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EDTA Chelation Effects on Urinary Losses of Cadmium, Calcium, Chromium, Cobalt, Copper, Lead, Magnesium, and Zinc

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ABSTRACT

The efficacy of a chelating agent in binding a given metal in a biological system depends on the binding constants of the chelator for the particular metals in the system, the concentration of the metals, and the presence and concentrations of other ligands competing for the metals in question. In this study, we make a comparison of the in vitro binding constants for the chelator, ethylenediaminetetraacetic acid, with the quantitative urinary excretion of the metals measured before and after EDTA infusion in 16 patients. There were significant increases in lead, zinc, cadmium, and calcium, and these increases roughly corresponded to the expected relative increases predicted by the EDTA–metal-binding constants as measured in vitro. There were no significant increases in urinary cobalt, chromium, or copper as a result of EDTA infusion. The actual increase in cobalt could be entirely attributed to the cobalt content of the cyanocobalamin that was added to the infusion. Although copper did increase in the post-EDTA specimens, the increase was not statistically significant. In the case of magnesium, there was a net retention of approximately 85% following chelation. These data demonstrate that EDTA

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chelation therapy results in significantly increased urinary losses of lead, zinc, cadmium, and calcium following EDTA chelation therapy. There were no significant changes in cobalt, chromium, or copper and a retention of magnesium. These effects are likely to have significant effects on nutrient concentrations and interactions and partially explain the clinical improvements seen in patients undergoing EDTA chelation therapy.

Index Entries: Chelation therapy; cadmium; chromium; cobalt; EDTA; iron; lead; magnesium; zinc.

INTRODUCTION

The efficacy of a chelating agent in binding a given metal in a biological system depends on the binding constants of the chelator for the particular metals in the system, the concentration of the metals, and the presence and concentrations of other ligands competing for the metals in question. The interaction of the numerous ligands and their concentrations and binding properties based on their environments may alter the clinical outcomes in patients treated with chelation therapy. Ethylenediaminetetraacetic acid (EDTA) is used therapeutically to remove undesirable elements such as lead and cadmium. This agent also simultaneously removes substantial quantities of the essential metals such as zinc, manganese, and iron *(1)*. The latter effects can have undesirable clinical consequences, especially in patients who are deficient or marginally deficient in these elements before starting chelation treatments. It appears likely that deficiencies of trace elements could be induced in some patients during the course of a series of chelation therapy sessions. For example, young females and children are often borderline or overtly iron deficient. If such a patient needed to undergo EDTA chelation therapy for lead intoxication, a worsening of the deficiency or actual anemia could be induced as a result of the treatment. Symptoms of zinc deficiency (i.e., scaling rash, poor appetite, and suboptimal growth) could be induced in an infant being treated for lead poisoning. Because many adults are thought to have low zinc nutriture *(2)*, EDTA-induced zinc deficiency leading to rash, diminished senses of smell or taste, and even reduced immune function could be adverse outcomes of EDTA treatment.

The binding constants for EDTA and various metals have been measured in vitro *(3,4)*. In vitro binding constants have been used to predict possible deficiencies that can be expected to occur in patients treated with EDTA chelation therapy for heavy metal intoxication and other conditions. A hierarchy for the relative binding affinities for metals is $Cr^{2+} > Fe^{3+} > Cu^{2+} > Pb^{2+} > Zn^{2+} > Cd^{2+} > Co^{2+} > Fe^{2+} > Mn^{2+} > Ca^{2+} > Mg^{2+}$ *(3,4)*. This hierarchy has been used by practitioners to predict which elements are more likely to be bound and excreted during EDTA therapy. A possible problem with this predictive analysis is that the binding constants are measured at specific pH's from 1 to 10 representing the minimum pH at which each metal

forms a metal–ion complex with EDTA. From a medical viewpoint, the relative constants should be measured under physiological conditions because EDTA binds metals exclusively in the serum *(5,6)*. In addition, competing ligands in biological systems could alter prediction of EDTA–metal interactions.

