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# PROTOCOL
# for the safe and effective administration of CHELATION THERAPY

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# *The Protocol for the Safe and Effective Administration of EDTA and Other Chelating Agents for Vascular Disease, Degenerative Disease, and Metal Toxicity*

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## FOREWORD

This protocol is a new work through compilation of data derived from numerous sources. A protocol was originally produced in 1973 through

the efforts of the incorporators of the American Association of Medical Preventics (AAMPS) through the pen of Gary Gordon. It was revised and updated in 1989 by Elmer Cranton and published in the Journal of Advancement in Medicine.

This new 1996 protocol, has been authored by Ted Rozema with input and suggestions from many practioners. I owe a great debt of thanks to Michael Schachter who has been "on my case" to get this work finished. It must be considered "a work in progress" as new information on the effects of EDTA and other chelation agents is produced every year. I trust the information contained herein is as accurate as possible, realizing that the translation of scientific data to meaningful biological effect sometimes produces interesting and unexpected results.

This protocol should enable an intelligent and careful practitioner to safely administer the chelating agents described in these pages. The goal of treatment is restoration of health to those afflicted with degenerative conditions based on mineral toxicity. No practitioner should attempt to use this protocol as the only source of meaningful information. Utilization of the bibliography is emphasized and encouraged. Clinical use of these compounds should only be done after thorough grounding in these principles through attendance at training workshops conducted by the American College for Advancement in Medicine (ACAM) and/or the Great Lakes College of Clinical Medicine (GLCCM).

After study of the procedures outlined herein, demonstration of knowledge may be documented by taking a written examination offered by the American Board of Chelation Therapy (ABCT) or the International Board of Chelation Therapy (IBCT). After appropriate clinical use of these compounds has been accomplished, passing an oral examination with chart review is required as outlined by ABCT and IBCT, in order to qualify as a Diplomat in chelation therapy. ABCT and IBCT both have accepted this protocol as the basis for certifying physicians as Diplomate in chelation therapy. For further information contact ACAM (714-583-7666—800-532-3688), GLCCM (800-286-6013) or ABCT / IBCT (800-386-6013).

May you receive as much pleasure helping your patients be restored to good health as they receive from once again being restored to good health.

Ted Rozema M.D., FAAFP

## I. OVERVIEW OF EDTA CHELATION THERAPY

The term "chelation" is derived from the Greek word "chele" which refers to the claw of a crab or a lobster, and implies the firm pincer-like binding action of an organic compound to a metal ion (cation). It may further be defined as "the molecular incorporation of a mineral ion or cation into a heterocyclic ring structure by an organic molecule, known as a chelating agent". A more complete definition is "an equilibrium reaction between a metal ion and a complexing agent characterized by the formation of more than one bond between the cation and the complexing agent resulting in a ring structure incorporating the metal ion". Chelated compounds are omnipresent in nature. For example, chlorophyll is a chelate of magnesium and hemoglobin is a chelate of iron. The most widely accepted use of chelation therapy in medicine is for the removal of toxic minerals, such as lead, from the body. A more controversial, but clinically useful indication for chelation therapy, and more specifically disodium EDTA chelation therapy, is the treatment of all forms of atherosclerotic diseases, including, coronary, cerebral, and peripheral arteriovascular disease as well as other degenerative conditions. Much of this protocol is focused on this treatment.

EDTA is an abbreviation for the compound Ethylene Diamine Tetraacetic Acid. The form approved by the FDA for the treatment of lead poisoning is calcium EDTA. (1,2,3,4,5) The form of EDTA used to treat atherosclerotic conditions, on the other hand, is disodium EDTA, for reasons that will become apparent later. (6,7,8,9) EDTA chelation therapy is part of a comprehensive therapeutic program for the treatment of atherosclerosis. Other components include nutritional and dietary recommendations, oral nutritional supplements, an exercise program, a stress management program, if necessary, and medication, if necessary. On rare occasions, surgical intervention may be beneficial, but the vast majority of patients can be effectively managed without surgical intervention.

EDTA chelation therapy for vascular disease is administered as an intravenous infusion, consisting of EDTA, and other components to be discussed, diluted in a sterile water solution, adjusted for proper osmolarity. This infusion is given over a 1.5 to 3 hour period, usually in a physician's office. The frequency of treatment is usually once or twice a week. For symptomatic patients, a series of thirty or more infusions may be indicated.

## II. PROTOCOL OBJECTIVES

The purpose of this treatment protocol is to assure maximum clinical efficacy and patient safety in the use of Ethylene Diamine Tetraacetic Acid, (otherwise known as EDTA or disodium Edetate or the disodium salt of Ethylene Diamine Tetraacetic Acid), and other chelating agents in a comprehensive therapeutic approach to the treatment of arteriosclerosis, atherosclerosis, and other disorders in which chelating agents have been shown to be beneficial. A knowledge of biochemistry, pharmacology and the basic clinical sciences is assumed. This protocol is also intended to establish international standards for the safest and most effective use of chelation therapy in a comprehensive multi-modality treatment program. In this protocol the use of the term EDTA will refer to the disodium form of the molecule as distinguished from the calcium disodium or magnesium disodium forms. Where appropriate, these other forms of EDTA will be identified as such.

Written and oral examinations are offered periodically by the American and International Boards of Chelation Therapy (ABCT-IBCT), to assure that sufficient comprehension of this discipline has been attained.

Physicians who pass these examinations (after taking an approved chelation therapy workshop course), follow the guidelines of this protocol and meet certain other requirements involving clinical experience with EDTA chelation therapy may be awarded Diplomate Status from ABCT-IBCT. Physicians should adhere to the standards outlined in this protocol and its appendices. This protocol cannot, however, substitute for the physician's best judgment. There are obviously significant cost benefit implications which may impact on the recommendations contained in this protocol.

Training courses, training manuals, books, articles, references and educational audio cassette tapes on chelation therapy are available from the American College for Advancement in Medicine (ACAM) and the Great Lakes College of Clinical Medicine (GLCCM).

## III. CHEMISTRY AND PHARMACOLOGICAL ACTIONS OF EDTA

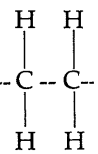
### A. Chemical Structure

The EDTA discussed in this protocol is the disodium salt of EDTA. It occurs as a white crystalline powder, soluble in water, slightly soluble in alcohol and mildly acidic. (10)

Structure:

EDTA = Ethylene Diamine Tetraacetic Acid

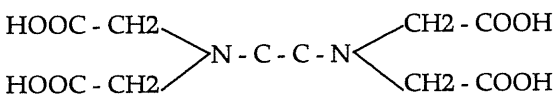
**Ethylene** =



**Diamine** = the two nitrogens or amine groups attached to the carbons of the ethylene group

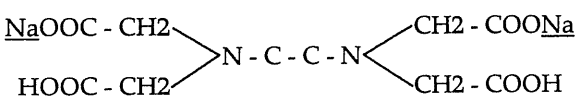
-- N -- C -- C -- N --

**Tetraacetic acid** = the four acetic acid groups, two attached to each nitrogen




**ETHYLENE DIAMINE TETRA ACETIC ACID (EDTA)**

Disodium EDTA




EDTA is a Polyamine carboxylic acid

The structural formula of EDTA bound to a calcium ion is depicted in Figure 1. EDTA has six pairs of unshared electrons that it can

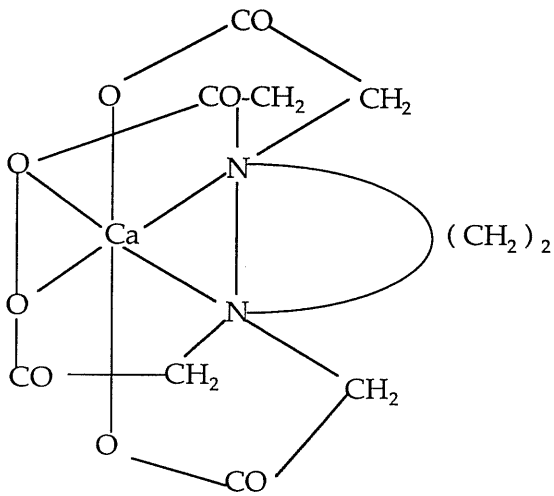



**FIGURE 1**

**Picture of EDTA complexed with calcium iron.**

donate to a cation. They are found on the two amino groups plus four oxygen radicals from the carboxy groups. These six atoms, which are known as the "dentates or teeth" of the EDTA molecule, bind the calcium ion.

Definition: *Chelation is the incorporation of a metal into a heterocyclic ring structure.* (11)

Chelating agents control metal ions by blocking the reactive sites of the ions and preventing them from normal activity. This phenemon is in effect as long as EDTA is present in the body. They also reduce total body content of troublesome ions, which is a lasting effect.

A number of factors are involved in determining the structure of the EDTA complex with metal ions:

The first factor is pH. As pH increases, EDTA chelates become more stable so that the molecule releases its metal ion less easily. Thus, in vitro, EDTA complexes metal ions most efficiently in basic solutions. In vivo, however, this is not an important consideration as physiologic buffers maintain a tight pH balance. (11)

A second factor is the binding strength of EDTA to various cations. Any mineral cation which complexes with a chelating agent has a certain affinity to that chelating agent. Given equal concentrations of two cations in solution with a chelating agent, the cation with the

greater affinity will be complexed to a greater extent with the chelating agent.

The affinity of a mineral cation to a chelating agent can be expressed mathematically by an equilibrium or stability constant ($K_s$). The higher the constant, the greater the affinity. (11)

The stability constant is related to the equilibrium reaction between the chelating agent and the cation to form the chelated complex as follows:

$$M^{n+} + Y^{-4} \quad MY^{(n-4)+}$$

Where $M^{n+}$ is the cation, $Y^{-4}$ is a chelating agent, such as EDTA, and $MY^{(n-4)+}$ is the chelated mineral complex. The stability constant $K_s$ is equal to the concentration of the chelated complex divided by the product of the concentration of the chelating agent and the concentration of the cation.

$$K_s = \frac{(MY^{(n-4)+})}{(M^{n+})\,(Y^{-4})}$$

The higher the stability constant, the greater the affinity of the mineral to the chelating agent and the more complexed mineral you get. Stability constants are usually expressed as the logarithm or Log K value. (11)

Table 1 is a table of Stability Constants of some of the more impor-

**TABLE 1**

**Stability Constants**

| Metal Cation | Log K | Metal Cation | Log K |
|---|---|---|---|
| $Fe^{+++}$ | 25.1 | $Co^{++}$ | 16.3 |
| $Hg^{++}$ | 21.8 | $Al^{+++}$ | 16.1 |
| $Cu^{++}$ | 18.8 | $Fe^{++}$ | 14.3 |
| $Pb^{++}$ | 18.5 | $Mn^{++}$ | 13.7 |
| $Ni^{++}$ | 18.0 | $Ca^{++}$ | 10.7 |
| $Zn^{++}$ | 16.5 | $Mg^{++}$ | 8.7 |
| $Cd^{++}$ | 16.5 | | |

tant minerals with EDTA. Heavy metals such as iron, copper and lead generally have high affinity for specific chelating agents.

The relative affinity of a particular mineral and the order of relative affinities of minerals to a chelating agent will vary from one chelating agent to another. With regard to EDTA, the alkaline earth metals, like manganese and calcium, are less attracted to the chelate and the monovalent alkali metals, such as potassium and sodium, have the lowest affinity.

A third factor is the relative concentrations of various metals. In considering the hierarchy of the minerals shown in the table above, high concentrations of lower affinity metals can partially displace metals of greater stability, which are present in low concentrations through the principle of simple mass action. (11) For example, although calcium is relatively low in the table, a great deal of it is chelated by EDTA because of its relatively high concentration in the plasma.

A fourth factor affecting the chelation process relates to the difference between reactions in-vitro and in-vivo. The stability constants discussed previously have been determined in-vitro. The behavior of EDTA with minerals in-vivo is determined not only by the stability constants of the various minerals and the concentration of the minerals, but also by competition with endogenous ligands. In the body, one finds numerous naturally occurring ligands which compete with the administered chelate for the mineral in question. Most physiologically active metal ions are tightly bound to proteins, metallo-enzymes or to transport proteins such as transferrin and ceruloplasmin. Therefore, these metals are not significantly displaced by EDTA. The main action is on the unbound ionic metals which are in small concentrations as compared to the total amount of minerals in the body. (11)

## B. Pharmacological Actions

Because of the presence of high amounts of available ionic calcium, rapid IV infusion of the disodium salt of EDTA may result in hypocalcemic tetany as a result of a relatively high concentration of the ionizable free calcium binding to EDTA. (12,13) SLOW INFUSION, however, (16.6 mg/min or less) generally results in only a slight lowering of serum ionizable calcium ion concentration and avoids hypo-

calcemic reactions. (14) If EDTA is administered as weekly, or twice weekly infusions, over time, (weeks to months), this slight reduction in serum calcium stimulates the production of parathyroid hormone (15,16) (and mobilizes calcium from vessel walls and other tissue stores. (9) This calcium EDTA complex is excreted in the urine. Theoretically, three grams removes 324 mg of calcium if administered intravenously. (17) This is only about twice the normal amount excreted daily and cannot account for all of the biological effects observed clinically with EDTA infusions in human subjects.

Another important aspect of disodium EDTA infusions relates to its effect on bone metabolism. As just mentioned, EDTA, by reducing serum ionizable calcium, causes a rapid rise in parathyroid hormone (18,19,20,21) which theoretically assists in restoring serum calcium to normal levels when the EDTA infusion is stopped. This action may also initially stimulate osteoclastic activity for approximately 21 days. However, it also stimulates osteoblastic activity which results in increased bone formation for 120 days, thus providing a theoretical net increase of calcium uptake for 100+ days following each infusion. Consequently, disodium EDTA chelation therapy should improve bone density. (22,23)

When using the calcium salt of EDTA, there is no change in serum calcium titers and calcium balance is unaffected. (24) Salt complexes other than sodium, such as magnesium EDTA, may also be employed to have an effect on undesired minerals as well as changing calcium balance. These salts also remove metals other than calcium the same as disodium EDTA does, necessitating mineral replacement for those physiologically essential minerals as they are lost. (25,26)

Keeping in mind that the only direct effect of EDTA is to bind minerals, the consequences of this action are many, resulting in multiple indirect effects. For example, EDTA decreases free radical pathology by binding free catalytic copper and iron ions which explosively accelerate lipid peroxidation. (27,28,29,30)

In addition, EDTA transiently reduces platelet aggregability, (31, 32) inhibits antibody formation, (33) lowers blood cholesterol, (34,35, 36) stimulates C-AMP, (37) reduces oxidized metals to their more efficient states which therefore restores enzymes to full activity, and affects many other cellular and physiochemical activities. However, not enough research has been done with EDTA to clearly define all of it's indirect modes of action.

The injectable form of disodium EDTA which is commercially avail-

able contains approximately 5.4 milliequivalents or 114 milligrams of sodium per gram of EDTA. The pH is adjusted with NaOH to between 6.5–7.5.

## IV. ABSORPTION AND METABOLISM OF EDTA

The disodium EDTA molecule is not metabolized in the body or reabsorbed by renal tubules to any significant degree. It thus passes very rapidly into the urine carrying its' metallic ion with it. The EDTA molecule leaves the body intact.

In patients with normal renal function, the half life of IV administered EDTA is approximately 45 minutes and therefore normally, within 24 hours, over 90% has been excreted. (38) However, in renal impaired patients, the excretion rate is often much slower due to depressed Glomerular Filtration Rate (GFR). Ionic calcium ($Ca^{++}$) and other metals present in the blood and interstitial fluids are attracted to the EDTA complex and are sequestered by the chelate in an octahedronal configuration.

Only about 5% of an orally administered dose of EDTA is absorbed from the gastrointestinal tract (39) although this may vary with the contents of the digestive tract. The bulk is excreted in the stool, thus this route of administration is much less physiologically effective than the same dose administered intravenously. (40)

Oral EDTA will bind with nutritional trace elements in the gut and may inhibit absorption of essential minerals which could lead to deficiencies depending on the concentrations of trace minerals present. Oral EDTA may also carry toxic metals into the body as it is absorbed, thus possibly negating detoxification effects.

Very little EDTA can be absorbed through the skin. Even after entering the bloodstream, whether by oral or intravenous administration, little gains access to the spinal fluid. (41)

Giving disodium EDTA intramuscularly is contraindicated as it may cause tissue sloughing and marked pain at the site of administration. However, tissue sloughing does not happen using disodium calcium EDTA although it can be painful. This form may be given intramuscularly, usually with procaine to reduce pain on administration.

