTA. Since it also binds Ca^{++} very avidly DTPA is employed usually as the Na_3Ca-salt in order to prevent toxicity due to the calciprivic effect. The few toxic side effects of Ca-DTPA are due mostly to the depletion of trace metals. They can be avoided by replacing the Ca-salt by Zn-DTPA which is almost equally effective (3,4). All polyaminopolycarbonic acids have one severe drawback: As very polar molecules they are not able to cross the cell membrane and are, therefore, poorly absorbed from the intestine. For the same reason they loose much of their effectiveness as soon as the metals to be removed have passed into the intracellular space. Moreover, they are very rapidly excreted.

DFOA (desferrioxamine B) is by far the most selective of all therapeutic chelating agents: the binding of Fe is many orders of magnitude greater than of other essential metals like Cu, Zn or Mn. There are moreover almost no adverse side effects even after prolonged administration. However, it has a very short half life in plasma and it is rapidly degraded. Therefore, it has to be administered by infusion.

D-PA and TRIEN (D-penicillamine, triethylendiamine) PA is one of the few chelating agents which can be given orally because it is quite well absorbed, 30-40%, from the intestine. If taken as D-PA the substance is relatively nontoxic and has found wide application e.g. in rheumatic arthritis, in Wilsons disease and as a metal mobilizing agent in poisoning with lead, Hg, and Au. Nevertheless in some cases after chronic treatment adverse side effects develop.

For patients with Wilsons disease the less toxic chelator TRIEN has been developed and can be taken instead of D-PA.

This survey has shown that of the very few chelating agents which are currently in clinical use not one is really satisfactory. Even so during the last 10 years almost no new agent has been adopted for the treatment of metal intoxication in human beings. So the question arises whether there is a need for new drugs in this field. The clinical need to treat the toxic effects of metal ions arises relatively seldom. In addition, many of the conditions for which chelation therapy is required are uncommon disorders for which drug research and development is not economically viable. So the lack of interest by the pharmaceutical industry seems understandable. However, apart from the pollution of many industrial areas with heavy metals like Cd, Pb or Hg and the possible danger of radionuclide contamination from nuclear plants or warfare, it may be that there are many more diseases or even fatalities which have their origin in metal accumulation than we currently recognize. For example Alzheimers disease shows many similarities to the encephalopathy caused by aluminium overload. Considerations of this kind and the detection of a number of new possibilities for chelation therapy have kept alive the scientific interest in chelation therapy.

Research in metal mobilization has concentrated mainly in three directions:

1. Better utilization of the agents presently in use e.g. by development of better treatment schedules.
2. Modification of the known agents to enable them to penetrate cell membranes (i.e. make them less polar).
3. Development of new drugs with higher affinity or even specificity for the particular metals.

Using the example of two metals, namely plutonium and cadmium, the possibilities and difficulties of such research will be discussed.

PLUTONIUM

Relatively few people have needed to receive chelating agents for Pu-decorporation. But in view of its industrial importance and high radiotoxicity it is one of the best investigated metals, and much research effort has been directed at finding means of removing Pu from the mammalian body. Until now, Ca-DTPA has been considered as the antidote of choice. It is, however, far from being an ideal drug, firstly because its efficacy in mobilizing insoluble Pu-compounds e.g. PuO_2 is extremely small and secondly the fraction of Pu removable by DTPA decreases rapidly once the radionuclide has been deposited in its target organs, liver and skeleton. There is, however, a small amount of Pu which can be removed even several months after incorporation of the radionuclide. This presumably is the extracellular fraction which is always in equilibrium with the

much greater intracellular one. Its removal will result in some of the intracellular Pu leaching back into plasma a process which at late times after incorporation becomes the rate limiting step for metal mobilization but nevertheless leads to some success in long term chelation therapy (5). The disadvantages of Ca-DTPA namely its poor efficacy for treatment begun late after exposure, or from the treatment of contamination with insoluble Pu-compounds plus the necessity of injecting the substance because of its poor absorption have provoked many investigations with the aim of improved treatment.