In this study, we measured urinary metal excretion before and after intravenous infusions of EDTA in an attempt to reveal if metals with large binding constants with EDTA in vitro are, in fact, excreted at significantly higher levels than those with smaller binding constants. In particular, we wanted to determine whether the biochemically important metals such as chromium, zinc, cobalt, and copper are bound and excreted at levels predicted by the theoretical data. In addition, we also measured urinary excretion of the toxic metals, cadmium, and lead, before and after an infusion of EDTA in a cohort of patients not known to have a definite source of exposure to these metals.

MATERIALS AND METHODS

The subject population consisted of two groups of subjects ranging in age from 51 to 77 yr. Most of these patients were on a monthly or bimonthly chelation treatment schedule. The first group consisted of nine patients who received their very first or second EDTA infusion during the study (new patients). The second group was seven patients who had undergone from 18 to 78 EDTA infusions over as much as a 4-yr period prior to the study (maintenance patients). The purpose of analyzing "new patients" versus "maintenance patients" was to determine whether there might be a variation in urinary metal excretion based on the total number of EDTA treatments given. Study was approved by the Clinic Human Studies Review Board, Wisconsin Dells, WI. Study was explained to the subjects and subjects signed an informed consent form. Data are available to the subjects upon request.

Patients were instructed in the accurate collection of 24-h urine specimens to avoid metal contamination *(7)*. Twenty-four-hour urine samples were collected in 4-L sample containers (Fisher Scientific Co., Pittsburgh, PA) 2 d prior to chelation therapy (d 1 and 2), the day of chelation therapy (d 3), and the following day (d 4). Control urine samples were collected on Monday and Tuesday and the chelation urine samples on Wednesday and Thursday. On Wednesday morning of the study week, an intravenous infusion of EDTA mixed in sterile water with 5 g of sodium ascorbate, 2500 units of heparin, 3 mL of 2% procaine, 100 mg pyridoxine HCl, 4 meq KCl, 1 mL of 8.4% sodium bicarbonate, 1000 μg hydroxycobalamin, 1 mL vitamin B complex, and 7 mL magnesium sulfate equivalent to 686 mg of elemental magnesium were given in an arm vein over a 2.5- to 3-h period *(5)*. The dose of EDTA was 3 g in 14 of the patients and 1.2 and 1.5 g in the remaining 2 patients. The dosage variation is predicated on measurement

of kidney function in each patient based on an estimation of creatinine clearance using serum creatinine, an estimate of lean body mass, and the Cockcroft–Gault equation *(8,9)*. Because 95% of a dose of EDTA is cleared by the kidneys and renal toxicity of EDTA is a well-known phenomenon, it is important to maintain the dose of EDTA at no more than 50 mg/kg body weight with normal kidney function and a correspondingly lower dose based on the above estimate of kidney function in patients with renal impairment.

Metal concentrations were determined with a VG PlasmaQuad II+ inductively coupled plasma–mass spectrometer (ICP-MS) (Fisons Instruments, Beverly, MA) with nickel sampler and skimmer cones, a Scott-type double-pass quartz spray chamber maintained at 1°C, and a Meinhard nebulizer. Urinary concentrations of cadmium cobalt, copper, lead, and zinc were determined by operating the instrument in the semiquantitative mode using indium and holmium as the internal standards. Concentrations of calcium and magnesium were measured by atomic absorption spectrometry (AAS) (Model 5000, Perkin-Elmer Corp., Norwalk, CT) using standard laboratory methods for flame atomic absorption and Cr by furnace atomic absorption *(7)*.

A urine control reference material (Seronorm Lot 108, Nycomed AS Diagnostics, Oslo, Norway) was analyzed along with each batch of samples to validate the accuracy and reproducibility of the analyses. Using the ICP-MS in the semiquantitative mode, the difference between the expected and experimental results for cadmium, cobalt, copper, zinc, and lead ranged from + 9.3% to – 3.3%. The control material results for calcium, magnesium, and chromium, run by AAS, ranged from + 5.8% to – 2.7% of the expected values.