Therefore the most effective route of administration for most of the currently recognized clinical benefits appears to be intravenous, although this route does carry with it several precautions. Once in the

bloodstream, no matter how administered, EDTA passes through the tissues in the extracellular fluids, but does not enter cellular compartments. (42)

## V. PATIENT SELECTION FOR EDTA CHELATION THERAPY

Many of the patients treated with magnesium disodium EDTA chelation therapy are victims of advanced atherosclerosis (43,44,45) with symptoms of cerebral vascular insufficiency, (46,47,48) coronary artery (43,44,48,49) or peripheral artery disease. (48,49,50,51,52)

It is recommended that these conditions should, whenever possible, be evaluated using some form of non-invasive diagnostic measures to provide a baseline for subsequent evaluation of the patient in order to determine an adequate response to treatment. Benefits from EDTA in the treatment of atherosclerotic occlusive arterial disease are well documented and although large scale double-blind controlled studies are not yet complete, the benefits of EDTA are equally as proven as those from bypass surgery and angioplasty. (53)

Scleroderma and Systemic Sclerosis benefits from intravenous EDTA, although published data are less conclusive. Clinical experience shows that chelation therapy is more effective than any other treatment for scleroderma. (54,55,56,57,58,59,60,61,62,63,64)

Diabetic patients usually demonstrate great improvement after chelation therapy with EDTA as many of their complications are related to insufficiency of the vascular system, especially small vessels not amenable to any other therapy. Frequently, the need for insulin or oral hypoglycemic medications for glucose control can be reduced or eliminated altogether. (65)

Calcinosis Universalis fortunately is not seen commonly, but can be devastating to the patient. Several authors comment about the favorable effects of chelating agents in calcium deposition diseases. (59,64, 66,67) Others find there were no real positive effects using EDTA for this condition. The amount of EDTA used was very small. (68)

Alzheimer's disease will often improve or slow down in its progression following a course of EDTA or deferoxamine chelation therapy. (69)

Collagen vascular diseases—Rheumatoid Arthritis (70) and multiple sclerosis (71) have been anecdotally reported to benefit from EDTA although clinical studies have not been done. When no other treatment offers hope, such patients are sometimes treated with

EDTA chelation therapy after being informed about the claimed experimental status of EDTA for treatment of their condition. EDTA is much less toxic than d-penicillamine, an oral chelator used to treat rheumatoid arthritis and lead intoxication.

Porphyria has been shown to improve greatly with administration of EDTA. There is a great diuresis of zinc and copper with a normalization of excretion of these elements with continued treatments. The improvements seen are postulated to be due to a normalization of several metallo-enzyme systems. (72,73,74,75,76,77,78)

Package insert indications for $Na_2EDTA$ include digitalis toxicity (79,80,81) and hypercalcemia. (13,24) $CaNa_2EDTA$ is to be used for lead intoxication. (82) (Note: EDTA is not to be used alone for acute lead encephalopathy as it will increase brain lead levels if the patient has greater than 80 mcg/Dl.) (83)

Healthy individuals often request chelation therapy to prevent the onset of age associated diseases before symptoms manifest. Treatment of such patients is fully justified as a form of preventive medicine. The amount and type of laboratory testing should be adjusted accordingly, always with patient safety and cost/benefit ratio's in mind.

## VI. CONTRAINDICATIONS, TOXICITY, SIDE EFFECTS AND PRECAUTIONS

### A. Contraindications

There are probably no absolute contraindications to the use of EDTA other than an extremely rare patient with severe, uncontrollable allergy to EDTA, or acute lead encephalopathy. (83) Renal dialysis may also be a relative contraindication although even these patients can be treated if their condition warrants it. (84) All other contraindications are relative to the severity of the disease being treated, and weighed against the risk of complications from EDTA

### B. Toxicity

Reports on the toxicity of EDTA date back to the beginning of its use in lead poisoning. Early investigators found renal irritation, mucocutaneous lesions, glucosuria, and trace elements depletion. (14,26,

85,86) Very rarely there can be a febrile systemic reaction that may occur 4 to 8 hours after infusion of EDTA. This reaction is characterized by a rapid onset of malaise, fatigue, and excessive thirst followed by the sudden appearance of chills and fever. This, in turn, is followed by severe myalgia, frontal headaches, anorexia, occasional nausea and vomiting, and rarely, increased urinary frequency and urgency. (38) Other toxic effects include a histamine-like reaction, with sneezing, nasal congestion and lacrimation. These rare reactions have usually been associated with excessive doses of EDTA and too rapid administration. The physiologic basis for these effects is unclear. These types of reaction are usually not seen if the protocol is followed, but still can occur rarely.

Early dosages were much higher than the 50 mg/kg/day now recommended. Infusion times were shorter than those now utilized in this protocol and the frequency of treatments was greater. (86)

A few deaths were reported in the early literature (87,88,89,90) these have been cited as proof that EDTA chelation therapy is dangerous. (91) However, with care, there should be no fatalities since the LD50 of EDTA is at least 10 to 20 times greater than the presently recommended dosage. (11,92)

### *Possible Toxic Effects*

*1. Nephrotoxicity*

Histologic changes which appear in those cases where the dosages, rate of infusion and/or frequency of treatment were too high, appear to be similar to sucrose vacuolization. (93,94) In 1970, renal tubular cell vacuolization in the outer renal cortex was demonstrated in rats.

It was proposed that part of the chelate might enter the cell via pinocytosis, the process by which minute amounts of liquid are engulfed in the cell membrane surface, which then actively closes and traps the fluid in tiny vesicles, (invagination). (94)

The process of pinocytosis has been accepted as the most likely explanation for renal vacuo-genesis. (95) It is a common physiological process, and is reversible, although some vacuoles have been shown to remain for days following toxic doses. (96) EDTA appears to be cleared from the kidney by glomerular filtration rather than tubular excretion. (97,98)

The consensus is, that although large or too rapidly administered doses of EDTA can be nephrotoxic, (38) EDTA chelation therapy, when administered at the proper rate, dose and frequency is *not*

nephrotoxic. (99,100) If there are signs of nephrotoxicity, (usually from too high a dose—hematuria, proteinuria, polyuria and oliguria), they are usually readily reversible and clear up within a few days after EDTA is discontinued.

Nonetheless, renal function must be carefully assessed before EDTA is administered and periodic creatinine clearance measurements as determined by 24 hour urine samples and/or calculations from serum creatinine (101) (according to the formula of Cockcroft-Gault—see Appendix II), as well as regular urinalyses should be performed during therapy. The amount of EDTA administered should be adjusted to kidney function as determined by creatinine clearance and serum creatinine.

If serum creatinine is normal before therapy and rises into the abnormal range while receiving EDTA or if serum creatinine is abnormal but at an acceptably low level prior to therapy and rises progressively above that pretreatment level, infusions should be temporarily stopped to allow time for kidney function to return to normal or baseline values. This usually occurs within 2 to 4 weeks. Minor transient proteinuria may also occur after EDTA infusion. During the course of EDTA chelation therapy, renal function usually improves compared to pretreatment levels. (100,102,103)

Medications which are routinely administered for the treatment of hypertension and cardiovascular disease have been shown to reduce renal function. NSAIDS and Methyldopa are notorious in this regard. Captopril, and other ACE inhibitors, are a two edged sword. They are indicated for use in diabetic nephropathy in patients with type I insulin-dependent diabetes mellitus and retinopathy, but may produce increases in BUN and creatinine in patients with pre-existing renal disease. If possible, other medications should be substituted which do not adversely affect renal function. (PDR)

In every known case of serious renal toxicity, excessive EDTA was administered without consideration for pre-existing or progressive renal impairment. (86) When proper monitoring and precautions as outlined in this protocol are followed, the incidence of lasting renal impairment from EDTA is less than one in 30,000, even in the treatment of debilitated and elderly patients with moderate pre-existing renal insufficiency. The risk is virtually nil in patients with normal pre-treatment renal function. (104)

An excessive body burden of lead has been reported to increase renal toxicity from EDTA, especially during the initial infusions. Even though EDTA binds avidly with lead, there may be some disassocia-

tion as the lead EDTA passes through the kidney. (105,106,107,108) Lead is known to be nephrotoxic and patients suspected of having significantly elevated body stores of lead may need to have serum creatinines measured before each infusion.

By reducing the frequency and dosage of EDTA infusions and prolonging the duration of the infusions it is possible to lower excessive levels of lead without incurring nephrotoxicity. It is also useful to ensure that the urine is alkaline, as this helps to prevent dissociation of the lead from the EDTA complex during the passage through the kidney tubules. (Note: EDTA is not recommended as a first line drug for use in acute lead induced encephalopathy, see section on BAL.) (83)

*2. Hypocalcemia*

Because of its high affinity for calcium, $MgNa_2EDTA$ or $Na_2EDTA$ can, if infused too rapidly or in excessive doses, cause transient hypocalcemia in animals and man. (13,109) This is not seen with $CaNa_2EDTA$.

Severely hypocalcemic patients may suffer muscle cramps, stridor, diplopia, convulsions, numbness and tingling, positive Trousseau's and/or Chvostek's signs and, rarely, tetany. (11,14,38)

$MgNa_2EDTA$ or $Na_2EDTA$ may cause transient lowering of the seizure threshold in patients with potential seizure disorders, possibly because of a brief drop in plasma calcium. (If this is a first-ever seizure, a thorough neurological workup should be done to rule out other causes of seizures such as an occult intracranial mass.)

A dose-rate of 16.6 mg per minute (utilizing the computed dose amount) infused over an appropriate time span, is unlikely to cause problems of hypocalcemia except in a rare patient with hypoparathyroidism. Clinically symptomatic hypocalcemia can be quickly reversed with intravenous calcium gluconate. (Note: This is seldom necessary unless occult hypoparathyroidism exists-watch patients that have had previous thyroid surgery.)

Unusual sensitivity to EDTA requires an investigation for hypoparathyroidism (IV $Na_2EDTA$ is a recognized test for hypoparathyroidism.) (19,20) The use of Magnesium $Na_2EDTA$ reduces side effects of hypocalcemia and improves patient tolerance.

*3. Allergy*

True allergy to EDTA is rare. Occasional allergic symptoms are most often caused by ingredients other than EDTA which are added to the solution or by a chemical preservative in one of those ingredients.

Even then, allergic reactions are infrequent and usually minor. EDTA normally contains no preservative. Labels should indicate whether chemical preservatives have been added. If an offending substance is present, it may be possible to find the needed ingredient without additives. Otherwise that substance may have to be left out of the final infusion solution.

Other components of the infusion which may cause allergic reactions include lidocaine or procaine. Thiamine, if given intravenously, has been known to cause anaphylactic reactions although this is very rare.

Reactions can usually be prevented during subsequent infusions by substituting ingredients, such as lidocaine for procaine, or by eliminating water-soluble vitamins which contain chemical preservatives.

Since an aggressive oral vitamin and mineral supplementation program is generally prescribed for all patients, both during and after a course of chelation therapy, their administration intravenously during the chelation process is not essential but may be helpful. For patients undergoing EDTA chelation therapy with malabsorption problems or patients who cannot tolerate oral supplements, intravenous or intramuscular nutrients may be essential.

Many, but not all constituents added to the infusion, are available without preservatives. Injectables without preservatives must be used or disposed of soon after a vial or ampoule is opened, to prevent bacterial contamination in the open container.

If it is not possible to identify an offending allergen, the infusion should contain only a minimum of ingredients required for therapeutic benefit. For example, an iso-osmolar carrier such as normal saline or 5% dextrose, containing only Magnesium $Na_2EDTA$ buffered to physiologic Ph with sodium bicarbonate will contain no extraneous chemical allergens, if all products used in the infusion are obtained without preservatives. The other ingredients are useful adjuncts but are not essential for therapy if they are not well tolerated.

The use of magnesium and buffering with bicarbonate both reduce discomfort at the site of infusion and may eliminate the need for an anesthetic such as lidocaine in the infusion.

*4. Thrombophlebitis*

Local irritation at the infusion site may occasionally lead to superficial phlebitis. (93) This uncommon complication can be minimized by adding from 1,000 to 5,000 units of heparin to each infusion. That

small dose will act locally but will not generally cause significant systemic anticoagulation.

Buffering the solution to physiologic pH with bicarbonate will also reduce the incidence of pain and possible phlebitis at the infusion site. Other helpful adjuncts for reducing pain and preventing thrombophlebitis are to use a larger vein, (to achieve more rapid dilution), and reduce the rate of administration.

If a superficial phlebitis should occur, topical moist heat is usually helpful. Analgesics and non-steroidal anti-inflammatory medications may also be used as well as natural anti-inflammatory substances such as proteolytic enzymes or homeopathic remedies. If progression to deep venous thrombosis is suspected, systemic anticoagulation may be indicated. This should rarely be necessary, but patients should be carefully followed to detect signs of progression towards the deep venous system.

Because of the slight possibility of thrombophlebitis, it is less desirable to use leg veins to infuse EDTA if another choice is available. However, when other sites are not readily accessible, the benefit from receiving the infusion of EDTA far exceeds the minimal increased risk associated with less customary infusion sites.

*5. Congestive Heart Failure*

Patients with limited cardiac reserve should be weighed at each visit to detect fluid retention. Diuretics continue to function as usual during EDTA treatment, although an increase in diuretic dose may be necessary at times. Patients on diuretics should be questioned prior to treatments to ensure they have taken this medication prior to treatment. If they have omitted their diuretic, you should give them their dose prior to the EDTA infusion.

The infusion for such patients should contain as little sodium as possible. Glucose in water or sterile water, made iso-osmolar with low-sodium solutes, are preferred to Ringer's lactate, saline and other carrier solutions which contain sodium. (Injectable ascorbate contains 11% sodium by weight.) (110)

The increased fluid load by itself might aggravate heart failure, irrespective of the sodium content. Slowing the infusion to last between 4 to 6 hours and reducing the carrier solution to 250 ml of fluid may be necessary for a precarious patient, with proportionate reductions in total solute content. It is safer to begin therapy with one-fourth of the calculated therapeutic dose of EDTA in 250 ml of fluid in patients

with a recent history of congestive heart failure, slowly increasing the dose and fluid volume once patient tolerance is established.

Acute pulmonary edema, requiring hospitalization has occurred during EDTA infusion in critically ill cardiac patients, even when these precautions were observed. EDTA itself, irrespective of Na and fluid load, can exacerbate marginally controlled congestive heart failure in some patients during the infusion even with no digitalis present. Patients who have gained weight due to water retention between treatments may require IV or PO diuretics before administration of the treatment and need to be followed very carefully.

Since a lowered serum ionizable calcium can reduce the contractility of the heart, transient hypocalcemia caused by EDTA may temporarily exacerbate heart failure necessitating a slower infusion rate. This may even occur 12–24 hours after a treatment. EDTA reduces the effect of digitalis, by lowering plasma calcium. (79,80) Digitalization should be carefully monitored in patients who are dependent on that medication.

*6. Hypoglycemia*

Blood glucose may fall during an infusion of EDTA for many reasons. (10,111) EDTA binds zinc which regulates pancreatic secretion of endogenous insulin. (26,113) Insoluble zinc-insulin complexes retard the systemic absorption of some brands of injectable insulin. This appears to be less of a problem today with the newer engineered insulins such as Humulin, as well as NPH and Lente.

Zinc is also required for renal tubular reabsorption of glucose. EDTA had been reported to trigger hypoglycemic reactions in patients using older types of protamine-zinc insulin. Careful monitoring of blood glucose is necessary when EDTA is administered to diabetic patients on insulin as diabetic patients may frequently require less insulin as treatment progresses. (114)

Hypoglycemia may also be seen as a response to hypocalcemia. (115) Subclinical adrenal insufficiency may be present. Adequate cortisol is required to support glucose levels through stimulation of glucagon and gluconeogenesis in the liver.

Hypoglycemic reactions can often be avoided with adequate caloric intake before and during treatment as well as careful regulation of insulin dosage in diabetic patients. Patients with diabetes often experience great benefit from EDTA and these extra precautions should not discourage the use of chelation therapy in such patients. As the

treatment progresses, control of diabetes often becomes easier, with narrower fluctuations in blood glucose and with less tendency to hyperglycemic or hypoglycemic complications. Diabetic patients should be cautioned to monitor their glucose frequently and adjust their insulin needs accordingly.

All patients should be instructed to eat a full meal before treatments. Patients who are susceptible to hypoglycemic reactions should be instructed to bring fruit or fruit juice to be taken as a snack during the infusion or if symptoms occur. A 50% glucose solution for intravenous administration should be available in the chelation area.