Development of improved methods for using the existing drug i.e. DTPA

Because DTPA is poorly (ca. 5%) absorbed from the intestine, oral therapy was considered impracticable. However, Taylor and Volf (6) showed that oral administration of Na_3Zn-DTPA can be effective in long term treatment if the dose is high enough (Table III). From this regimen no adverse effects were observed within the

TABLE III

RETENTION OF ^{239}Pu IN RAT ORGANS AFTER 28 DAYS

% of untreated controls. Chelating agents were administered 3 times per week for 3 weeks starting 4 days after i.v. injection of ^{239}Pu-citrate.

Chelating Agent	Total Dose (μmol/kg)	^{239}Pu Retained Sceleton	Liver	Kidneys
Ca-DTPA	270 s.c.	57.3	29.3	44.8
Zn-DTPA	9000 p.o. (∿300 absorbe)	59.9	27.1	45.9

(Calculated from (6))

4 weeks of treatment. If this lack of toxicity can be corroborated by further studies oral treatment could be introduced as a much more convinient and safer alternative to intravenous injections.

Search for more lipophilic substitutes for DTPA

Many efforts have been made to develop lipophilic derivatives of DTPA in order to enable it to permeate the cell membrane and thus more easily remove Pu from its intracellular binding sites. But most substances thus constructed were either extremely toxic or ineffective. The most recent attempt was that of Bulman (7) who introduced lipophilic moieties with slightly polar functions into DTPA. Of the many substances thus designed only one, Puchel, was interesting. It is more

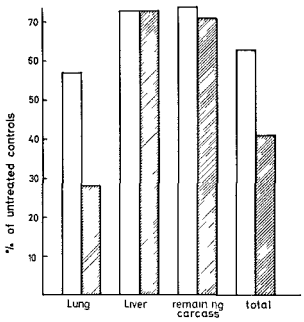

Fig. 1. The effect of Puchel (hatched areas) or Ca-DTPA (open areas) administered as an aerosol 24 hours after Pu on Pu-retention 8 days after incubation of Pu-nitrate. Puchel 5.7 mg kg^{-2}, Ca-DTPA 5.3 mg kg^{-1}. (Calculated from (8)).

effective than DTPA at removing Pu from the lungs of rats (Fig. 1), (8) and from the liver of Syrian hamsters (7) though not from the liver of Chinese hamsters or rats (9). The efficiency of Puchel however, never markedly exceeded that of DTPA. This had been already predicted by the computer simulation model mentioned above (10). Unfortunately this substance turned out to be too toxic so that further investigations were discontinued. High toxicity has been reported for all lipophilic chelating agents and seems to be due, at least in part, to the binding of intracellular essential trace metals and/or to the binding to proteins (especially enzymes).

Metal specific substances

To avoid the problems discussed above the development of compounds with high selectivity for the target metal - in this case Pu - would be desirable.

To meet this necessity a different class of compounds has been designed. This was based on the fact that in mammals Pu IV is associated with the Fe III transport and storage systems and therefore Fe-chelating substances should also bind Pu. In fact it had been shown some time before that DFOA was able to chelate Pu although because of its metabolism its decorporating ability is rather restricted (11). One of the most stable complexes which Fe III forms is that with enterobactin and, therefore,compounds containing similar binding groups together with a steric structure which met the coordination needs of Pu were constructed. A series of substances were synthesised the most promising of which were polycatechoylamide ligands based on terephthalic acid. One substance LICAM(C) proved to be more effective than DTPA in removing Pu from its binding protein in plasma, transferrin, in vitro (12). In vivo it was able to reduce Pu retention in the

TABLE IV

EFFECT OF CHELATING AGENTS ON THE RETENTION OF ^{238}Pu IN SOME ORGANS OF THE RAT. % of controls. Chelate dose: 30 µmoles per i.v. injection. Early treatment 1 hour, delayed treatment days 1-4, sacrifice day 7 after ^{238}Pu i.v.