Statistical analyses of the data were performed by analysis of variance. Individual mean comparisons were identified with Duncan's Multiple Range Test (SAS Institute, Cary, NC). Values are mean ± SEM unless noted.

RESULTS

Two of the metals found to be significantly increased in the postchelation urine were, in fact, present in the chelation solution as additives and, therefore, the increased excretion could be unrelated to EDTA chelation. Because 2000 µg of cyanocobalamin (4.3% cobalt by weight or 83.4 µg) were added to the chelation solution, the increase in cobalt excretion could be the result of to the added cobalt in the infusate. Another metal added to the chelation solution was magnesium (686 mg of elemental magnesium as magnesium sulfate). Although there is a significant increase in urinary excretion of magnesium over the baseline of d 1 and 2 (Table 1), there is, in fact, a net retention of magnesium after EDTA chelation therapy (d 1 and 2 have been combined because there was no significant difference between them).

Table 1
Effect of Chelation Therapy on Urinary Excretion of Cobalt and Magnesium

	Cobalt (μg)	Magnesium (mg)
Content in infusate	87	686
Days 1 & 2	0.44 ± 0.06	105 ± 19
Day 3	72 ± 4.3	200 ± 36
Day 4	5.5 ± 2.2	92 ± 2.5

Note: Days 1 and 2 are an average of the urinary excretion on the 2 d prior to chelation therapy; d 3 is the day of chelation therapy and d 4 is the following day.

Table 2
Chelation Therapy and Excretion of Zinc, Cadmium, Lead, and Calcium

	Zinc (μg)	Cadmium (ng)	Lead (μg)	Calcium (mg)
Avg excretion (Days 1& 2)	758 ± 105[a]	674.± 141[a]	1.0 ± 0.2[a]	114 ± 23[a]
Day 3	13,690 ± 823[b]	3468 ± 470[b]	38.3 ± 6.5[b]	258 ± 31[b]
Day 4	1,792 ± 208[b]	1922 ± 280[b]	8.7 ± 2.2[b]	110 ± 24[a]

Note: Values are for 16 patients.
[a,b] Values with different superscripts are significantly different at $p < 0.05$.

Table 2 displays the urinary excretion data of the elements found to be increased significantly in the urine following EDTA chelation therapy and which were not present in significant amounts in the chelation solution. The data for d 1 and 2 have again been pooled and averaged because no significant differences in element concentration were found between those days. Data for the new and maintenance patients were also pooled because there were no statistically significant differences in urinary excretion of the metals between the groups. These data verify previous reports that large quantities of zinc are removed by EDTA during the chelation process. Table 2 also reveals that EDTA chelation therapy induces large losses of the toxic metals, cadmium, and lead. Following chelation therapy, levels of cadmium in the urine averaged threefold to fourfold over the prechelation baseline values. Lead was also found increased in every patient and averaged more than 35 times higher on the day of EDTA treatment. As with zinc, the urinary excretion of cadmium and lead was highest in the first 24-h urine specimen following chelation and continued to be elevated the following day (Table 2).

EDTA treatment produced an approximate doubling of calcium in the urine on the day of chelation (Table 2). Urinary calcium returned to baseline on the day following chelation (d 4). Urinary copper excretion of the

Table 3
Effects of Chelation Therapy and Number of Sessions on Urinary Copper Losses

	New Patients[1]	Maintenance Patients[1]	Both Groups
Days 1 & 2	13.7 ± 2.5^{A}	9.8 ± 0.7^{A}	12 ± 1.5
Day 3	21.4 ± 3.0^{B}	12.8 ± 1.7^{A}	17.6 ± 2.1
Day 4	14.8 ± 3.8^{A}	12.3 ± 2.8^{A}	13.7 ± 2.4

[1] New patients are patients that have undergone 1 or 2 sessions of chelation therapy and maintenance patients had undergone 18–79 sessions.