Patients with a family history of diabetes should be carefully monitored during chelation since there exists a chance that EDTA can unmask latent diabetes.

*7. Hormone Effects*

EDTA affects blood levels of various hormones either directly or indirectly. Its direct lowering effect on ionized serum calcium immediately stimulates the parathyroid, causing it to release and secrete parathyroid hormone, resulting in levels as high as double or triple the original concentration. (22,109,116)

In primary hyperparathyroidism, resting PTH levels are elevated above normal, and response to EDTA is exaggerated; in sub-clinical hypoparathyroidism, resting PTH levels may be within the normal range, but EDTA therapy produces low or no response. (117) In subclinical hypoparathyroidism, calcium levels remain suppressed even after twelve hours post-EDTA stimulation. (15,16,20,118)

Intravenous $Na_2EDTA$ suppresses calcitonin secretion within fifteen minutes but no suppression occurs when $MgNa_2EDTA$ is used. (86) Response time in secretion of calcitonin in osteoporotic patients after EDTA appears to be somewhat slower than in age-matched normal control patients, but essentially within the normal range. (119)

EDTA stimulates renin release. (120) Renal vasodilation, increased renal blood flow, renin release, urine flow and urinary sodium excretion after intra-renal arterial infusion of EDTA has been demonstrated in the laboratory. (121) With calcium infusion, the effects were reversed. Theoretically, patients with renal hypertension may need to have renin levels monitored due to the possible effects of elevated renin through the period of chelation therapy.

Research work remains to be done on EDTA's effects on other hormones, particularly T3 or T4 and the hypophyseal hormones.

*8. Fatigue*

Fatigue is seen in a some patients who will complain of feeling "washed out" and having no energy for 24–48 hours or longer after a single treatment. This is most probably due to the need of the body to utilize it's energies for internal detoxification while not having the necessary metabolic energy to do so without causing fatigue.

These effects can be reduced by continuing oral supplementation and administering a few intravenous nutritional infusions of vitamins and minerals without EDTA. The nutritional infusions may be administered several times in a row or alternated with EDTA infusions until the patient regains sufficient intrinsic energy to make the changes required by the EDTA treatments without the patient feeling overly exhausted.

Another approach is to increase the time interval between treatments. In any event, make sure the patient has adequate oral vitamin and mineral intake. Some physicians routinely give nutritional infusions after every four or five EDTA infusions.

Some postulate that fatigue may be a secondary effect of heavy mineral mobilization. However, most patients, while having some toxic metals present, are not sufficiently overloaded for this to be a concern.

*9. Arrhythmias*

Arrhythmias can occur in predisposed individuals due to several mechanisms, which include hypocalcemia, hypomagnesemia, and a lessening of the anti-arrhythmic effects of digoxin. (38) You may wish to administer additional magnesium and possibly calcium if the patient is experiencing increased cardiac irregularity.

Fortunately this is not a common problem, but one with potentially life threatening consequences and one that you must be aware of. Baseline EKG's and interval tracings are advisable in sensitive patients.

Often anti-arrhythmic medication need only be given for a short time as cardiac arrhythmias frequently clear with adequate EDTA chelation therapy.

*10. Intestinal Toxicity*

In a few patients intestinal cramping is a complaint following a chelation treatment. (38)

Since enteropathy has been seen in animals overdosed with EDTA

some physicians postulate that suppressed intestinal villi turnover due to zinc depletion or hypocalcemia might be the cause of the enteropathy. However this is a rare complaint and may simply be coincidental and due to the usual causes seen in routine patient populations.

*11. Rash*

A skin eruption resembling seborrheic dermatitis had previously been reported in patients undergoing chelation. (38) This rash is usually a response to Pyridoxine deficiency and is now infrequently seen due to the administration of vitamin B-6 in the infusion solution and/or orally. (26)

*12. Teratogenesis*

EDTA has caused birth defects in animals experimentally.

Even though this potential for teratogenicity has been partially reversed and/or prevented with zinc supplementation, (122,123) it is recommended that chelation therapy with EDTA not be given to pregnant women or those contemplating pregnancy, unless in the physician's judgment, the benefits outweigh this remote risk which has never been observed or reported in human subjects.

Theoretically, EDTA may exert a negative effect on spermatogenesis due to it's zinc depleting effects, thus possibly affecting male fertility. This should not be a practical problem when zinc is supplemented orally.

*13. Tuberculosis*

Because latent or arrested Tuberculosis may remain in the lungs within calcified foci, the theoretical risk exists of reactivating a dormant infection due to the decalcifying action of EDTA. Therefore a pre-chelation chest x-ray may be warranted to monitor those patients with calcified Ghon's complex or Simon's foci.

At least one instance (out of the over 1 million patients we believe have safely received intravenous chelation therapy) of reactivated tuberculosis has coincided with administration of EDTA, although causality has not been proved. Arrested tuberculosis or a positive tuberculin test are not a contraindication to chelation therapy.

*14. Embolization of Plaque*

Embolization of plaque during EDTA chelation therapy is also only a theoretical risk. There is no "breaking-off" of plaque as emboli, as

may occur during surgical procedures. Embolization from ulcerated plaques most often occurs in patients not taking chelation and may bring them to receive chelation treatments. There is no evidence of embolization increasing during chelation. Usually there is a reduction in this occurrence after a series of EDTA chelation treatments since EDTA's action is to slowly remove only molecular quantities of calcium

## C. Precautionary Measures

*1. Renal Impairment*

The most important relative contraindication to the use of intravenous EDTA is severe renal insufficiency. In the presence of renal impairment, further renal compromise from EDTA can be avoided by adjusting the EDTA dosage after performing a urinalysis and serum creatinine measurement before starting each infusion. (BUN cannot be substituted for creatinine, as creatinine is a much more reliable indicator of renal function. BUN fluctuates more widely with diet, protein intake, cardiac output, and other variables which are not directly related to kidney function.)

A 24 hour urinary creatinine clearance measurement should be obtained or calculated from serum creatinine before beginning EDTA chelation therapy, at the fifth treatment, and at each tenth infusion thereafter if the initial serum creatinine was within normal limits. Creatinine clearance should be monitored more often in patients with diminished renal function, or if they receive EDTA infusions more than twice per week.

As an alternative, creatinine clearance can be computed with the Cockcroft-Gault equation, using serum creatinine, age and lean body weight instead of collecting 24 hour urine specimens. The Cockcroft-Gault computation is now accepted as an alternative to 24 hour urine collection and is probably even more accurate for out-patients as it is more difficult to get accurate control of urine collections for outpatients than for hospitalized patients. (See Appendix II.)

In patients with normal kidney function the recommended dose of intravenous EDTA for safe and optimal benefit is 25 to 50 mg/Kg of lean body weight, up to a maximum of 5 grams. Doses over 3 grams should be individualized and will depend on patient's lean body weight and tolerance as well as the body burden of toxic metals.

When urinary creatinine clearance is less than 100 ml/min, the

dose of EDTA is reduced proportionately. For example: if creatinine clearance is 70 ml/min, the dose of EDTA is 70 percent of the full calculated dose. If the creatinine clearance is 50 ml/min, the dose administered would be 50 percent of the full calculated dose.

Lean body weight for males is computed as 50 Kg plus 2.3 Kg for each inch of height over 5 feet. Lean body weight for females is computed as 45.5 Kg plus 2.3 Kg for every inch of height over 5 feet. Actual weight is used for thin individuals when the patient weighs less than his computed lean body weight.

*a. Mild renal insufficiency:*

This is defined as a loss of up to one-half of normal renal function with a serum creatinine of 1.6 to 2.0 mg/dL. Renal function is normally less in elderly patients, even without specific renal disease. Patients with mild renal insufficiency will usually tolerate chelation without problems.

The dose and rate of infusion and interval between treatments is adjusted based on clinical judgment and frequent creatinine determinations. (See Appendix II.) Further elevations in serum creatinine may call for a smaller dose of EDTA and/or less frequent treatments.

If renal function tests show a consistent tendency to worsen, EDTA infusions should be stopped until tests have returned to base-line values. Creatinine will usually return to baseline (or better) within a few weeks.

It is common for later treatments to be better tolerated. Most patients with mild renal insufficiency experience an improvement in renal function after a course of chelation therapy. (100,103,124,125)

*b. Moderate renal insufficiency:*

This is defined as a loss of between one-half and two-thirds of normal renal function with a serum creatinine of 2.0 to 2.5 mg/dL.

Serum creatinine rises at an accelerating rate with progressive loss of renal function, rising much more rapidly after 50 percent of the glomular filtration rate (GFR) is lost.

Most older patients with moderate renal insufficiency have a vascular component to their renal problem and thus, when treated cautiously with intravenous EDTA will usually show significant, although slow improvement in renal function.

To prevent further renal compromise, it is necessary to monitor

these patients closely with frequent renal function tests using reduced doses of EDTA, (See Appendix II), less frequent treatments, (every one to two weeks), and slower infusions lasting from 4 to 6 hours. Patients with moderate renal impairment should not receive intravenous EDTA more often than once each week and might do better if the EDTA infusions are spaced less frequently. Patients with this amount of renal insufficiency will exhibit varying degrees of responsivity to EDTA.

An occasional patient in this category will show a rapid worsening in renal function following an infusion of EDTA. These patients are not suitable candidates for EDTA chelation therapy unless the condition to be treated justifies the potential risk of further renal damage.

It is not possible to predict in advance which patients will tolerate treatments well and which patients will not. The only way to avoid further renal impairment is by paying careful attention to frequent serum creatinine measurements and computing creatinine clearance. Properly treated, such patients can experience gratifying responses.

*c. Severe renal insufficiency:*

This is defined as loss of two-thirds or more of normal renal function with a serum creatinine of more that 2.5 mg/dL. Patients with severe renal insufficiency should not receive intravenous EDTA except for an otherwise untreatable and life-threatening illness for which, in the physician's judgment, EDTA is the most desirable therapeutic approach. The risk of additional renal impairment must be offset by the potential benefits, taking into consideration the severity or nature of the disease being treated.

Some such patients may benefit from a reduced dose of EDTA administered over 6 or more hours at an interval of 14 or more days between infusions.

With these creatinine levels, it is important to measure or compute a 24 hour urinary creatinine clearance before each infusion and, if considered necessary, during the interval between infusions. (See Appendix II.)

Patients should be informed in advance in writing of the remote possibility of complete renal failure and the subsequent need for prolonged or permanent renal dialysis.

*2. Pregnancy*

*Caution:* because safe use of intravenous EDTA therapy has not been determined in pregnancy, IV EDTA therapy should not be used except for life-threatening disease states such as severe lead toxicity, weighing the potential benefits against the risks. In teratogenic studies in rats, EDTA increased intrauterine death and caused fetal malformations. These deleterious effects of EDTA therapy have been postulated to be related to a dietary zinc deficiency which may possibly be prevented, however, by simultaneous supplements of dietary zinc with the EDTA. (122,123)

Finally, the possible adverse effects of transient induced hypocalcemia and transient decreased availability of other essential minerals, however brief or minute, on the growing fetus, must be considered.

*3. Congestive Heart Failure*

A history of congestive heart failure is not uncommon among chelation patients with ischemic heart disease. Careful control of fluid and electrolyte balance, diuretic therapy, sodium restriction and special care to prevent potassium and magnesium depletion will prevent difficulties in all but the most sensitive of these patients. Unnecessary sodium should be avoided in the infusion. Even though there is a subpopulation of patients with CHF that can be suddenly worsened irrespective of Na and fluids (because of EDTA's lowering of serum ionic calcium resulting in a reduced inotropic effect on the myocardium) (38) most patients with congestive heart failure can be successfully but carefully chelated without complications, with improvement of cardiac status after therapy. (See Appendix VI.)

*4. Liver Disease*

When pretreatment examination reveals significant liver disease, (enzymes or bile greater than 2 times the upper limits), diagnosis and proper treatment of the liver condition would normally become the paramount clinical problem. Significant elevation of liver enzymes or bilirubin, diminished plasma proteins or prolongation of prothrombin time secondary to active liver disease pose relative contraindications to intravenous EDTA. Chelation therapy may still be appropriate when no other treatment is available, particularly for cirrhosis with portal hypertension, and esophageal varicies.

Usually, however, chelation therapy should not be given until the

active liver disease is properly treated and resolved or is stabilized at a clinically acceptable level. There is no evidence that EDTA will worsen a moderate degree of liver impairment.

All patients in this category may warrant more frequent laboratory testing and closer physician observation, nurse monitoring, and auxiliary medical treatment. Lower doses of EDTA should be used until repeat laboratory testing confirms improvement of liver function.

*5. Anticoagulation*

Patients on long-term anticoagulation with warfarin should have prothrombin times monitored frequently during chelation therapy. EDTA, like many other medicines, may alter prothrombin time and require changes in warfarin dosage. While EDTA is not known to add to the risks of warfarin therapy, the complications of long-term anticoagulation are well known and those same complications may occur during chelation therapy. Chelation physicians may reduce the dose of anticoagulant medication while administering EDTA infusions if testing warrants this change. This may not be advisable in patients with a history of recurrent, life-threatening deep venous clotting or embolic complications from a cardiac source with atrial fibrillation.

Heparin, as used in this protocol, should pose no additional risk as the mechanism of action is different from that of coumadin. These compounds are often given together in hospitals while switching from subcutaneous or IV heparin administration to oral coumadin.

Interestingly, there are anecdotal reports that episodes of recurrent thrombophlebitis have reduced or ceased in patients receiving periodic infusions of EDTA. This is apparently a long lasting benefit, (after the anticoagulating effects have ceased). EDTA might exert an additive, but transient, in vivo anticoagulant effect by binding calcium, a necessary element for blood clotting, However, this has never been reported as a problem in clinical practice.

This may be a clinical indication for the anti-platelet activity of low dose oral EDTA which would be far safer than aspirin, now used for this purpose.

*6. Other Clinical Considerations*

*a. Nutritional Supplementation*

Intravenous EDTA can deplete essential nutritional trace elements while it removes unwanted and toxic metals from the body. Zinc is especially susceptible to depletion. Before administering EDTA, trace

element status should be assessed by obtaining a careful dietary history and by testing urine, and/or hair, and/or blood, as appropriate, for adequacy of essential nutrients.

Urine measurements of a spectrum of metallic elements is recommended. This is done to screen for an excess of toxic elements and deficiency or excess of trace elements. Fasting urine specimens are used to measure trace and toxic elements relative to urine creatinine. Creatinine corrects for dilutional variations caused by water intake and output, eliminating the inconvenience, poor patient compliance, and other sources of error involved with 24 hour urine collections.

Reliable information about element excretion levels can be derived if urine specimens are collected immediately before and after an infusion of EDTA and corrected for urine creatinine. This provocative test shows the percent of increase in excretion caused by EDTA.

Hair analysis may be useful as a screening test although it has many limitations and sources of error, and must be interpreted with great care. (126,127,128,129,130) No single type of testing is reliable by itself, to assess the status of the many different trace and toxic elements. Elements vary widely in their respective distributions in organs, body tissues and fluids. The distribution of each element and its movement between body compartments with time after intake is unique. Each element must be evaluated with consideration for its individual characteristics. Several different types of multi-element screening tests on urine and hair are helpful to make a reasonable estimate of body stores.

Chelation patients should routinely take nutritional supplements containing a balance of essential minerals and trace elements with special emphasis on trace elements which are marginal or low. If a patient's nutritional status is unusually poor and if time permits, oral or IV replenishment of deficient nutrients for several weeks before beginning chelation therapy with EDTA is sometimes advisable, especially in patients with congestive heart failure.

EDTA inactivates pyridoxine during chelation therapy. (26) (Supplementing with vitamins containing B6, therefore, is essential. Patients with suspected pyridoxine deficiency should be treated prophylactically both before and during chelation with additional vitamin B6, since research indicates that a vitamin B6 deficiency causes arteriosclerosis. In patients with disorders of methionine metabolism such as homocystenuria, a 100–200 mg daily oral supplement would seem prudent. A peripheral neuropathy, which is generally reversible, has been reported in patients taking doses as low as 200 mg daily. (131)

Chelation patients often have imbalances of calcium metabolism associated with their cardiovascular disease as well as deficiencies of total magnesium stores as measured by hair and element excretion levels. This may be due to long term inadequate oral intake as well as inadequate absorption from the gastrointestinal tract.