		Early	Delayed
Skeleton	DTPA	65	61
	LICAM(C)	28	68
Liver	DTPA	26	17
	LICAM(C)	29	76
Kidneys	DTPA	67	84
	LICAM(C)	879	950

(calculated from (13))

skeleton considerably more than DTPA even at much lower doses (13) but as Table IV shows this occurred only with early treatment. With inhaled Pu (LICAM(C) is even less effective than DTPA in reducing the metal concentration in all organs. Another disadvantage of LICAM(C) derivatives is the enhancement of the Pu-burden in the kidneys of some experimental animals (e.g. Table IV). This could only partly be suppressed by the simultaneous administration of Ca-DTPA (13).

In this short overview I could present only 2 examples of the many attempts which have been made to find a chelator with better mobilizing efficiency than DTPA. Until now success has been marginal. This is in part due to the incompatibility of the properties an ideal chelator should possess, but in part also to the metabolic behaviour of the chelating agents. One of the possible ways to overcome these difficulties could be the development of synergistic chelation therapy combining chelating agents of different biological properties which complement each other.

CADMIUM

Research efforts in chelation therapy for Cd-poisoning have always been numerous although neither acute nor chronic Cd-poisoning are very common. As with Pu, the design of specific agents for Cd has been tried but also in this case with little success (14, 15).

The metal has been selected here not to report on new developments but because Cd is one of the metals which show most clearly how much a successful chelation therapy depends on a knowledge of the metabolic behaviour of both the metal and

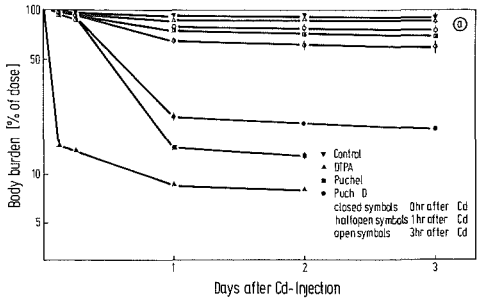

Fig. 2. Cd body burden of control animals and animals injected 0.1 or 3 hr after Cd with 0.1 mmol/kg of chelating agent. Geometric $\overline{X}$±SE (6 animals per group (16)).

the chelate. For example Cd-DTPA has a high effective stability constant but while it is very effective at removing Cd from the bloodstream it becomes virtually ineffective as early as one hour after Cd intake because of the extremely rapid uptake of the metal into the target organs where the hydrophilic DTPA molecule cannot follow (Fig. 2) (16). Together, with the rapid uptake, there is also a very fast binding of Cd to special intracellular proteins, the metallothioneins. This prevents the metal from diffusing back into the blood stream and so, even with prolonged treatment DTPA is not able to cause a substantial reduction of the Cd body burden at later times.

The rapid Cd clearance from the bloodstream makes it understandable that for delayed treatment only lipophilic substances, such as Puchel and BAL are able to cause decorporation. A comparison of these shows that the less efficient

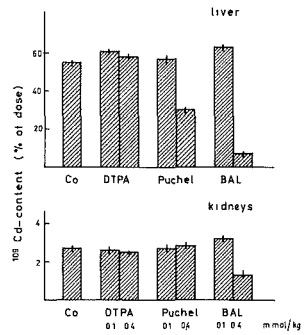

Fig. 3. ^{109}Cd-content in liver and kidneys 17 days after i.v. injection of 3,0 µmol/kg Cd. Chelate treatment started 3 days after Cd and was given 5 times a week for 2 weeks i.p.: means of 6 animals ± SE.