[A,B] Numbers with different capital letter superscripts denote significant differences between the new patients and the maintenance patients.

new patients was significantly higher on the day of chelation than that of the maintenance patients who had been chelated 18 to 78 times (Table 3). When the data for both groups were combined, the increases in copper excretion following chelation therapy were not significant.

DISCUSSION

It is clear from the data that almost all of the cobalt excreted from the body after EDTA chelation therapy can be explained via the inclusion of vitamin B_{12} in the chelation solution and that EDTA does not significantly chelate cobalt in this form in this system. This would be expected because the cobalt in vitamin B_{12} is tightly bound in the tetrapyrrole ring structure of vitamin B_{12}. The small nonsignificant increase in Co in the urine over and above the administration of cobalt in vitamin B_{12} is probably related to the general increase in mineral excretion resulting from the stress of treatment as well as the diuretic effect of the intravenous fluids. Additionally, patients are encouraged to increase their water intake on days of chelation.

Copper is an element with biological significance to the cardiovascular disease patient *(10)*. It is an essential element in its role as a metal activator of monoamine oxidase enzymes, in elastin and cystine synthesis, in tryptophan metabolism, and as a component of cytosolic superoxide dismutase. Its binding constant as the 2+ copper ion with EDTA is of the order of 10^{19} higher than that of lead and cadmium. Therefore, it has been postulated that copper would be an element lost during EDTA chelation therapy. Other authors have measured increases in urinary levels after EDTA infusion *(11,12)*. Our data showed that no significant increases in copper excretion occurred after EDTA infusion despite its very high theoretical binding constant. The most likely explanation for this is that copper is more tightly bound by native ligands. Ninety-five percent of the copper in plasma is bound to ceruloplasmin *(13)*. This protein is a metalloenzyme with three binding sites for copper. The copper atoms are tightly bound

and not in equilibrium with the surrounding aqueous medium. For metalloprotein bound metals, it is very difficult to obtain reliable binding constants for the metal in question. The small increase in urinary copper excretion following EDTA indicates that this chelating agent is unable to effect a dissociation of copper from ceruloplasmin. There was a difference in copper excretion between new patients who had 1 or less prior chelation therapy session and the maintenance patients who had from 18 to 78 EDTA infusions. It is possible that the copper status of the two groups differed at the onset of the study. Others have also reported significantly less copper excretion in patients who had additional chelation treatments. Copper excretion began to fall from 12.3 to 6.72 mg/mg creatinine after the fourteenth EDTA treatment *(1)*. This decrease in copper excretion corresponds closely to the differences we found between our new and maintenance patients. Because of these similar findings, another interpretation of the copper data could be considered. Even though we and Cranton et al. *(1)* found a nonsignificant increase in urinary copper after EDTA, this could be the result of chelation of available copper by EDTA or to a change in copper biology in the system induced by EDTA over time. In the early treatments of Cranton's patients and in our new patients, more copper could have been excreted because the binding constant for 2+ copper is much higher than those for lead and cadmium. After several EDTA treatments, more and more lead and cadmium may have been mobilized and eliminated from the system that may have impacted on the normalization of copper metabolism.

It is known that there is an inverse correlation between copper content of arterial tissue and degree of arteriosclerosis *(10)*. Perhaps with the removal of toxic elements, improvement in magnesium status and the consequent improved biochemical milieu, copper biology is improved and the element is able to re-establish itself in binding sites previously occupied by toxic elements. This is highly speculative but further study of the EDTA–copper excretion interaction is needed.

The small increase in chromium excretion following chelation therapy may be the result of nonspecific increases in metals found after the administration of the chelator and by the chromium present as a contaminant in the solution *(14)*. The first explanation is a result of a nonspecific increase of metal excretion seen after stressful events such as an iv treatment as well as the diuretic effect of the iv fluid.