There are intellectual differences in the recommendations for calcium and magnesium supplimentation. Since many patients have a generalized magnesium deficiency, some authors recommend a ratio of calcium/magnesium 1:1 to 1:2 although conventional wisdom has been to use calcium/magnesium in a 2:1 ratio. Supplemental calcium with magnesium should be administered to women over age 30 to prevent osteoporosis. Gastric acidity should also be determined (and corrected if deficient) as calcium must be ionized to be absorbed. Studies show that EDTA, when administered according to this protocol, does not cause or aggravate osteoporosis, but actually adds calcium to bone stores, reversing osteoporosis. (23)

Supplemental antioxidants are also synergistic with EDTA including vitamins C, E, beta carotene, selenium, Co-Q-10, and a spectrum of B-complex vitamins.

Supplemental iron should not be given unless laboratory assessment shows a deficiency. Serum ferritin is the single most reliable test for body stores of iron in the absence of inflammatory disease. Transferrin saturation is also highly recommended as false elevations of ferritin are not uncommon. Without these tests, anemia of chronic disease can be mistaken for iron deficiency. When indicated, iron supplementation should be continued only for as long as necessary to correct a deficiency. (132,133,134,135,136)

If iron deficiency persists in spite of therapy, investigation should be done to exclude causes of pathological blood loss such as bowel cancer. Iron is a free-radical catalyst and excesses slow the benefits of chelation therapy by speeding up the development of free-radical related diseases.

A major benefit of chelation is the removal of unwanted accumulations of freely catalytic, unbound iron.

Many chelation patients in the United States are copper deficient as determined by element testing and need more copper than is contained in the average multiple supplement. (137) Copper deficiency can cause insomnia, depression, hypercholesterolemia, anemia, leukopenia, impaired immune function, cardiac arrhythmias and aneurysms. (138,139)

A small percentage of patients have excess copper and should not

receive supplemental copper. Excess copper can also speed up free radical pathology. (27,140,141,142,143,144,145,146,147) Patients with adequate but not excessive copper can still benefit from a multiple supplement containing an RDA amount of copper as insurance against depletion.

## VII. ADMINISTRATION AND DELIVERY OF CHELATION THERAPY

### A. Consent Form

Each chelating physician should retain a representative, signed copy of an acceptable "informed consent" in each patient's file.

Informed consent is a process, not just a document. According to Dr. Fay Rozovsky, informed consent is "[a]uthorization for treatment . . . the culmination of a discussion between a patient and a health care provider, the disclosure of risk and benefit information, the disclosure of reasonable alternative forms of care, and the posing of questions and answers by both the patient and the provider." (148)

Informed consent is also described as the "duty imposed by law on a physician to inform his patient of the nature of the surgery he intends to perform, the probable consequences, risks, and hazards of this procedure, and the benefits that can be anticipated, that a physician who fails in this responsibility and duty has failed to give his patient sufficient information on which to base a consent to any operation or treatment procedures; and that breach of this duty is recognized as tortious misconduct actionable as medical negligence where harm proximately results." (149)

In some states, informed consent is recognized as valid if the consent is either written or verbal. Idaho, for example, does not require that a consent be in written form.

"It is not essential to the validity of any consent for the furnishing of hospital, medical, surgical or dental care, treatment or procedures that the same be in writing or any other form of expression; however when the giving of such consent is recited or documented in writing and expressly authorizes the care, treatment or procedures to be furnished, and when such writing or form has been executed or initialed by a person competent to give such consent . . . such written consent, in the absence of convincing proof that it was secured maliciously or by fraud, is presumed to be valid." (112) Keeping this point in mind, it

is recommended that all physicians include at least the following information in any informed consent they use.

MINIMUM REQUIREMENTS FOR INFORMED CONSENT

1. The nature and purpose of the procedure(s);
2. The likely outcome of the procedure(s);
3. The likely outcome of diagnostic tests;
4. The likely benefits of diagnostic tests performed to determine a patient's illness or injury and the extent of same;
5. An explanation of the known risks and possible complications of the procedure(s);
6. An explanation of any permanent results of the procedure such as an impairment or scar;
7. An explanation of the availability of reasonable alternative procedures;
8. The likely risk and/or complications of such alternatives;
9. The names of the physicians who shall perform the intended procedure(s);
10. An acknowledgment by the patient that disclosure of information has been made and that all questions asked about the procedure(s) have been answered to the patient's satisfaction; and
11. The signature of the patient on the informed consent prior to any treatment given or the signature of a person who has the legal authority to consent on behalf of the patient in such circumstances.

In addition to the minimum requirements listed, we recommend that you consider including the following information that may be of particular concern to a specific patient:

1. Notification of the risk of allergic reaction being triggered by the proposed procedure(s) or treatment; and an explanation of the possible complications that could result from the trigger of such reaction;
2. The means by which risks are likely to occur;
3. The technical aspects by which an injury could occur;
4. The length of recuperation for the proposed treatment or procedure(s); and
5. The impact the proposed treatment and/or procedure is likely to have on the patient's lifestyle.

Please be advised that these requirements are suggested provisions and may not comply with your own state's requirements.

Please see Appendix VII for a sample informed consent.

## B. Clinical Evaluation Before Chelation Therapy

Before beginning a program of intravenous EDTA chelation therapy, a complete medical history should be obtained, a thorough head-to-toe, hands-on, physical examination should be performed and recorded. Relevant past medical records, including written reports of arteriograms and other pertinent vascular studies should be requested, if available. A complete list of current medications including name, strength, and frequency should be recorded. Special note of allergies should be taken.

Notes should also be made about present exercise programs, vitamin and mineral intake as well as tobacco, caffeine and alcohol use. The patient should also be asked about his sleep patterns, the major stressors in his life and how he responds to stressful situations.

As part of the physical examination, special attention should be paid to quality of arterial pulses, presence and quality of arterial bruits, skin temperature of the extremities, hair loss of extremities, dystrophic nails and mental status. Any other symptoms of atherosclerosis and related conditions should be recorded. A recent electrocardiogram with written interpretation should be available. Non invasive vascular studies, as clinically indicated, should be performed. As a minimum, segmental Doppler systolic blood pressure recordings of the extremities should be recorded.

Recognizing that laboratory panels will vary in different geographical areas and that special arrangements may have to be made to obtain the select panel or specific tests you may need for good patient care, it is recommended that the initial evaluation should include: complete blood count with differential, a chemistry panel of the usual blood chemistries and electrolytes (including Na, K, Cl, Blood sugar, BUN, creatinine, calcium, phosphorous, uric acid, total cholesterol, HDL cholesterol, triglycerides, liver function tests including enzymes and serum proteins). Additionally, a complete urinalysis, thyroid function tests including TSH, T4, T3 uptake, and calculated T7, and if indicated, a chest x ray (report of a prior film will usually be adequate).

Twenty-four-hour urinary creatinine clearance (or a Cockcroft-Gault computed creatinine clearance) should be obtained. (See Ap-

pendix II.) Mineral status should be assessed for possible heavy metal toxicity and mineral deficiencies. This may include a mineral analysis of hair, urine, and blood or blood elements. Which particular test or combination of tests are ordered may vary with the physician's experience, the particular patient being evaluated, as well as the availability of testing in your area or country.

Provocative urine specimens for trace and toxic metal levels may be collected immediately before and after the first infusion of EDTA as an excellent indicator of the toxic and trace metal load present.

Nutritional supplements containing minerals and trace elements should not be ingested for at least 24 hours prior to testing and not resumed until all urine specimens have been collected.

Patients should be screened for abnormalities of carbohydrate metabolism. Appropriate tests might include a 2 to 5 hour glucose tolerance test, post priandial blood sugar, fructosamine or glycohemoglobin. Some chelating physicians feel strongly that if the patient has a family history of diabetes or has other symptoms related to glucose metabolism), the glucose tolerance test should be done, perhaps with insulin levels as well.

Additional laboratory or clinical tests may be indicated in specific cases. Other procedures might include: non-invasive radioisotope blood flow and heart wall imaging studies, plethysmography with pulse wave measurements of the extremities, stress electrocardiography, stress echocardiography, digital subtraction angiography, computerized axial tomography, magnetic resonance imaging, positron emission tomography, intravenous pyelography, echo or phonocardiography, thermography, oculoplethysmography, Ultrafast CT scan, platelet aggregation studies and /or PTT. These, and additional tests, would be up to the clinical discretion of the examining physician. (See Appendix III for expanded suggestions).

Referral for heart valve replacement, aneurysm repair, or other surgery may be needed. Many chelating physicians believe that surgery is better tolerated and less likely to cause complications if a presurgical course of chelation therapy is administered first, if time permits. If chelation fails, bypass surgery or angioplasty are still options.

### C. Keeping Proper Records

In addition to your patient's informed consent, history and physical examination, you are encouraged to keep the following items within each patient's chart, and easily accessible if needed:

*1. Biological Tests*

Copies of all biological tests, both routine lab tests and others required by this protocol should be available at all times in the patient's chart.

Every effort should be made to provide patients with their laboratory test results whenever possible, especially those tests analyzing nutritional and mineral status.

*2. Vascular Monitoring Tests*

Copies of all tests and reports evaluating a patient's circulatory status obtained before, during, and after chelation should be in the patient's chart. These data, should they indicate rapid deterioration or significant improvement in any aspect of the patient's health, are immediately available to demonstrate these changes.

*3. Recap Sheet*

A recap sheet of all required and essential laboratory tests should be maintained with the patients records.

*4. Progress Notes*

Progress notes of every patient visit and/or treatment must be maintained.

*5. Flow Sheet*

A flow sheet of each chelation treatment with all ingredients included must also be maintained.

## D. Treatment Procedures

*1. Infusion Solution*

*a. Carrier solution*

The carrier solution should be an iso-osmolar or slightly hyper-osmolar carrier solution of 250 to 500 ml. The infusion bottle is mixed individually for each patient, using sterile water for intravenous use and adding the desired ingredients in amounts calculated to produce iso-osmolality. Great care must be taken in combining ingredients with a distilled water carrier to insure that the resulting solution is

not significantly hypo-osmolar, which will cause erythrocyte hemolysis and hemoglobinuria. Normal or one-half normal saline, or 5% glucose may also be used, but the final infusion solution will be hyper-osmolar. Hyper-osmolar infusions will not normally cause problems and their use is acceptable. (See Appendix I.) (110)

If sterile, pyrogen-free distilled water is used as the carrier solution, it is essential that ascorbate be used in a dose calculated to produce an iso-osmolar concentration of total solutes at the time of infusion.

*b. EDTA*

EDTA in the carrier solution is normally infused at a rate not to exceed 16.6 mgm/min, (1 gram/hour) adjusted for body weight and creatinine clearance. If creatinine clearance is less than 100 ml/min, the dose based on body weight is reduced by multiplying that dose by a fraction equal to creatinine clearance/100. (See appendix II)

*c. Magnesium*

An intravenous solution of magnesium chloride or magnesium sulfate to provide approximately 214 mg of elemental magnesium is added to each infusion bottle (9 ml of 20% $MgCl_2$ solution or 4.5 ml of 50% $MgSO_4$ solution). That amount of magnesium converts 3.0 gm disodium EDTA to $MgNa_2EDTA$. Proportionately more magnesium should be used for large patients, when more than 3.0 gms of EDTA is given. You should reduce the dose of magnesium for lower doses of EDTA as hyper-magnesemia has been shown to reduce the release of parathyroid hormone from the parathyroid gland. (150,151)

Magnesium has three basic functions: 1), it reduces pain from the EDTA infusion 2), it is therapeutic for many conditions treated with EDTA and 3), magnesium seems to be delivered intracellularly with great efficiency during IV chelation therapy. (109) Most patients who enter EDTA chelation therapy have suboptimal amounts of body magnesium and many are quite deficient as determined by element testing.

*d. Sodium bicarbonate buffer*

EDTA releases hydrogen ions into solution when it combines with magnesium to form $MgNa_2EDTA$, in vitro. The resulting acid pH of the infusion may cause localized pain and inflammation at the site of

infusion with the remote possibility of a localized phlebitis. Sodium bicarbonate for intravenous use should be added in a ratio of approximately 10 mEq bicarbonate to 3 gms EDTA (1 mEq bicarbonate per 300 mg EDTA) to buffer the infusion solution to physiological pH.

*e. Local anesthetic*

Even with the use of magnesium and bicarbonate buffer, lidocaine or procaine may be needed to prevent pain at the infusion site for an occasional patient. This need occurs more commonly during the first few infusions. Allergic sensitivity is less likely with lidocaine.

Five to 10 ml of a 2% solution of either anesthetic agent is usually adequate and is added directly into the infusion bottle. The dose should not exceed 20 ml of a 2% solution given over 3 hours.

*f. Heparin*

Heparin in a dose of approximately 1,000 to 5,000 units may be safely added to an infusion to reduce the incidence of localized phlebitis proximal to the site of infusion. Heparin is contraindicated for patents with bleeding tendencies and reduced for patents who are already receiving full anticoagulating doses of warfarin. This small amount of heparin is not enough to cause systemic anti-coagulation.

*g. Ascorbate*

Vitamin C, in a dose of 4 to 20 grams may be added to the infusion bottle. Ascorbate helps to make a distilled water carrier solution isoosmolar, however, at higher doses of ascorbate, the solution along with the other components may be hyper-osmolar Ascorbate is also a weak chelating agent and is synergistic with EDTA.

Ascorbate enhances the ability of EDTA to remove lead from the central nervous system. (154) Ascorbate is also an antioxidant and free radical scavenger. CAUTION should be used in patients on strict sodium restriction because intravenous ascorbic acid is buffered to physiologic pH with sodium hydroxide and contains approximately 11% sodium by weight. Patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency may be worsened by high doses of ascorbate.

*h. Miscellaneous*

Modest doses of B-complex vitamins, including B1, B6, B12, and Pantothenic acid are often added to the infusion. EDTA depletes vitamin

B6, which should be supplemented during therapy. B-complex vitamins are synergistic with antioxidant defenses. Potassium chloride may be added to the infusion for patients who are taking potassium-wasting diuretics or are otherwise found to be in need of potassium by laboratory testing. All of these ingredients are usually well tolerated and absorbed when supplemented by mouth. Preservative-free parenteral vitamins may be obtained from compounding pharmacies (even though they are more expensive) and should be used immediately once opened.

*2. Treatment Techniques*

EDTA is administered intravenously between 1.5 and 3 hours. Factors include: the dosage of EDTA given, the patients' renal function, the patients' reactions to previous EDTA treatments and the physicians clinical judgment. The rate of administration should be no faster than 16.6 mgm/min, (1 Gram/hour) as adjusted for body size and renal function. A 25 gauge butterfly needle or 24 gauge intravenous catheter, are preferred by many physicians. These reduce the incidence of infiltration even if the patient is not careful about movement.

This small needle serves two purposes: 1, it is easier and less painful to insert, and 2, the small lumen prevents an excessive rate of infusion, should the patent become impatient and attempt to speed up the flow. It is difficult to infuse 500 ml through a 25 gauge needle in much less than three hours but possible, therefore nurses must carefully monitor the rate of infusion.

The frequency of treatment depends on the patient's condition, individual tolerance and convenience. Eventual benefit depends more on the total number of infusions and is less related to the time between infusions.

If pretreatment renal function tests are not completely normal or if treatments are given more often than twice per week, serum creatinine measurements and computed creatinine clearance should be performed before each infusion. An upward trend in serum creatinine is a reason to discontinue therapy until creatinine returns to baseline levels. Renal function will normally improve to pretreatment levels or better within 2 to 4 weeks. (100,102,103)

Debilitated patients and patients with pre-existing renal insufficiency may require a space of 2 weeks or more between infusions. Patients vary in their individual tolerance to EDTA. The treatment schedule for each patient will depend on clinical judgment and the

results of renal function tests. Urinalysis (dip stick) should be done before each infusion. A 24 hour urinary creatinine clearance measurement should be obtained before beginning EDTA chelation therapy, at the fifth treatment, and at each tenth infusion thereafter as an absolute minimum.

IN NO CASE SHOULD INFUSIONS BE GIVEN MORE OFTEN THAN ONCE IN 24 HOURS.

If a rising trend in serum creatinine is not detected early and if treatment is continued in the face of progressively impaired renal function, more serious renal damage will result. Lasting renal impairment from EDTA has never been reported when the precautions described in this Protocol were followed. In fact, renal function improves on the average, after a series of properly administered EDTA infusions.

Reports of lasting renal damage have stemmed from excessively large doses of EDTA administered too rapidly or too often for individual tolerance and without close monitoring of renal function. Variable tolerance among patients makes frequent renal function testing imperative to protect an occasional patient with unusual sensitivity to EDTA.