Puchel is unable to remove any Cd from the kidney (Fig. 3). The reason becomes clear if one considers the Cd-distribution in the cytosol of a rat which was treated with Puchel one hour after Cd injection (Fig. 4). The agent removes all

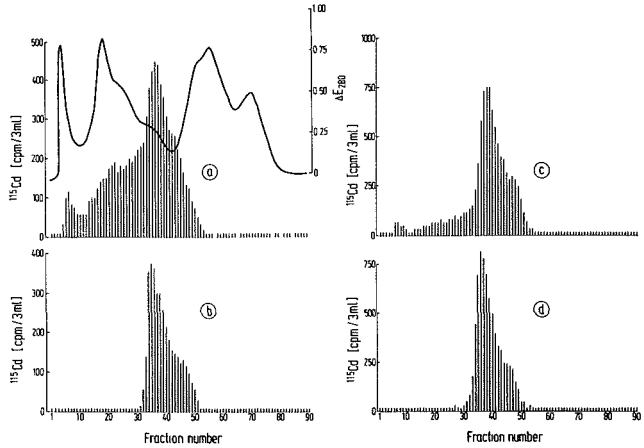

Fig. 4. Influence of Puchel on the distribution of cadmium in liver cytosol (Gel filtration on a Sephacryl S-200 column, 2.5 x 56 cm). (a) Cd and protein distribution 1 hr after Cd. (b) Cd distribution 24 hr after Puchel which was injected 1 hr after Cd. (c) Cd distribution 3 hr after Cd. (d) Cd distribution 24 hr after Puchel which was given 3 hr after Cd. (In experiment c a different Cd solution was injected which contained more ^{115m}Cd but the same amount of total Cd)(16).

the Cd from the high molecular weight proteins, to which in the liver always some of the metal is bound, but none from metallothionein. Since in the kidney all the Cd is bound to metallothionein Puchel does not influence the kidney burden. However, BAL obviously is able to compete successfully with this protein for the metal. Calculations using the computer simulation model of May and Williams (2) indicate that the chelating agents DMPS and dimercaptosuccinic acid (DMSA) which have structures very similar to BAL, should be similarly effective mobilisers of Cd from plasma proteins (17). In agreement with this DMPS was equally effective as BAL at removing Cd from metallothionein in a cell free system (18). The reported inefficiency of DMPS in rats when given some time after Cd (16) can be explained by the polarity of the chelate which prevents it from permeating into the cell. In experiments with Cd-laden cells in vitro, however, DMPS was almost as effective as in the cellfree system in contrast to DTPA which is confined to the extracellular space (Fig. 5) (18). These results indicate that the distribution of DMPS in a compartment different from Cd cannot be the only reason for its limited efficacy in vivo. A possible

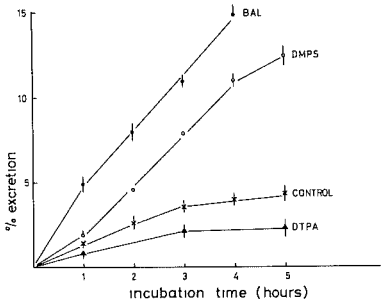

Fig. 5. Release of ^{109}Cd (% of uptake at zero time) from CHO cells under the influence of chelating agents (0.3 mM) Means of 6 experiments with 3 samples each ± SE. The cells were labelled with ^{109}Cd by incubation for 18 hours with $^{109}CdCl_2$ in vitro (Data from (17)).

explanation may be the rate at which the ligand exchange Cd metallothionein → Cd DMPS occurs. If this is slower than the rate at which DMPS (biological half life 20 min) is excreted from the body mobilization must be very low no matter how tenaciously the metal may be bound.

The investigations in Cd mobilization during the last few years have not produced an ideal, nor even a moderately satisfactory, chelating agent. However, it has been shown that a combination of in vivo and in vitro experimental work together with theoretical considerations leads to a better understanding of the biological behaviour of metal and chelating agent which then can be the foundation for the design of more effective agents.

Conclusion

In this paper I have tried to outline briefly the actual situation of chelation therapy for the treatment of metal intoxication, and to indicate the developments which are at present under way.