This finding of a lack of binding and removal of chromium by EDTA is of clinical significance because Cr status may be marginal and chromium plays a role in cardiovascular diseases and improved Cr status leads to a decrease in the signs and symptoms of cardiovascular diseases and diabetes *(15–19)*. The theoretical binding constant curve of Skoog and West *(3)* lists chromium as the most stable complex in the in vitro measured hierarchy with a log K of about 29. However, this binding constant was reported to be measured for the 2+ chromium–EDTA complex. Chromium is present in the 3+ state in biological systems.

In addition to the delayed excretion of lead and cadmium in this cohort of patients and its relationship to renal toxicity of EDTA, our lead and cadmium data may have importance to the clinical picture of the patients in our study. It is well recognized that these metals are toxic to biological systems. The original use of EDTA in clinical practice in the 1950s was for treatment of lead toxicity *(20)*. Only 1 of our 16 patients was known to be exposed to lead via his occupation as a mechanic. Studies have shown that subclinical lead and cadmium accumulation have been associated with cardiovascular disease *(21–23)*.

Half of our patients were diabetic, about one-third were hypertensive, and all but one showed evidence of various forms of arteriosclerosis. Other authors have reported that 80–90% of patients undergoing chelation therapy for such degenerative disease states experience improvements in their symptoms of these diseases and in various clinical and biochemical parameters associated with these conditions *(24–26)*.

Zinc is an important trace element and a participant in numerous biochemical processes. It is an integral component of nearly 300 enzymes. Zinc is necessary for the formation of hydrochloric acid in the stomach via its role as the activator of the enzyme carbonic anhydrase. This role of zinc as well as its presence in the metalloenzymes carboxypeptidase A and B make it especially important to gastrointestinal digestive function. Zinc is also a component in the metalloenzymes superoxide dismutase, alkaline phosphatase, alcohol dehydrogenase, as well as RNA and DNA polymerases.

Because the RDA for zinc is 15 mg for males and 12 mg for females *(27)* and because zinc absorption is thought to be only 20–30% of intake *(28)*, the loss induced by chelation therapy of an average of about 15 mg over the 48 h after treatment could be clinically significant especially in patients undergoing chelation therapy two or more times per week. In addition, a number of studies have indicated that many Americans have marginal zinc intakes. NHANES data reveal that the median zinc intake from food for men and women 20–59 yr old in the United States to be 12.7 and 9.3 mg, respectively *(29,30)*. If we assume a maximum absorption of 30%, the zinc absorbed daily would be 3.8 mg for men and 2.8 mg for women. It is also known that about 1.5 mg of zinc is excreted daily by the pancreas and another 0.5 mg is lost in the urine daily. Our patients excreted in the urine an average of 0.75 mg on d 1 and 2 before chelation. This means that the average male absorbs and retains at most 1.8 mg of zinc daily from the diet, with women averaging 0.8 mg daily. There are also losses via perspiration and storage of zinc in metallothionein in the liver *(31)*. Overall however, if we use the mean of 1.8 mg for men and 0.8 mg for women, we get an average of 1.2 mg daily as an intake for adults to produce a steady state of approximately 2 g present in a 70-kg adult. It is therefore clear that the removal of 15 mg of zinc as a result of one chelation treatment would be in excess of the weekly intake and absorption of 8.4 mg. (1.2 mg/d for 7 d). Two chelation treatments would produce a 28-

Table 4
Excretion Ratios and EDTA Binding Constants for Lead, Zinc, Cadmium, and Calcium

	Lead	Zinc	Cadmium	Calcium
Days 1 & 2	1	1	1	1
Day 3	2169	25	12	3.3
Day 4	155	2.8	6.1	1
Binding Constant, Log K	18.1	17.4	16.9	10.8

Note: Average excretion of d 1 and 2 (before the chelation therapy session) were set as 1 and values for d 3 and 4 (d 3 is the day of chelation therapy and d 4 is the following day) are the relative increases as a result of chelation therapy.

mg loss weekly compared with a gain from diet of only 8.4 mg. Over a series of 30 chelation treatments, a net loss of about 450 mg (15 mg/treatment × 30 treatments) zinc could occur. This could represent 20–25% of the total-body zinc in an average patient.