The total number of infusions for optimal therapeutic benefit varies from patient to patient. A series of 30 or more infusions are usually required for patients with symptomatic disease for optimal results. It is not uncommon for 40 or more infusions to be administered before a patient reports significant benefit. Occasional patients have received more than 100 infusions over a period of several years.

Full benefit may not normally occur for up to 3 months after a series of infusions have been completed.

Follow-up treatments may be given once or twice monthly for long term maintenance, to sustain improvement and to prevent recurrence of symptoms. After a series of 30 infusions, it is generally advisable to continue once a month for a year and then decrease or maintain the interval depending on patient response.

*3. Supplies and Equipment*

a. *Intravenous carrier solutions* are used in 250 or 500 ml units, calculated to be iso-molar to mildly hyperosmolar in the final infusion. (See Section VII,D,1a)

b. *Butterfly needles* of 25-gauge are used, although some physicians prefer other types of needles as a matter of individual preference.

Flexible intravenous catheters may be necessary to prevent infiltration in uncooperative or agitated patients.

c. *Tubing for intravenous infusion.*

d. *Intravenous starting tray,* appropriately equipped with tourniquet, alcohol swabs, bandaids, hypoallergenic paper tape, scissors, armboards, etc.

e. *Disodium EDTA* (Ethylene Diamine Tetraacetic Acid), NOT the calcium-disodium salt), is readily available in the United States in 20 ml (3 gram) vials, and is best tolerated without a chemical preservative.

f. *Magnesium chloride* for injection, 20% solution or magnesium sulfate for injection, 50% solution is obtainable in ampoules and multiple-dose vials, and is best tolerated without a chemical preservative. Magnesium solutions for intravenous use are normally compounded from hydrated magnesium salts. The label will often state the content of a magnesium "heptahydrate or hexahydrate".

Calculations to account for the water molecules in the original hydrated magnesium will show that the elemental magnesium content of the final solution is often only one-half what would be present if fully desiccated magnesium salts were used. Before calculating the administered dose of elemental magnesium for a specific product, read the label carefully and consult with the manufacturer if there is any doubt.

g. *Sodium bicarbonate* for injection, 1 mEq/ml, is readily obtainable for use as a buffering agent. Infusion pH should be adjusted to a physiologic range between 6.5 and 7.5.

h. *Lidocaine or procaine* for intravenous use (preservative free) is usually provided as a 2% solution but other concentrations are available. Lidocaine or procaine may not be necessary if $MgNa_2EDTA$ is used and buffered to physiologic pH.

i. *Padded arm boards* will increase patient comfort and decrease the incidence of infiltration. Elevating the arm will increase venous flow and also reduce discomfort.

j. *Vitamin C* (ascorbate) for injection 250 or 500 mg/ml is buffered to physiologic pH with sodium hydroxide which creates a sodium content of 11%. This is true regardless of whether the label states "ascorbic acid" or "sodium ascorbate". Many preparations labeled "no preservative" contain a sulfite "stabilizer" which imparts a disagreeable odor and causes adverse reactions in some chemically-sensitive patients. Ascorbate is also available with no preservative except EDTA to inhibit bacterial growth and is better tolerated by some patients.

k. *Pyridoxine* (vitamin B6) for injection can be obtained in multi-dose vials containing 100 mg/ml but other forms are also available. Injectable B6 may also be obtained in combination with thiamine (vitamin B1) 100 mg/ml and cyanocobalamin (vitamin B12) 1,000 mg/ml.

l. *Heparin* is available in concentrations of 5,000 or 10,000 units per ml, usually in multiple dose vials.

m. *Other water-soluble B-complex vitamins* are sometimes added and can be purchased as an injectable multiple B-complex formula. All readily available injectable B-vitamins contain chemical preservatives which can cause adverse reactions in some patients. B-vitamins can be obtained from compounding pharmacies without preservatives.

n. *Potassium chloride* for intravenous use may be medically indicated for hypokalemic patients, but is not used routinely by all chelating physicians. A well tolerated dose is 3 to 5 mEq per infusion.

However, doses as high as 20 mEq of elemental potassium may be added for patients deficient in potassium. Potassium chloride is also well absorbed by mouth. Intravenous potassium can be somewhat painful and increases the probability of localized phlebitis and sclerosed veins.

o. *Other considerations* would be for patient comfort. Recliner chairs with extendible foot rests are very desirable for patient comfort during the lengthy sessions of therapy. Wooden blocks should be available for placement under the front legs of a reclining chair in the case of an emergency, such as a hypotensive reaction or shock.

A variety of devices have been used to hang the intravenous bottles above the patient, ranging from standard hospital-type intravenous stands to coat hooks mounted on the wall or the ceiling. The decision as to what works best must be left to each individual facility.

*4. Emergency Kit*

A "crash cart" type of emergency kit should be readily accessible in the treatment area which also contains the usual medical supplies and equipment needed for cardiopulmonary rescusitation. Dated injectables and medications should be periodically checked and replaced when dating expires. The kit should contain a laryngoscope, with an adequate light source and fresh batteries, endotrachial tubes of various sizes and an Ambu bag (or equivalent by another manufacturer).

Other needed emergency supplies are more specific for possible complications of EDTA (such as hypocalcemia or hypoglycemia) and include vials of injectable calcium gluconate, or another form of cal-

cium suitable for intravenous use, a 50% solution of glucose for intravenous use and 10 to 50 ml syringes with appropriate needles.

A standby bottle of 500 to 1000 ml 5% dextrose in water, normal saline or lactated Ringers solution with tubing, but without any added medication should be nearby. If an adverse reaction is suspected, the EDTA infusion should be discontinued and the standby bottle connected to the same needle to keep the vein open. If resuscitative measures seem imminent or if blood pressure is falling the standby bottle should be restarted with a large bore needle or intravenous catheter before shock or circulatory collapse can occur.

A variety of sterile needles and syringes should be in the patient treatment area, arranged for immediate use without delay and without confusion in the event of an emergency.

*Oxygen* with a regulator, equipped for emergency administration by mask or nasal catheter should be available along with tubing for emergency connection to an Ambu-bag.

Remember: Cardiovascular patients are at unusual risk for myocardial infarction, stroke, heart failure and other complications, irrespective of the therapy they are undergoing or where they happen to be.

Chronically ill patients will be spending considerable time in a facility where chelation therapy is administered and resuscitative measures may eventually be required. A defibrillator and a cardiac monitor should also be available in the treatment facility. Staff should be trained in CPR.

*5. Additional Suggestions*

The professional staff treating patients with EDTA chelation therapy should be prepared to handle emergency situations that may arise during administration of the treatment.

It is recommended that a trained physician be on the premises at all times, however, state law may permit otherwise if the professional staff is adequately trained and equipped to deal with the occasional emergency that arises while the treatment is being given.

A rare patient may show unusual sensitivity to EDTA as can occur with any type of medication It is common practice to administer half the usual dose of EDTA in the first infusion to detect such idiosyncrasies. If that first infusion is well tolerated, EDTA in subsequent infusions is increased to a full therapeutic dose which is calculated as described previously.

To help monitor the rate of infusion, a vertical strip of tape may be applied to the side of the inverted infusion bottle, with a horizontal

line placed at the initial level and then divided below into thirds or fourths.

The starting time is written at the top and hourly time increments are written at each line below when the infusion is started. This helps medical staff to insure at a glance that each infusion is proceeding at the proper rate.

It is not uncommon for patients to increase the flow rate surreptitiously in an attempt to complete the infusion sooner than is safe. Even with a 25 gauge needle it is possible with adequate bottle height and a large vein to infuse 500 ml within 2 to 2-1/2 hours. Close regulation of the drip rate is therefore necessary although the potential of a dangerously rapid infusion is much less with a 25 gauge needle.

A short length of tape over the drip regulator helps to discourage meddling with the rate of infusion. Small gauge plastic intravenous catheters are less likely to infiltrate.

Other than possible transient interactions with digitalis medications and some older forms of insulin, as previously described, EDTA is quite compatible with the simultaneous use of most commonly prescribed cardiovascular drugs and other medications. Disodium EDTA is also effective for treatment of arrhythmias caused by digitalis toxicity since it lowers serum calcium.

A hypothetical consideration suggests that propranolol can block some of the therapeutic benefit of EDTA by antagonizing parathormone. It might be appropriate to substitute a cardioselective beta-1-blocker.

Beta blockers should never be abruptly discontinued. This may lead to angina and possibly a myocardial infarction. Usually low to moderate doses of beta blockers and cardioselective agents will not interfere with EDTA chelation and may provide some benefit in preventing a second heart attack.

The concomitant use of calcium supplements by mouth or an occasional injection of intravenous calcium to reverse or prevent hypocalcemic irritability, do not seem to have an adverse effect on the outcome of therapy. Partial benefit from EDTA has been reported using injections of calcium $Na_2EDTA$. Although the direct effect of EDTA on calcium and parathyroid hormone levels may be an important mechanism from which therapeutic benefit is derived, normalization of calcium homeostasis can also occur through arrest and reversal of free radical pathology and improved integrity of cellular membranes, independent of any transient effect on calcium during the infusion.

Nitrates, calcium blockers, (associated with premature death) diuretics, beta blockers, antihypertensives and vasodilators are often prescribed and managed clinically in the usual manner during chelation therapy.

Potassium supplements and additional magnesium may be needed for patients receiving diuretic therapy. Unless continued anticoagulant therapy is strongly indicated, the use of oral anticoagulants may be reduced or stopped.

### E. Evaluations During Treatments

Each patient should receive a routine urinalysis (dip stick) before every chelation treatment and more frequently if borderline renal abnormalities are present.

After every five to ten treatments, a repeat creatinine is necessary to follow up on renal status.

These may be done more frequently as the patients medical condition and treatment regimen dictate. This may be included as part of a more inclusive blood panel to check on other abnormalities noted on the initial blood screen done before the first treatment or to check that none have developed during the course of treatment.

More frequent testing of serum ionizable calcium or PTH may be warranted for patients who appear to be tolerating chelation therapy poorly. However, each physician must rely on good clinical judgment and not test just to be testing.

### F. Post Treatment Evaluation

After a series of 20 to 30 treatments at regular intervals, (depending on the patients medical condition, distance from the treatment facility, the physicians' clinical judgment, etc.), it is advisable to maintain a continuing medical relationship with the patient. Many physicians recommend a series of once-a-month treatments for perhaps one year after the initial series to continue the healing process. Then it would make good sense to see the patient at least quarterly for re-evaluation and booster treatments. At these visits, additional laboratory tests might be indicated as well as an interim medical history and appropriate examinations.

Any change in the patients requirement for medications to control

symptoms and objective tests indicating change from the original findings should be serially recorded. Nutritional and lifestyle counseling should be stressed at each visit. Nutritional supplementation must be maintained. In one followup study on chelation patients, those who continued supplements were better clinically than those who did not. (152)

Within three months following the initial series of chelation treatments, patients should have their non-invasive vascular studies repeated to demonstrate objectively the changes that have taken place. If these were done at another facility, arrangements should be made to have them repeated and reports requested for the patients' in-office chart.

The chelating physician should consider compiling a comprehensive post-treatment progress report, which includes a complete review of the patient's primary presenting symptoms and any change in these symptoms which may have occurred in the interval.

He should also consider sending such a report to other physicians who have been involved in the patient's care. Such an action may be helpful to the patient and lead to a better mutual understanding between doctors who perform chelation therapy and those who don't.

Physicians should maintain a continuing medical relationship with chelation patients after a series of 20 or more infusions, seeing these patients at regular intervals for evaluation and continued care.

## VIII. OTHER ADJUNCTIVE HEALTH MEASURES

### A. Diet

With regard to dietary recommendations, there are certain points that are agreed on by virtually all chelating physicians. There are other areas where disagreement is the rule rather than the exception. Points of agreement include: eliminating, as much as possible, refined carbohydrates, such as foods containing white sugar and white flour, hydrogenated fats, fried foods and foods containing synthetic additives. There is agreement on the notion that whole foods, as free of contaminants as possible should be eaten.

The disagreement comes in relation to the optimal relative amounts of macronutrients, namely protein, fat and carbohydrates for the cardiovascular patient. One end of the spectrum believes that the diet should be very low in fat (the percentage of calories should be be-

tween 10 and 20 percent), low to moderate in protein (approximately 10 to 20 percent), and high in complex carbohydrates (70 to 80 percent). (155,156,157)

The other end of the spectrum emphasizes a low carbohydrate, high fat, relatively high protein diet. The percentages here could be 30 to 40 percent each of fat and protein and 20 percent carbohydrate. (158) More recently, attention has focused on a diet somewhere in-between, with 40 percent carbohydrate, 30 percent fat and 30 percent protein. (159)

One of the reasons for such a disagreement is the fact that the optimal macronutrient ration for an individual patient will vary, relating to that patient's individual biochemistry and genetic make-up. Some patients do well on a fairly strict vegetarian diet and some will not.

This is an area that requires special study by the chelating physician to see what system works best for him and his patients. This system may include varying the ratios from person to person, depending on their particular needs.

## B. Physical Exercise Conditioning

There is general agreement among conventional and chelating physicians that physical exercise is important for all people in general and cardiovascular patients in particular. Most of the studies showing the benefits of exercise for a cardiovascular patient involve some type of sustained aerobic exercise program. Aerobic exercise may be defined as an exercise that involves large groups of muscles in a rhythmic exercise which uses the amount of oxygen being inhaled. This implies that the person is not exercising so vigorously that an oxygen debt occurs, resulting in an accumulation of lactic acid in the muscles, as in so-called anaerobic exercise. Examples of exercises that may be used for aerobic conditioning are: walking at a brisk pace, jogging, Nordic track, rowing machine, bicycle riding outdoors or in place, and swimming.

All of these exercises need to be done at a moderate pace in order for them to be aerobic and what is aerobic for one person may be anaerobic for another, depending on the conditioning of that person. A good rule of thumb is: patient's should be just mildly out of breath and should at all times during the exercise be able to sing or talk. If a person is not able to do this, he/she needs to slow down or stop.

Another way to monitor the intensity of the exercise is via the pulse rate, as long as the patient is not on a beta blocker or another drug which slows down the heart rate or otherwise has a cardiac arrhythmia. A rough estimate of an appropriate aerobic pulse rate is 180 minus the patient's age. So, for example, an appropriate aerobic pulse rate for a fifty year old person is 180 minus 50 or 130 beats per minute.

A person starting an aerobic exercise program should start slowly and gradually over a period of weeks, working up to about thirty minutes of aerobic exercise at least every other day. The thirty minutes aerobic exercise period should be preceded by a five minute warm-up and ended with a five minute cool-down. Patients with advanced coronary artery disease should probably be on a continuous monitored exercise program, utilizing an electrocardiographic monitor as done in cardiac rehabilitation programs.

For very debilitated patients, the exercise program must be carefully individualized. At no time should an exercise program exhaust the patient. If a patient feels worse after exercising compared to before exercising, the program needs to be modified.

Aerobic exercise has many benefits for the cardiovascular patient including stimulating the formation of collateral circulation and improving the efficiency of energy utilization by the heart and other organs. Another proposed mechanism is the possible chelating effects of lactic acid, which forms as the result of exercise. Furthermore sweating as a result of exercise helps to remove toxic chemicals from the body. Aerobic exercise will also remove beneficial minerals from the body which must be replaced. To vigorously exercise without nutrient replacement is not wise.

In addition to aerobic exercise, stretching exercise may also be beneficial to cardiovascular patients. This type of exercise increases flexibility of muscles and may take the form of yoga or other systems of gently stretching all the muscles of the body.

## C. Nutritional Supplementation

EDTA depletes vitamins and essential nutritional trace elements. Patients undergoing chelation therapy should receive, as a minimum, a high potency multiple vitamin/mineral/trace element supplement to prevent depletion.

Zinc is especially prone to removal by EDTA and zinc is essential

for defense against free radical insult. Zinc supplementation is therefore needed during chelation therapy with careful consideration of copper status as they are antagonistic.

CAUTION SHOULD BE USED WITH TRACE ELEMENT SUPPLEMENTATION. Trace elements are all toxic in excess. Marked interaction and competition between elements can occur at sites of intestinal uptake, transport and metabolic utilization. Chromium, zinc, copper, manganese, and iron for example share common mechanisms of uptake and transport. An excess of one can block utilization of the others.

Copper supplementation by itself can cause a relative zinc deficiency. Zinc supplementation in large doses can create a relative copper deficiency. Iron is not only a potent free radical catalyst, but it also competes for absorption and transport with other essential trace elements.