On one hand it has been shown that changes in the therapeutic schedule can lead to more convenient and safer treatment. The possibilities for optimization are certainly not yet completely explored. With regard to the design of more potent drugs one must admit that the success has been very limited. But we think that progress may be possible if the chemical design is combined with a more profound knowledge of the mechanisms which govern the biological behaviour of the metal and the chelate, as has been pointed out for Cd.

In recent years chelating agents have been used more and more in conditions other than metal poisoning. Antiviral, antimicrobial and anticancerogenic

properties have been explored, copper chelates (19) were found to be effective as antiarthritic drugs etc. This will no doubt intensify research in the field of chelation therapy because the application of such substances in such a wide range of diseases will call for a sounder knowledge of how they influence the biological equilibrium e.g. metal ion distribution, metalloenzyme activity etc. This in turn might then fertilize research in metal mobilizing agents and lead to faster progress than in the last 10 years.

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Discussion - Chelating agents: new perspectives.

A.L. de Weck

There are a number of new calcium chelators that are fluorescent and are used to study intracellular calcium. These compounds are esters and as such penetrate into the cell where they are split by esterases. Do you know whether any of them has been used in metal poisoning?

F. Planas-Bohne

No, I do not, but they would probably act also as zinc chelators.

G.J. Mulder

Are multiple doses of these agents always more efficient than single daily doses?

F. Planas-Bohne

Yes, but the problem of side effects should be taken into account. For instance, if approved, zinc DTPA could be given in multiple daily injections but if calcium DTPA is given more than once daily, toxicity arises out of removal of zinc and manganese.

G.L. Plaa

Is the toxicity of these new chelators similar to that of EDTA? And, if one administers a chelate of plutonium when renal excretion is impaired does dissociation of the metal occur, with the result of plutonium toxicity?

F. Planas-Bohne

DTPA is only a higher homologue of EDTA and its toxicity is similar. For a long time, hydropic degeneration of the kidneys was thought to be the most important side effect of these chelators, but now increasing attention is paid to the interference on DNA synthesis which is due to the removal of zinc and manganese, and that affects the intestine and the bone marrow and the kidney as well. Concerning the second question, the main toxic effects of plutonium are due to radiation and, therefore, if it is kept in the body this toxicity is not modified by it

being chelated or not. What could change, of course, is the organ toxicity.

R. Lauwerys

I believe that some time ago it was suggested that oral treatment with calcium chelating agents may be dangerous in the sense that calcium chelation may modify the permeability of the intestinal mucosa facilitating the absorption of substances that normally do not enter the body, and that could provoke immunological reactions.

F. Planas-Bohne

That is right. With some chelators, severe impairment of the intestinal mucosa, that is somehow similar to radiation damage, can be produced.

M.M. Reidenberg

You mentioned criteria to define an ideal chelating agent. Among them, which one do you value most?

F. Planas-Bohne

Specificity. One of the least toxic and most beneficial chelating agent currently in use is deferoxamine, because it is so specific for iron that it almost binds no other metals, and this spares it from many side effects.

A.L. de Weck

Do you have any comments about the elimination of cesium?

F. Planas-Bohne

Cesium cannot be eliminated from the body by chelation therapy because it does not have the necessary affinity for chelators. However, its excretion, as that of thallium, can be accelerated by the administration of ferric ferrocyanide ("Prussian blue").

E.E. Ohnhaus

What is the elimination half-life of chelate DPTA?

F. Planas-Bohne

It is about 20 minutes, and approximately 95% of the drug is excreted by the renal route.

L.F. Prescott

Are some of these chelates excreted into the bile when the molecular weight of the metal is high?

F. Planas-Bohne

The route of excretion depends on the nature of the chelating agent and does not seem to be influenced by the bound metal. Thus, DPTA is excreted into the urine, whereas Puchel, which is not so different in structure, is 80-90% excreted into the bile.