Considering that the average adult zinc intake is probably marginal especially resulting from the high cereal grain content of the American diet, physicians administering chelation therapy should be diligent in supplementing zinc lost during therapy. Laboratory testing (e.g., a simple test of serum zinc) before commencing chelation therapy could also identify patients with relatively poor zinc nutriture.

In this study, we were able to show that the calcium, zinc, cadmium, and lead increased significantly in the urine after EDTA chelation. The ratios, or percentage increases, of the excretions of these metals when compared to the baseline levels displayed the same hierarchical relationship as the in vitro binding constants of these metals *(3)*. In Table 4 is shown the relative excretion of these metals on d 3 and 4 after chelation as ratios of a set baseline of 1 for the average of d 1 and 2 before chelation. Table 4 also displays the in vitro binding constants for these metals with EDTA. These data demonstrate that, on a relative basis, the increase in urinary lead was greater than that of zinc, which was greater than that of cadmium and which, finally, was greater than that of calcium. The amounts of the elements excreted were not proportional to their theoretical excretion based on their binding constants. For example, there was a 2169-fold rise in lead after chelation compared to a 25-fold increase for zinc, even though their binding constants differ by less than an order of magnitude. The actual difference is almost two orders of magnitude. Obviously, factors other than binding constants would be involved in the chelation of the various metals. The in vitro binding constant for zinc is 0.5 units higher than that for cadmium, whereas the percentage increase for zinc was about double the

increase for cadmium. When lead and cadmium are compared, it is clear that even though their binding constants are only different by one order of magnitude, the rise over baseline for lead is over two orders of magnitude higher than that for cadmium.

The deviations from in vitro expectations results in part from the relative amounts of cadmium and lead available for binding in serum. Cadmium is bound by metallothionein, a native ligand that binds both zinc and cadmium, and acts as a route of detoxification for cadmium and other toxic elements *(32)*. In addition, body burdens of lead are probably higher in the general population than they are for cadmium.

Zinc is under physiological control as an essential mineral. It is carried in plasma by various proteins and EDTA may not be capable of removing zinc from all of these ligands. Nevertheless, the amount of zinc that is bound and excreted from the body by EDTA is substantial and of clinical significance.

Calcium is also under physiological control and calcium losses increased more than two-fold following chelation therapy, far lower on a percentage basis than the levels seen for lead, cadmium, and zinc. This finding is expected based on its far smaller binding constant in vitro and binding of calcium by native ligands such as albumin and globulins. About 60% of serum calcium is present in ionic free form or bound to anions and, therefore, chelatable by EDTA *(33)*.

Of possible interest is the relative rates of the return of the physiologically essential elements, calcium and zinc, to baseline (calcium) or near baseline (zinc) by d 4 as compared with the toxic elements, lead, and cadmium. For these two elements, especially lead, there is still substantial urinary excretion between 24 and 48 h after EDTA administration. Because the half-life of intravenously administered EDTA is only about 45 min *(34)*, this continued spillage of heavy elements indicates their temporary residence in the kidneys after binding in the serum. Whether they are bound to EDTA or are removed by other ligands while in the kidneys is a topic of interest to the study of the dynamics of metal binding. The answer to questions in this area has clinical relevance in view of the known renal toxicity of EDTA. It is known that EDTA chelation therapy of severely lead poisoned patients was found to cause a lead nephrosis when patients so treated died and were autopsied *(35,36)*. The patients in those studies had been subjected to numerous, frequent, and, sometimes, large doses of EDTA. Lead and other toxic metals accumulated in the kidney tissue and resulted in renal shutdown.