It is difficult to actually diagnose an excess of copper for several reasons. With regard to hair mineral analysis, copper is frequently elevated due to an external source of contamination. For example, this could happen by swimming in a pool disinfected with copper sulfate, or by utilizing water that is slightly acidic and flows through copper pipes. Elevated copper in hair, urine blood or plasma may be due to an inflammatory condition such as cancer and rheumatoid arthritis. During these conditions, copper is mobilized from the liver as part of the body's defense. As copper is depleted from the liver, resulting in an overall copper deficiency, elevations may be seen in specimens tested.

Short of a liver biopsy, there is no certain way at the present time to be sure of a copper excess. Consequently, careful clinical evaluation of patients response to copper is necessary.

Excess copper has the potential to be a free radical catalyst, although deficiency is far more common. Copper absorption varies greatly from person to person. Copper should not be supplemented in patients with proven excess, although most patients will benefit from at least 2 mg of copper per day. More may be needed to replenish deficiencies.

Chromium is transported on the iron binding protein, transferrin. High iron intake interferes with chromium uptake. Iron accumulates excessively with age in most adult males and post menopausal women. Iron should not routinely be supplemented unless a deficiency exists. Iron supplementation should only be given for as long as needed to replenish normal body stores.

NOTE: Zinc supplements, without adequate intake of selenium, can potentiate selenium deficiency, increasing the risk of atherosclerosis and cancer.

When larger amounts than the RDA are given to correct a deficiency, it is advisable to give those added doses at a time other than with regular meals, not at the same time as a multiple supplement. For example: replenishment doses may be given at bedtime or on first awakening in the morning to prevent competition with other essential nutrients in food and multiple supplements.

Both vitamin D excess and deficiency may be a problem. Deficiency may occur when a person does not get sufficient exposure to sunlight, avoids vitamin D fortified foods, such as milk, or has gastrointestinal absorption problems. Vitamin D deficiency may result in bone density problems and increase one's risk to certain cancers. In such a situation, it is important for a person to supplement with at least 400 international units of vitamin D daily.

On the other hand, excessive vitamin D may contribute to soft tissue calcification and a worsening of atherosclerosis. A person who spends a good deal of time in the sun and/or ingests vitamin D fortified foods and does not have absorption problems, should not supplement with vitamin D or should restrict supplementation to 100 to 200 I.U.'s daily.

The ratio of calcium to magnesium as supplements is controversial with optimal ratios varying from 2:1 to 1:2. Absolute amounts of daily supplemented elemental calcium and magnesium may vary from 300 mg of each up to 2,000 mg of each. Excess calcium tends to cause constipation and excess magnesium tends to cause diarrhea.

Chelation patients who develop muscle cramps in the legs or elsewhere often respond to more supplemented magnesium, more calcium or more of both. Generally, it is better to avoid calcium supplementation on the day of chelation treatments as not to interfere with the therapeutic effects of the hypocalcemic reaction of EDTA. Patients with osteoporosis or risk factors for this condition should generally be supplemented with at least 1,000 mg of calcium and all other nutrients necessary for building bone.

Multiple vitamin/mineral/trace element supplements contain many nutrients with antioxidant activity which are synergistic with chelation therapy. Suitable products are marketed by many manufacturers which contain a spectrum of ingredients similar to and within the approximate daily doses listed in the generic formula shown in Appendix IV. The total daily dose of the broad spectrum multiple V/M is

usually contained in six tablets, taken two at each meal or three twice daily with the morning and evening meals.

This type of formulation has been found satisfactory by many chelating physicians. A full month's supply of all listed ingredients can be purchased at reasonable cost in a single bottle. Most patients with established disease or demonstrated specific deficiencies will require higher separate doses of individual vitamins or minerals.

Other nutritional supplements may include essential fatty acids including cold water fish oil (Omega 3-EPA) and Evening Primrose, Borage or Black Current Seed oil (Omega 6-GLA), additional vitamin E, coenzyme Q10, L-carnitine, proanthocyanidins, cholesterol-binding fiber and polysaccharide products. Additional niacin (nicotinic acid) is useful to lower cholesterol, but the possible annoying niacin flush must be acceptable to the patient. (This flush can be minimized by administering 80 mg of aspirin prior to the niacin dose.) Regimens of nutritional supplementation vary according to preferences of both patients and physicians.

Since many older patients have a deficiency in gastric acid production, it may be advisable to use Betaine hydrochloride or Glutamic acid to aid digestion. This deficiency can best be documented with the Heidelberg Tubeless Gastrogram. Whole pancreas enzymes may also be indicated as an aid to digestion. Aspirin in low daily doses of 80–100 mg inhibits platelet aggregation and may be combined with coumadin derivatives, especially in patients with prosthetic valves or recurrent deep vein thrombosis (DVT).

Alcohol should not be consumed before treatments.

The use of tobacco reduces the therapeutic benefit of EDTA and shortens the duration of benefit. Patients should be strongly counseled against the use of tobacco in any form and assisted in quitting.

Patients should be encouraged to drink large quantities of fluids, preferably purified, filtered or distilled water. Water purified by reverse osmosis through activated charcoal is excellent. A good rule of thumb is to use one ounce of water per kilogram of body (scale) weight.

### D. Stress Management

Stress is a "natural" phenomenon in today's world. However, when an "overload" exists, it puts the patient at greater risk for survival.

With the overproduction of cortisol and catecholamines, the body

thesias, urticaria and tachycardia associated with systolic and diastolic hypertension, increasing in frequency with increasing doses. These side effects are usually mild and transient. There are fewer side effects with the 2.5 mg/Kg dose than with the 4 or 5 mg/Kg doses. The side effects peak within 10–30 minutes and usually subside within 30–50 minutes. (163) Peak plasma concentrations of BAL are reached between 30–60 minutes. Within 4 hours, absorption and detoxification are complete. (164) Unless a patient has postarsenical jaundice, BAL is contraindicated when liver dysfunction is present. BAL should not be given to patients with a glucose-6-phosphate dehydrogenase deficiency as it may cause hemolysis. (165,166) It should not be used to chelate short-chain mercury compounds, for there is evidence that the chelated mineral is then more readily taken up into the brain. (167,168)

Medicinal iron should not be given to patients receiving BAL. (166) Although it will increase the excretion of cadmium, there is a concomitant increase in renal cadmium concentration so that its use in cadmium toxicity is to be avoided. (169) It also enhances the toxicity of selenium and tellurium and should not be used to remove these metals. Maintenance of an alkaline urine helps to protect the kidney from dissociation of the BAL-metal complex. (160,169)

BAL should not be used for children who are allergic to peanuts or peanut products as the product is dissolved in peanut oil.

For acute arsenic or gold poisoning, BAL is used immediately—3 to 5 mg/Kg IM every 4 hours for 2 days. Then four times on the third day and twice a day for the next 10 days. An alternative therapy is to give D-Penicillamine orally at 100 mg/Kg/day to a maximum of 2 grams per day for adults and 1 gram in children following the first two days of BAL therapy. This should be given in 4 divided doses for 5 days. If symptoms reoccur, a second course can be initiated. (170)

BAL increases the urinary excretion of arsenic by about 40% with maximum excretion occurring within 2 to 4 hours following the injection of BAL.

For mild poisoning, use 2.5 mg/Kg four times a day for two days then two times on the third day and once a day for the next 10 days. (170)

For Lead poisoning, BAL chelates both intra and extracellularly. The main route of excretion is the bile and therefore it can be used in the face of renal impairment.

BAL is used preferentially initially in the child with acute lead en-

will function less effectively and produce aberrations in the orderly repair processes necessary for existence. Coronary artery spasm needs to be avoided at all costs, as this can cause angina and occasionally myocardial infarction and death even when the coronary arteries are free of atheromatous disease. Chelation patients should be evaluated for the role of stressful circumstances in their life and their way of handling stress, as it may contribute to their disease. If necessary, the patient should be enrolled in or referred to a stress management program.

## IX. OTHER CHELATING AGENTS

### A. BAL

BAL (British Anti Lewisite) or 2, 3-dimercaptopropanol, the first clinically useful chelating agent, was developed as an antagonist for arsenical war gases during World War II. (160)

It is a relatively colorless liquid with a sulfur odor. It has been found to form stable chelates in vivo with many toxic metals including copper, inorganic and elemental mercury, antimony, arsenic, bismuth, cadmium, chromium, cobalt, gold, lead and nickel. (160,161, 162)

It differs from other chelating agents in that it is a neutral molecule and is soluble in both water and lipids. It diffuses well into erythrocytes. (83) It can readily pass through cellular membranes and remove toxic metals from sites which are inaccessible to chelating agents such as $Na_2CaEDTA$ and $Na_3CaEDTA$ where the chelating agent itself is an anion with a negative charge of $-2$ or $-3$. Molecules with such negative charges cannot pass through most cellular membranes and are therefore restricted to the extracellular spaces. Because it is predominantly excreted in bile, BAL can be administered in the presence of renal impairment. (5)

BAL has been used less commonly as time has passed because of the discomfort associated with its administration (intramuscular injection in a peanut oil/benzoyl benzoate solution). It has been used to treat encephalopathy of childhood lead poisoning, (along with $Na_2CaEDTA$) where it has been reported to be more effective than alternative treatments. (83) It has also been used for nephrotoxicity resulting from an overdose of gold in the treatment of arthritis. (160)

Side effects of BAL include nausea, vomiting, headache, dyses-

cephalopathy. This is because high dose $Na_2CaEDTA$ can increase brain lead levels in the presence of high blood levels of lead. (83)

BAL for Mercury. The treatment protocol for acute mercury intoxication is: 3–5 mg/Kg every 4 hours for 2 days; then 2.5–3 mg/Kg every 6 hours for 2 more days; then every 12 hours for 7 more days. The BAL-Hg complex is excreted in both the feces and urine. Urinary mercury levels will help to assess the effects of therapy. Close attention to electrolyte and fluid balance is vital throughout the treatment period. (171) The infusion of N-Acetyl-Cysteine during hemodialysis in a patient with methylmercury intoxication has been found to reduce whole blood mercury levels. (172) In the laboratory, the concurrent administration of selenite and $HgCl_2$ can prevent renal damage (173) through the formation of an insoluble and stable HgSe. (174) This would indicate that administration of selenite to a mercury toxic patient may reduce the risk of mercury toxicity to the kidneys.

Although BAL can be used for acute mercury intoxication, other chelators should be used in chronic conditions because in animal studies BAL can transiently increases brain mercury levels, and should be used with caution. (171) Elemental mercury vapor inhalations with subsequent CNS symptoms are probably best treated with DMPS or D-Penicillamine. See their protocols.

Monitoring of chelation effectiveness is done by measuring the urinary excretion of arsenic, lead or mercury. If levels remain high or rebound, additional courses of treatment may be indicated.

BAL is supplied in 3 ml ampoules of 100 mg/ml in peanut oil. It is given only by deep IM injection.

## B. DMSA—Succimer—Chemet

DMSA or meso-2,3-dimercaptosuccinic acid, reacts with the same group of toxic metals as BAL: primarily, lead, mercury, arsenic, and gold. (175,176) Because DMSA has two carboxy acid groups, it is soluble in water and ionized at physiological pH values. It can be given orally, as it is well absorbed from the gastrointestinal tract, and in comparison with BAL, has only a moderate odor and somewhat unattractive taste. It is 30 times less toxic than BAL. (177) It can be administered with orange juice or apple sauce, both of which have been used when DMSA is given in the treatment of infant or childhood lead intoxication. DMSA is a compound of quite modest toxicity,

though as with all sulfhydryl compounds, there are individuals who may become sensitized to it. It has been approved by the USA-FDA for treatment of lead intoxication. During the past thirty years considerable evidence has accumulated in the medical literature of other nations suggesting that it is an effective chelator of mercury and arsenic, as well. (178)

As DMSA can be given orally, it may be administered to children for lead toxicity, outside of a hospital setting. This gives it considerable advantage over disodium calcium EDTA, which is given intramuscularly, usually in the hospital. One suspects that the main difficulty with home treatment with this compound would arise in those individuals who have an adverse reaction to the drug, but who continue to take it as prescribed.

DMSA, in contrast to $Na_2CaEDTA$, does not have a clinically significant effect on the excretion of essential minerals, including calcium, magnesium, iron, and copper. It does increase the excretion of zinc but to a much less degree than EDTA. (178,179)

DMSA is eliminated almost exclusively through the kidneys, with only small amounts excreted through feces or expired air. Approximately 23% of an orally administered dose is absorbed. DMSA is rapidly and extensively metabolized. (180) It is presently available in 100 mg capsules, but also can be custom formulated by compounding pharmacies in differing strengths.

Approximately 20% of the administered dose is recovered in the urine, presumably reflecting the quantity of the drug absorbed from the gut. On average, of the total amount of DMSA eliminated in the urine, approximately 89% was eliminated in altered form as mixed disulfides with L-cysteine and 11% as free DMSA. Maximum excretion of DMSA occurred in the 2 to 4 hour urine specimen. 75% will be excreted in 24 hours. (181)

Apart from the occasional elevations of serum ALT (which can also be lead related), reported adverse effects of oral DMSA (such as dizziness and weakness) have been rare and mild. Other adverse effects are largely confined to abdominal complaints including distress, gas, or pain.

Oral DMSA increases the absorption of lead from the GI tract similarly to D-Penicillamine and oral EDTA, however it does not enhance retention as a larger part of the absorbed lead is excreted. (182) In contrast to BAL which is contraindicated in patients with confirmed glucose-6-phosphate dehydrogenase (G6PD) deficiency, DMSA may be administered to such patients. Since DMSA does not significantly

chelate iron, it can be used concomitantly with iron supplementation. (183)

DMSA is approved by the FDA for use in lead toxicity with blood levels greater than 45 micrograms/Dl. However, some physicians treat patients with much lower serum levels of lead, as no body burden of lead is truly safe.

Another off label use of DMSA is to treat arsenic toxicity or an increased body burden of arsenic. In all of these cases, up to three courses of therapy may be given using laboratory determinations of these minerals to determine when the treatment should be stopped. (184)

The treatment protocol is: 7 days of DMSA at dosages of 10 mg/kg every eight hours followed by 14 days at 10 mg/kg in two divided doses. No treatment is administered for the next 21 days. Then repeat this same course as follows:

7--14--[21]---7--14--[21]---7--14--[21].

This compound is usually used orally but can also be administered IM-Not IV. It is prudent to do 24 hour urines before starting the first course of therapy to determine mineral excretion and then monitor the removal response with subsequent urine specimens (24 hours). This is in addition to testing blood arsenic or lead levels before and during the treatment process. Do a chemistry profile after 10 days to check liver functions and hemoglobin levels as DMSA can increase liver enzymes and decrease hemoglobin. If a skin rash appears, stop the therapy until it is gone then resume at a lower dose.

There are several protocols for use of DMSA in mercury toxicity with some disagreement as to the relative effectiveness of DMSA compared to other chelating agents. The German literature according to Heyl, (the manufacturer) claims that DMPS is best for organic, inorganic and metal mercury but American researchers claim that the effectiveness of DMSA is stronger than that of all other comparable complexing agents (DMSA > DMPS > D-Penicillamine > Acetylcystein). DMSA also appears to complex easily with organic mercury; DMPS complexes more easily with inorganic mercury. (175)

For use in patients having mercury amalgam removal, the treatment protocol according to Godfrey and Campbell is: (185)

Oral sodium ascorbate to bowel tolerance (4–12 Gms in divided doses), seleno-methionine, 200 ug/day, and specifically prepared multimineral tablets depending upon the results of element analysis.

Specific chelation therapy, in the form of DMSA oral powder is administered after each dental treatment and subsequently at a dose of 0.5 Gm once a week for three months if the patient had high initial mercury levels after DMPS urine mercury challenge. The challenge can be repeated 6 months or a year later to check on residual body levels of mercury.

They also recommend intravenous sodium ascorbate to 0.7 Gm/Kg body wt, e.g. 25 Gm/250 ml or 50 Gm/500 ml sterile water during each dental amalgam removal session. These usually involve a quadrant taking approximately 2 hours. IV vitamin C appears to greatly increase mercury excretion via the bile and stool.

## C. DMPS

*This chelating agent is not at present certified for any use in the United States by the FDA. It should only be used in research under the umbrella of an Institutional Review Board certification and IND. It may be used legally in other countries depending on their regulations.*

DMPS or 2-3-dimercaptopropane-1-sulfonate, is another compound designed to be a water soluble analog of BAL. This agent was first developed in China, was then introduced into Russia and used for workers injured by exposure to heavy metals. Later it was introduced into Germany. Its properties are similar in many respects to DMSA. DMPS chelates lead, cadmium, mercury, silver, tin, arsenic, and inorganomercury compounds. (186)

It is well absorbed from the gastrointestinal tract, so can easily be administered orally. It is slightly more toxic than DMSA yet 10 times less toxic than BAL. Its use may be associated with a somewhat higher incidence of erythema multiforme. Stevens-Johnson syndrome is a rare and contested event.