The use of EDTA chelation therapy for the treatment of degenerative diseases has been criticized by physicians not experienced in its use for such conditions. The criticism has generally centered around lack of published evidence for reduction in arteriosclerotic narrowing in arterial systems in patients so treated. Although there are a number of studies revealing objective evidence of reduction of plaque and improvement in cerebral blood flow and in a number of parameters associated with vascu-

lar disease *(37–45)*, the underlying mechanism whereby chelation therapy accomplishes these improvements is still being debated. Mechanisms of action proposed have included removal of toxic metals, improvement in calcium metabolism via a parathyroid hormone effect, actual reduction in plaque calcium with consequent plaque reduction, reduction in platelet aggregation, improvement in blood lipid levels, and reduction in free-radical-related oxidative damage *(46–49)*.

Magnesium sulfate is added to the chelation cocktail for three reasons by practitioners using EDTA chelation in the treatment of degenerative diseases. When $MgSO_4$ is added to the solution containing calcium disodium EDTA, it displaces the calcium ions from the EDTA-binding sites, yielding magnesium disodium EDTA. This complex produces much less burning at the site of intravenous administration. The magnesium also acts as a vasodilating agent thereby decreasing the concentration at the site of infusion and reducing pain and burning. The third reason for adding magnesium to the chelation solution is for its therapeutic properties. There is extensive literature *(50–58)* correlating low magnesium levels in various tissue compartments with the risks of hypertension and diabetes. Therapeutic administration of magnesium has been shown to be efficatious in hypertension, atrial fibrillation, and reduction of mortality in acute myocardial infarction in the coronary care unit *(59–61)*. A problem in assessing the need for supplementing magnesium in the clinical setting has been lack of reliable laboratory tests to diagnose magnesium status. Serum magnesium is not diagnostically useful except in extreme cases. One study *(62)* recommended immediate iv administration for patients with acute myocardial infarction without thrombolytic therapy. Magnesium supplementation was recommended to begin as early as possible following the infarct for maximal effects.

Syndrome X described by Reaven *(63)* includes magnesium deficiency along with blood fat abnormalities, hypertension, and blood glucose dysregulation as the constellation of biochemical and clinical abnormalities leading to premature cardiovascular disease.

Our study showed that a combination of toxic metal removal and systemic retention of the administered magnesium occurs following a single treatment with magnesium EDTA. The concept of a "push–pull" mechanism of therapeutic action of chelating agents-[i.e., "pushing in" an essential element and simultaneous "pulling out" of toxic elements has been proposed by Chevion *(64)*]. In his work with zinc desferoxamine (DFO) in ischemia reperfusion experiments, he was able to reduce free-radical generation following reperfusion of cat retina and isolated rat heart after induction of ischemia. He theorized that the desferrioxamine pulled out free-radical-generating transition metals, namely iron, whereas the zinc delivered as the zinc–DFO complex pushed out other free-radical-generating transition metals by competing for their binding sites. Zinc has also been shown by other workers to act as a free-radical quencher in its own right as an ion *(65)*. His concept and experiment involved control of tran-

sition-metal-generated free-radical formation following reperfusion rather than consideration or discussion of the effects of toxic metals in the causation of free-radical-mediated cellular injury in chronic disease states. Other workers have shown that administration of EDTA during ischemia dramatically reduces free-radical-induced reperfusion injury in experimental myocardial infarction in the pig *(66)*. The authors postulated that EDTA binding of calcium was the basis of the dampening of free-radical generation and subsequent reduction reperfusion injury. That study made no particular mention of chelation of iron by EDTA, but recent studies of the relationship of iron overload to coronary heart disease and myocardial infarction might suggest that iron chelation was also a factor in reducing the reperfusion injury.

In summary, the increased losses of cadmium, lead, and calcium and the increased retention of magnesium help explain the beneficial effects of chelation therapy. The lack of increases of chromium and copper are also important because of the essential roles of these metals and also the fact that normal dietary intakes of these are often suboptimal. The increased losses of zinc document that zinc nutriture must be monitored to prevent zinc deficiency.

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