Depression may manifest during the process of mercury detoxification. This clears with continued treatments. DMPS is somewhat more difficult to prepare chemically and is much more expensive than DMSA. With the possible exception of inorganomercury intoxication, it does not appear to possess any obvious clinical advantages over DMSA although some authors feel that it is an ideal agent to "clean" the kidneys of heavy metal residues and improve kidney function in patients who have been exposed to heavy metals. (187,188)

DMPS does not cross the blood brain barrier. It is not contraindicated in pregnancy. It is an extracellular chelator. Intravenous DMPS

is primarily excreted in the urine and to a minor extent in the feces. The IV half life is six hours, with 90% being excreted in 24 hours.

Oral DMPS leads to excretion of heavy metals mostly in the stool. The oral form is 60% absorbed through the GI tract, and reaches peak blood levels in 45 minutes. The half life is 45 minutes. It can be used to treat lead intoxication but is not as effective as DMSA.

At the present time DMPS is sold under the trade label of Unithiol, (USSR), or Dimaval, the oral form, the IV form is known as: DMPS-Heyl (Germany). It is supplied as 5 ml-250 mg vials for IV use (use immediately upon opening as it oxidizes rapidly) or as 100 mg oral capsules. See the package insert for more information.

Even though DMPS has a high affinity for mercury, the highest affinity appears to be for copper and zinc, which are the metals that appear first in high levels (after chelation) in the urine. The "normal" urine challenge test will show high copper levels and low manganese levels. Only consider someone copper toxic if the level excreted is more than four-fold the upper limit of the reference range. If the patient has a high body burden of these metals, no mercury is removed with the first test. Only subsequent DMPS tests will show the mercury. As long as there is a high body burden of mercury, virtually none of the other heavy metals come out. Only as the mercury level starts to drop does the lead, nickel, silver, and cadmium appear in the urine. This is important to understand: as different heavy metals appear in the urine test at different times, so the patient's symptoms change while going through detoxification.

As with other chelating agents, the patients' mineral status should be determined before administering DMPS and repletion of deficient minerals accomplished. Watch magnesium status as most adverse responses are due to magnesium inactivation. (DMPS does not chelate magnesium).

IMPORTANT: According to some authors intravenous DMPS should not be used in patients who still have silver mercury amalgam fillings. DMPS appears in the saliva and may dissolve the surfaces of the existing amalgam fillings. This process occurs over several days. Theoretically, as the blood concentration of DMPS decreases very quickly, the patient with amalgam fillings could become acutely toxic from heavy metal injury to the mucosa of the gut following DMPS use.

DMPS has been used for a challenge test to determine if a patient is carrying a greater load of mercury than is desired once the amalgams have been removed. Chorella and garlic capsules are given—2

each, 3 times a day, for one week. Then a pre-DMPS challenge 24 hour urine collection for mercury is done followed by a post-DMPS challenge 24 hour urine collection after the DMPS has been given.

When the patient has had the last amalgam removed, the first treatment is given. In patients who have had the amalgam taken out month, years, or decades before, this diagnostic test and treatment method can and should still be used as soon as the problem of heavy metal toxicity is suspected.

The content of the ampoule at a dose of 3 mg/Kg of body weight up to a maximum of 250 mg contained in the vial, is drawn up into a 5cc syringe and slowly injected IV into the patient with a 25 gauge butterfly over a 20 minute period. Faster delivery times can cause a drop in blood pressure.

The patient is then asked to collect all urine for 24 hours in the proper container, then fill the provided mailing tube with a sample from the urine collected over the 24 hour period. After voiding the first urine into the collection container, the provided ampoule of nitric acid is added to the urine in the container. Depending on the laboratory used, the patient may be responsible for the mailing of his own urine.

Paravenous infiltration of DMPS is harmless, but creates an itching sensation at the injection site for half an hour or so. Once the toxic metals have been removed from the extracellular space, there will be a new equilibrium established. The patient will feel better for several days after the injection, then may start feeling bad again, indicating the need for continued treatment. Often the patient will have a feeling of "emptiness in his head" and difficulty concentrating for a few days. This is usually temporary.

Chromium, copper and zinc should not be given for 24 hours before and 48 hours after the test. Otherwise DMPS may bind to copper, zinc, and other "good "minerals and not get to the mercury. If any of the toxic metals are elevated above normal urinary levels or mercury excretion is more than 1 mcg/24 hours, the next injection is given. Repeat the urine test at the time of the third infusion. Infusions are given every two weeks or at monthly intervals. People who had exposure to mercury through their amalgam fillings will typically require six to ten injections, but in some cases many more are indicated. To be specific, urine can be monitored for mercury excretion, and treatments ended when no more mercury is excreted. People who have never had amalgam fillings, but show evidence or suspicion of mer-

cury toxicity through other sources typically require one to two injections.

According to the World Health Organization (WHO) there is no "safe" level of mercury.

If you get a high copper level, do a second challenge to confirm that mercury is available for excretion.

Even though there is a remote possibility of Stevens-Johnson syndrome, the side effects are usually mild. These are occasional temporary lowering of blood pressure, allergic reactions, and skin rashes. DMPS is not mutagenic, seems to have no teratogenic effects and is not carcinogenic.

FOR MERCURY INTOXICATION: consider DMSA (organic) > DMPS (for inorganic) > D-Penicillamine. DMPS may also be used for arsenic, antimony and lead intoxication as well. The patient may require as few as 5 or as many as 30 treatments before the mercury has been eliminated.

Even though Zinc is not chelated well with DMSA or DMPS, it is wise to replete zinc as you do not want to create a zinc deficiency. There is no real problem with selenium.

For Arsenic or lead toxicity: Use 3 mg/kg or 100 mg (Oral) four times a day for adults for 5 days. Then five days rest before the second course. Repeat this program for six courses.

5--[5]----5--[5]----5--[5]----5--[5]----5--[5]----5--[5]

It is prudent to do 24 hour urines before starting the first course of therapy and the monitor the removal response with subsequent urine specimens (24 hours). This is in addition to testing blood arsenic and lead levels before and during the treatment process.

Do a chemistry profile after 10 days to check liver enzymes and hemoglobin levels as DMPS can increase liver enzymes and decrease hemoglobin. If a skin rash appears, hold the therapy until it is gone then re-institute at a lower dose.

Additional adjuncts to this therapy include:

alkalization of the urine
addition of high sulfur foods : eggs, garlic, chlorella to stimulate mercury excretion through the liver.
decrease bowel transit time : add activated charcoal and digestive enzymes

watch fluid balance : sauna may be helpful
antioxidants: specifically N-acetyl-cysteine, Glutathione and Selenium
IV or oral vitamin C : acts as a reducing agent

**D. Deferoxamine or DFO**

Ferrioxamine-B is a water soluble compound containing trivalent iron which is synthesized by *Streptomyces pilosus* as an agent which it uses to extract needed iron from the environment of the organism. Deferoxamine, is then produced by the removal of the trivalent iron from Ferrioxamine-B. It is very effective as an agent to selectively enhance the urinary excretion of iron. (189)

DFO wraps itself around a ferric ion and forms an extremely stable complex which is then readily excreted in the urine. DFO does not induce a significant excretion of any of the other essential metal ions, but does induce the excretion of trivalent metal ions such as Aluminum, $Al^{+3}$. (69,190)

DFO is used primarily to control iron overload which results from the use of repeated blood transfusions in the treatment of disorders in which defective hemoglobins are synthesized, such as thalassemia major and sickle cell anemia.

Since iron is retained tenaciously by the human body, such repeated blood transfusions ultimately result in the accumulation of toxic and then lethal levels of iron. High ferritin levels have been associated with increased risk of heart disease and cancer and ferric ions are known free radical promoters. (191,192) Patients with thalassemia may have ferritin levels in the 3000 to 8000 mg/Dl range and some have been recorded as high as 20,000. (Personal communication with Kontoghiorghes G.)

The use of DFO has allowed treatments of thalassemia major to be developed in which the lifespan of such individuals has been approximately doubled. DFO cannot be given orally and is generally administered SQ, IM or IV according to a scheduled treatment protocol. (193) It is also a compound of relatively low solubility. DFO probably works both intra and extracellularly.

DFO will bind to iron as free iron, or the iron in transit between transferrin and ferritin, ultimately decreasing ferritin stores. (194, 195) DFO does not affect the iron of hemoglobin, cytochrome, hemosiderin or ferritin directly. The binding constants of iron and aluminum are high: iron: $K = 10^{30.7}$ and aluminum: $K = 10^{22}$. (193)

The half life of deferoxamine is around 1 hour. (196) IV ferrioxamine-B is entirely eliminated by the kidney within 5 hours, whereas only 70% of the same IV dose of deferoxamine appears in the urine after 72 hours. (189) A small amount is excreted in the bile. It is believed that the remaining DFO is metabolized by a plasma enzyme. Subcutaneous injection of DFO is twice as effective as the intramuscular route and 80% as effective as IV administration which is the most effective route. Concomitant use of oral vitamin C (500–1000mg) is a useful adjunct to enhance iron excretion.

One mole of DFO binds 1 mole of $Fe^{3+}$, therefore, 100 mg of DFO can bind 9.35 mg of $Fe^{3+}$. (197)

DFO is supplied commercially as Desferal (Ciba-Geigy) in sterile vials of 500 milligrams each.

Side effects and adverse reactions of long prolonged therapy include: cataracts, pigmentary changes in the retina, tinnitus and hearing loss. (198) The ocular and auditory changes are usually completely reversible on cessation of treatment. If DFO is given too rapidly IV, there may be flushing of the skin, urticaria, hypotension and shock.

DFO treatments cause very little essential mineral loss and no substantive renal problems. It is contraindicated in patients with severe renal disease or anuria, since the drug and the iron chelate are excreted primarily by the kidney.

Subcutaneous administration is twice as effective as the IM route, and since the half life is so short, DFO is sometimes given with a portable pump as a continuous clysis. (195) The dose would be 0.5 to 2 grams (20–40 mg/Kg/day) over 8 to 24 hours. This may cause some redness, tenderness and induration at the infusion site that can last for several days. Too superficial needle placement can lead to vesicle formation and loss of skin pigmentation.

If used IM, (at the discretion of the physician), use 1 gram initially, followed by .5 gram every 4 hours for 2 doses with a maximum of 6 grams in 24 hours, (199) (dosages as high as 16 grams/24 hours have been administered without incident). Watch for pain, flushing, lightheadedness, and throbbing headache (which could be due to an accidental IV injection).

It is important to intermittently monitor serum ferritin levels as this is the best indicator of iron storage levels. Total storage iron can be calculated and the necessary amount of DFO can be determined. Patients with thalassemia receive regular infusions of iron with their transfusions and it may not be possible to reduce their ferritin levels substantially even with continuous SQ clysis.

If used IV, the rate of DFO administration should not exceed 15 mg/Kg/hour, with an initial dose of 1 gram followed by two 0.5 gram doses separated by 4 hours and a total dosage not to exceed 6 grams in 24 hours. Watch for hypotension, generalized erythema, urticaria and possibly shock. This would most likely be due to too rapid infusion. The DFO is added to 250 ml normal saline, or 5% dextrose in water. (200)

If the patient is receiving blood transfusions, use 1.5 grams/unit of blood, (20 to 40 mg/Kg/day).

Since DFO is an efficient trivalent chelator, some investigators are now suggesting it to reduce high body burdens of aluminum. This did occur with dialysis patients. DFO is being used in patients with Alzheimer's disease as well. (190,201)

Innovative uses: Aluminum overload in dialysis patients : 45 to 90 mg/Kg/day

Alzheimer's disease : 250 mg twice a day (SQ), 5 days per week

Diabetes with high ferritin : 10 mg/Kg IV—twice a week until the ferritin levels are in acceptable range, (40–60 mg/Dl).

Malaria—to inhibit parasites : 100 mg/Kg/24 hours IV for three days.

## E. D-Penicillamine

D-Penicillamine, 3-mercapto-D-valine, was introduced for the treatment of hepatolenticular degeneration (Wilson's Disease). In this hereditary disorder, the accumulation of copper from the diet proceeds until it reaches lethal levels, presumably because of a defect in the processes by which copper is excreted from the liver into the bile. The incorporation into ceruloplasmin is also impaired. (202)

The disorder allows accumulation of excess copper in the body which is deposited in several organs, most notably in the brain, (widespread degeneration) liver, (fatty infiltration, inflammation, and hepatocellular damage which may progress to postnecrotic cirrhosis) kidney, (tubular and glomerular dysfunction) and the eye, (Keyser-

Fleischer rings). The oral administration of D-Penicillamine causes a substantial increase in the urinary excretion of copper and has been used, to control the course of this disorder over a period of decades. (203) The accumulation of copper can cause neurological and psychiatric symptoms and such individuals are often treated as psychiatric patients while their condition deteriorates. Treatment with D-Penicillamine can result in considerable reversal of neurological symptoms in favorable cases. Unfortunately, as with all sulfhydryl containing drugs, serious adverse reactions may occur which require stopping the administration of D-Penicillamine. Adjunctive factors also include a diet low in copper. (204,205,206)

D-Penicillamine is well absorbed from the gastrointestinal tract. One gram of penicillamine causes the excretion of about 2 milligrams of copper. (207) The biological half life is 16 hours. It is an oral chelator of iron, mercury, lead, arsenic and copper. (179)

D-Penicillamine is primarily excreted by the kidneys. Optimal dosage can be determined by measurement of urinary copper excretion and the determination of free copper in the serum. The urine must be collected in copper-free glassware, and should be quantitatively analyzed for copper before and soon after initiation of therapy with D-Penicillamine. It is wise to initiate therapy with 250 milligrams a day and gradually increase to as much as 2 grams a day. Patients with Wilson's disease will have to be treated for life. Control and dosage must be titrated to laboratory levels.

D-Penicillamine is also used in the treatment of cysteinuria with stone formation. Penicillamine forms a penicillamine-cysteine mixed disulfide and helps to dissolve the stones. This is used along with a diet low in methionine, high in fluids, and alkaline enough to produce an alkaline urine. For cysteinuria, the usual dose is 2 grams a day for adults with a range of 1 to 4 grams a day in four divided doses. For children, the dose is based on 30 mg/Kg/day. Initiate therapy with 250 mg and increase the dose gradually to minimize side effects. Cysteine excretion should be held to around 100 milligrams per gram of creatinine per day. (207)

Rheumatoid arthritis may respond to treatment with D-Penicillamine although the exact mechanism is not known. It lowers IgM rheumatoid factor but produces no significant depression in absolute levels of serum immunoglobulins. Symptoms may not show regression for months and the optimal duration of treatment has not been established. (208,209)

The schedule for administration of D-Penicillamine for rheumatoid

arthritis begins with a single daily dose of 125 to 250 milligrams which is increased at 1 to three month intervals. If the dose goes to 1000 to 1500 milligrams after three to four months of treatment with no discernible improvement, it may be assumed the patient will not respond and treatment should be discontinued. (207)

Treatment with D-Penicillamine is also used for mercury toxicity. Four divided doses of 20–40 mg/Kg/day to a maximum of 1 gm/day in children. The adult dose is 250 mg q.i.d. and should be given on an empty stomach for 3 to 10 days. (210)

If a second course of therapy is indicated because of persistent elevation of urinary levels of mercury, the D-penicillamine should not be restarted for 10 days. Renal failure would be a contraindication for treatment with D-Penicillamine, unless accompanied by hemodialysis.

D-Penicillamine should not be given until the GI tract has been cleansed of mercury, otherwise absorption may be facilitated.

D-Penicillamine is given orally on an empty stomach, at least one hour before meals or two hours after meals, and at least one hour apart from any other drug, food, or milk. Doses of up to 500 milligrams may be given in single doses. More than 500 milligrams should be given in divided doses. (207)

Contraindications are: pregnancy (except in the case of Wilson's disease), nursing mothers or renal insufficiency.

Caution: Because of the potential for serious hematological and renal adverse reactions to occur unexpectedly, (which have resulted in severe toxic reactions and death,) routine urinalysis, white and differential blood cell count, hemoglobin determination and direct platelet count must be done every two weeks for at least the first six months of regular penicillamine therapy and monthly thereafter.

Patients should be encouraged to report symptoms such as fever, sore throat, chills, bruising or bleeding. Watch for proteinuria or hematuria as this may indicate a nephropathy that may lead to a nephrotic syndrome. For additional information please refer to the PDR under the names; Depen, (Wallace) or Cupramine, (Merck).

An oral chelation challenge of D-Penicillamine to test for evidence of nutritional and heavy (toxic) metals has been suggested by Dr. Russell Jaffe, M.D., Ph.D. His protocol is:

Take 2 capsules of 250 mg before each meal and before bedtime for 3 days. (2 grams a day for 3 days). Collect all the urine excreted for the 24 hours of the second day in a heavy metal free container. (It is important to collect *all* the urine). Take the entire container to the

laboratory as soon as possible after collection. The reason for the second day 24 hour urine specimen is that it takes 24 hours for the D-Penicillamine to get into deep tissue sites. This is a test for iron, mercury, lead, arsenic as well as copper excretion.

The reason that you continue with the D-Penicillamine for the third day is that some patients will have a great load of toxic minerals mobilized by the test. It takes the third day of D-Penicillamine to remove these so as to not leave too high a toxic mineral concentration floating in the blood stream to cause toxic reactions.

Unlabled uses: primary billiary cirrhosis and scleroderma. Some physicians use D-Penicillamine selectively for lead poisoning in children as it is an oral preparation and not as painful to administer as BAL or $CaNa_2EDTA$.

## X. SUMMARY AND CONCLUSIONS

This protocol is designed to assist physicians who are interested in using chelating agents in a safe and effective manner in their practice. Physicians should supplement knowledge of this protocol with appropriate workshops, conferences, tapes and reference materials found in this protocol. As of this writing, chelation therapy workshops are offered both by the American College for Advancement in Medicine (ACAM) and the Great Lakes College of Clinical Medicine (GLCCM), whose present addresses and phone numbers are listed below. A Physician interested in becoming proficient in these treatment modalities should also take the written and oral examinations, as well as fulfill other requirements, so that he/she may be certified as to competence in this field. (See Appendix V.) This certification is offered by the American and International Board of Chelation Therapy. The physician is then known as a diplomate, board certified in chelation therapy.

To better understand the history (211) and current status of EDTA as well as the salient points presented in this protocol, you are advised to review all of the appendices of this protocol.

The American College for Advancement in Medicine
23121 Verdugo Drive, Suite 204
Laguna Hills, CA 92653
714-583-7666
1-800-532-3688

The Great Lakes College of Clinical Medicine
1407-B, North Wells Street
Chicago, IL 60610
1-800-286-6013

## APPENDIX I.

A standard chelation therapy infusion will consist of:

| | cc | milliosmoles |
|---|---|---|
| 500 cc sterile water | 500 | 00.00 |
| 3 grams of Na2EDTA | 20 | 26.80 |
| 2 grams of magnesium chloride | 10 | 29.50 |
| Procaine HCl, 100 mgm | 5 | 01.40 |
| Heparin, 2500 units | 0.5 | 00.46 |
| Ascorbate, 7 grams | 14 | 81.20 |
| Potassium Chloride, 2 mEq | 1 | 04.00 |
| Pyridoxine, 100 mgm | 1 | 01.11 |
| Thiamine, 100 mgm | 1 | 00.62 |
| Sodium Bicarbonate, 840 mgm | 10 | 17.90 |
| Pantothenic acid, 250 mgm | 1 | .85 |
| | 563.5 | 163.84 |

163.84/563.5 * 1000 = 291 milliosmoles

blood laboratory normals (Roche labs.) = 274–295

Third world countries may have to use 5% D/W with the appropriate amount of $MgNa_2EDTA$ and lidocaine or procaine. This may suffice with appropriate oral vitamin and mineral supplementation.

Some physicians leave out the lidocaine or procaine altogether as being unnecessary and possibly increasing the risk of an allergic reaction.

## APPENDIX II.

**Creatinine Clearance Calculation**
(as derived from serum creatinine)
**Cockcroft-Gault Equation, Modified**

$$\text{Creatinine Clearance (ml/min)} = \frac{(140 - \text{age in years})}{\text{serum creatinine in mg/dL}}$$

EDTA DOSE to be administered in each infusion is computed as:

$$\text{50 mg/kg of lean body weight} \times \frac{(\text{creatinine clearance})}{100}$$

Correct for creatinine clearance only if less than 100

The Lean body weight is always used in above computations

The Lean body weight for males is computed at 50 kg plus 2.3 kg for each inch of height over 5 feet

The Lean body weight for females is computed at 45.5 kg plus 2.3 kg for each inch of height over 5 feet

The Actual weight is used for thin patients, whenever the actual weight is less than the computed lean body weight.

## APPENDIX III. Additional Comments on Testing for EDTA Chelation Therapy

Much ado has been made about medical testing related to a chelation therapy treatment program. There are tests that should be done following good medical care principles and there are tests related specifically to the chelation process itself.

Good medicine dictates that a thorough history, hands-on physical, pre-chelation chemical and vascular status be determined prior to the actual chelation treatment program. The treatment regimen will be determined by the parameters obtained before starting the first infusion.

To be somewhat crass, some have said that the only test necessary prior to chelation therapy for vascular disease is a serum creatinine so that the kidney status can be determined and the treatment program adjusted accordingly. This is an absolute travesty. Any physician with this philosophy will eventually get into trouble by missing other deficiencies that need to be corrected.

A human being is not a static phenomenon, but an ever changing bio-physiological entity. It makes good sense to ask for and obtain any

and all prior laboratory tests so that a time track of change can be made.

The basic tests include:

A broad based chemical profile or equivalent, with cholesterol, triglycerides and HDL

Complete blood count with differential

Iron metabolism : serum iron, transferrin, ferritin, total iron binding capacity, (TIBC) and % saturation

Thyroid function : including TSH and $T_3$ by RIA

Blood sugars : hemoglobin—A1C or fructosamine

Glucose tolerance test—if clinically indicated

Urinalysis

Mineral studies: hair, urine, blood, blood elements

Electrocardiogram

Non invasive vascular studies-dependent on the part of the body involved

Creatinine clearance by 24 hour urine collection and/or by formula (Cockcroft-Gault)

24 hour urine collection for minerals before and after a chelation challenge

| | |
|---|---|
| Cardiac : | E K G |
| | Thallium or technetium stress test |
| | Electrical impedance cardiography |
| | Echocardiography |
| | Cardiac catheterization |
| | Digital subtraction angiography |
| | Positron emission tomography (PET) |
| | Ultrafast CT |
| Carotid : | Stethoscope exam for bruits |
| | Doppler, single or real-time with ultrasound |
| | OPG—oculoplethysthmography |
| | Angiograms |
| Peripheral Vascular : | Stethoscope exam for bruits |
| | Plethysmography |
| | Segmental blood pressures with A/B ratios |
| | Color doppler with ultrasound |
| | Angiograms |

Chest x-ray—if indicated
Heidelberg gastrogram—if indicated
Creatinine clearance (by formula or by urine)

Additional tests would be considered depending on the presenting symptoms of the individual patient. For example:

Arthritis might need an RA test, CRP, ASO titer, and sed rate.
Diabetes or sugar imbalance : glucose tolerance test (GTT). Perhaps an insulin GTT if diabetes is suspected or hypoglycemia is a presenting complaint. Serum insulin levels.
Lupus erythematosus: an LE test
Adrenal deficiency: urine or blood tests before and after ACTH challenges. Salivary adrenal stress index (ASI)
Specific cardiovascular risk factors (blood tests)
Homocysteine, lipoprotein (a), fibrinogen and platelet aggregation.

Other specialized tests would be done such as:

β-carotene, B1, B2, B3, B5, B6, B12, folate, biotin,
inositol, choline, E, D, C, etc.
Amino acid profiles
Hormone levels: parathyroid, testosterone, estrogen, progesterone, DHEA, cortisol, Somatamedin-C, (IGF-1). LH, FSH
Cerruloplasmin
Urinalysis for B2-microglobulin or retinal binding protein
Platelet aggregation—fibrinogen
Fatty acid profiles
Antithyroid antibodies
Immune profiles
Viral antibody profiles
Pro albumin
Food and mineral allergies-Elisa ACT-IGG4 immunologic studies
Hepatic detoxification profiles
Comprehensive diagnostic stool analysis (CDSA)

What is important is to select and order those tests that will contribute information that aids in specifying the patients condition (diagnosis) and provide follow-up tracking of return to health. To test, just to test, is not justified.

Practicing excellent medicine is the goal of every physician. When you are "above mainstream medicine," your records must be able to

stand up to close scrutiny by anyone entitled to examine them. Before and after documentation of your patients prior conditions and post treatment changes are part of good medicine as well as contributing to the growing documentation of health benefits of chelation therapy.

## APPENDIX IV.

Sample Multi-vitamin/mineral/trace element supplement formula containing the following total daily amounts:

Calcium–500 to 1,000 mg
Magnesium–400 to 600 mg
Manganese–15 to 25 mg
Zinc–15 to 25 mg
Chromium–150 to 200 mcg
Selenium–150 to 200 mcg
Copper–2 to 3 mg
Boron–0.5 to 1 mg
Vanadium–15 to 30 mcg
Molybdenum–50 to 100 mcg
Potassium–50 to 99 mg
Iodine–100 to 200 mcg
Beta carotene–10,000 to 20,000 IU
Bioflavonoids–50 to 150 mg
Inositol–50 to 100 mg
Thiamin (B1)–50 to 150 mg
Riboflavin (B2)–25 to 50 mg
Niacin (B3)–25 to 100 mg
Niacinamide (B3)–5– to 150 mg
Pantothenic Acid (B5)–250 to 500 mg
Pyridoxine (B6)–15 to 25 mg
Vitamin B12–50 to 200 mcg
Folic Acid–400 to 800 mcg
Biotin–200 to 300 mcg
PABA–50 to 100 mg
Vitamin A–5,000 to 10,000 IU
Vitamin C–1,000 to 2,000 mg
Vitamin D–50 to 400 IU
Vitamin E–200 to 800 IU
Choline–50 to 100 mg

Other nutrients to be considered include:

L-Carnitine 500 to 1500 mg
L Glutathione 25 to 200 mg
Coenzyme Q-10 150 to 300 mg
Proanthocyanidins
Ginkgo Biloba (24%)
L-Cysteine/n-Acetyl l-cysteine
L Proline
Lecithin(w/phosphytidylcholine)
Glutamic Acid/L-Glutamine
L-Aspartic Acid
L Lysine

Other minerals or nutrients may be added depending on the status of the individual patient

## APPENDIX V. American Board of Chelation Therapy: Patient Record Evaluation

The items listed below are mandatory to be found in the charts submitted to the ABCT for examination leading to initial Board Certification in Chelation Therapy. Although there may be individual differences of opinion as to what is necessary for adequate safety and ultimate patient benefit, The ABCT board, at the time of this writing, requires all of these items, some of which are regarded as important teaching tools relevant to the use of EDTA in the chelation process. Questions about each of these items will be asked at the oral examination.

Informed consent
Medical history
Current medications (names, strength and frequency)
Patient records from other doctors and/or hospitals (if available)
Physical examination (hands-on in detail)
Recap of laboratory results
Electrocardiogram
Chest x-ray (when indicated for non-smokers)
Non-invasive vascular studies (when indicated by symptoms)
Complete blood count
Urinalysis
Blood profile (SMA 18 or 24)
Thyroid function (T3–T4–T7)
5 hr glucose tolerance test (if positive family history or patient with glucose imbalance)
Creatinine clearance (by 24 hr urine or calculation-Cockcroft-Gault)
Mineral studies on blood, urine and /or hair
Urinary mineral excretion pre and post EDTA challenge
Flow sheet of chelation treatments
Progress notes
Post-treatment follow-up program
Summary of the chart

## APPENDIX VI. Additional Clinical Pearls

This protocol has been reviewed by many chelating physicians who have great experience and knowledge in this field. It is a compilation

of expertise and scientific common sense. However, since it is impossible to add all of the clinical pearls in the body of this work, this appendix will add comments that may be useful in select circumstances.

For patients with Congestive Heart Failure or hypersensivity to EDTA; you may use the patients own blood as a carrier for EDTA to increase the tolerance of EDTA. To do this, 250 ml of blood is drawn from the patient, EDTA is added, and the blood is returned back to the patient by slow drip.

The hypotheses as to why it works for cases of hypersensitivity that have developed after many treatments, (usually after 40) is that the antibody-antigen reaction will be completed in the patient's blood when it is still outside the body. After this reaction, the patient will usually tolerate the chelation treatment without an allergic reaction.

*Laboratory Testing*

An excellent objective evaluation of the heart pre, as well as post-treatment is some type of exercise tolerance test. This is an excellent objective determination of increased work capacity and will give an accurate measure of pre to post chelation therapy work ability.

A physician who has done over 25,000 stress tests concludes that in coronary patients the subjective improvement precedes the objective improvement by a long interval. Stress tolerance does improve, but ischemic changes on the EKG usually do not improve at the same pace. He considers the patient out of the risk zone when improvement of electrocardiographic ischemia is achieved in stress tests, and/or if EKG ischemic changes disappear by continuing the stress test, while increasing the load. (212)

Other delivery systems are now being investigated. One such is the use of a patch to deliver EDTA into the body. Another recent development is the use of rectal retention enemas as EDTA delivery systems. (213) We are watching the science behind these systems.

## APPENDIX VII. Sample Consent Form

I, _____, do hereby give consent to _____ and specifically to Dr. _____ to perform intravenous $MgNa_2EDTA$ chelation therapy ("Chelation Therapy") for the purpose of treatment of atherosclerotic disease and/or heavy metal toxicity, and/or preven-

tion or treatment of degenerative diseases. I understand that Chelation Therapy is a standard therapy widely approved for the treatment of heavy metal toxicity; however, its usage is considered controversial for the generalized treatment of atherosclerotic vascular disease and other degenerative diseases, and the view that it is of benefit in the treatment of such disorders is accepted by a minority of the medical community and is considered "experimental" by most physicians and insurance companies. I am advised that my treating physician believes that Chelation Therapy does have positive clinical benefit. I have been informed that other treatment approaches have been used in these conditions, including but not limited to bypass surgery or angioplasty and these alternatives have been explained to me to my full satisfaction.

I understand that the benefits of Chelation Therapy are much greater if I follow a healthy lifestyle, (non-smoking, weight control, proper exercise, proper diet, and nutritional supplementation). I understand that an initial series of _____ treatments are anticipated, and that these treatments may be extended over a number of months. I have been informed that Chelation Therapy may need to be repeated from time to time in the future in order to maintain the benefits. I understand that it is my option to stop this treatment protocol at any time without incurring any further expense after I have directed that such treatment be stopped.

I have been informed of possible risks and side effects including but not limited to: discomfort at the injection site, thrombophlebitis, hypocalcemia, fatigue, muscle cramps, kidney problems including nephrotoxicity, allergic reaction, congestive heart failure, liver disease, anticoagulation, lowering of blood sugar levels and/or hypoglycemia, mineral loss and generalized complaints.

If I have suffered from any previous kidney disease, I agree to execute a medical release so that all previously identified medical records of mine may be obtained from previous treating physicians, and I have disclosed openly any known previous kidney disorders. I understand that this therapy should not be used if I am pregnant unless I have a severe life-threatening disease. I understand that if I have a history of tuberculosis, Chelation Therapy may reactivate arrested tuberculosis and I agree to inform my physician of any occurrence of this disease. I understand the nature of the proposed procedure and the

risks and dangers have been explained to me to my full satisfaction. I have not been asked to discontinue care with any specialists.

While I understand that there have been no warranties, assurances or guarantees of successful treatment made to me, I desire to undergo this treatment after having considered the information contained in this document, the information provided to me through my conversations with my treating physician and through materials provided to me by the office to educate me about the treatment. I acknowledge that I have had the opportunity to ask any questions of my physician with respect to the proposed therapy and the procedures to be utilized and all of my questions have been answered to my full satisfaction. I also acknowledge that I have received a copy of this signed, informed consent.

I understand that Medicare does not pay for chelation therapy with EDTA for vascular disease and may not pay for laboratory testing after chelation therapy has been instituted. I also understand that there are very few commercial insurance companies that will pay for chelation therapy with EDTA for vascular disease.

Date: _____

Patient's Name _____
Signature

Patient's Name _____
Printed or Typed

Witness _____

Relative or Representative _____

Relationship to the Patient _____

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## *Appendix*

These additional references are here for your use and edification.

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