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EDTA and Chelation Therapy: History and Mechanisms of Action, an Update

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ABSTRACT: Twenty-four years have elapsed since my first article on EDTA, co-authored with Dr. Robert C. Vance[i] first appeared. In the past 50 years, it is estimated that over one million patients have received intravenous chelation therapy with one widely used chelator, EDTA. Unfortunately, I believe we may have still failed to discover the primary mechanism(s) of action responsible for the frequently dramatic clinical improvements seen in numerous apparently unrelated conditions treated with EDTA and/or other chelators, unless it is simply that the binding and/or removal of toxic metals permits improved metabolic functioning in a variety of conditions. With science documenting the adverse effects of commonly encountered low levels of heavy metals on health, it is possible that chelation therapy is being vastly underutilized in standard medicine and that combinations of new and existing Chelating agents may need to be employed to deal with the broader spectrum of toxic metals now being identified as contributors to many if not most diseases, including aging.

INTRODUCTION

I am currently a medical consultant to two companies that are involved in food supplement sales and both of these companies sell oral EDTA containing products. Since my initial review of the available literature[1] many more references to EDTA are now available[ii,iii]. Unfortunately, today's excessive focus on the potential benefits to patients suffering symptomatic cardiovascular disease has significantly, stifled the utilization of EDTA and other chelators in other conditions where I believe it should be routinely utilized, at least as an adjunct to other therapies. These indications include many common and difficult to treat conditions from acute rheumatoid arthritis and psoriasis, to cirrhosis of the liver and cancer, where clinical benefits have been described. I hope to refocus attention to the metal binding activity of chelating agents in general, so that this treatment may soon achieve its proper recognition as an adjunctive therapy in the management of many common health problems.

A BROAD VIEW OF CHELATION IN MEDICAL PRACTICE

Brain[iv] and renal function[v,vi] diseases, macular degeneration[vii], arthritis[viii] and arteriosclerosis,[ix,x,] are all conditions that have been reported to show benefits from IV EDTA chelation. Over thirty documented mechanisms of action associated with the use of this form of chelation therapy have been published. Newer developments in molecular medicine and cell signaling suggest, however, that there may be other, far more important basic mechanisms waiting to be discovered. One of these might be regulation of transcription factor NFKappaß activity, which plays a pivotal role in immune dysregulation. The dramatic responses in some cases of rheumatoid arthritis in the literature may be explained with inhibition of Nfkappaβ by EDTA.[xi,xii,xiii,xiv] This opens up many interesting possibilities for future chelation research in several seemingly unrelated conditions. Recent research in Alzheimer's disease involves the cortical deposition of Abeta. This has been found to be completely reversible with zinc and copper chelation[xv].

I believe that Chelation therapy for subclinical metal toxicity could soon become far more widely employed by many health care practitioners, many of whom probably will never become trained by either one of the organizations providing advanced training, or become fully certified by the American and/or the International Board of Chelation Therapy. There are many natural substances, including all weak organic acids, that are chelating agents and the public will undoubtedly soon begin self-treating with these various chelators as the health benefits of lowered levels of toxic metals becomes more widely appreciated. Accurate medical advice concerning oral chelating agents is essential. For example, research strongly suggests that cysteine-based oral chelators may, for example, re-deposit tissue-extracted mercury in the brain[xvi]. Neither Chlorella, nor PCA (Peptidyl Clathrating Agent) significantly chelate mercury out of the body in spite of the claims[xvii]. Garlic, on the other hand, appears to be generally beneficial and is documented to lower the level of lead in tissues,[xviii] as well as to decrease platelet aggregability[xix] and demonstrate significant cardiovascular and anti-atherosclerotic benefits.[xx,xxi,xxii]

Chelators may also provide beneficial effects through their influences on other substances. For example, Morrison[xxiii] documented as much as 90% reduction[xxiv] in incidence of acute heart attacks, using his polysaccharide-based formula[xxv]. By adding EDTA to his orally administered formula, we found that blood coagulability was reduced using the Chandler Loop test[xxvi,xxvii] (Gordon, GF, unpublished observation).

BYPASS VERSUS NEW IMPROVED COMPREHENSIVE CHELATION THERAPY

New developments focusing on the role of inflammation in cardiovascular disease[xxviii,xxix,xxx,xxxi,xxxii,xxxiii], clearly suggest that intravenous EDTA chelation therapy can no longer reasonably be considered as a primary or single complete therapy for the long-term management of cardiovascular disease[xxxiv].

Administration of IV EDTA offers many dramatic benefits including improved blood flow, and it deserves far greater recognition as a part of any comprehensive cardiovascular support program. With the recent recognition that some heart conditions have as much as a twenty thousand times increase in the level of some toxic heavy metals, chelation therapy, should be far more routinely employed. Some chelators believe that there is a worthwhile distinction between arteriosclerosis and atherosclerosis, which might improve treatment outcomes. They believe there is a higher content of calcium in the arteriosclerosis and a higher lipid content of the plaque seen in atherosclerosis. One of ACAM's co-founders, David J. Edwards (written communication, October 14, 2000), has indicated that he is observing significantly enhanced benefits from IV chelation in the atherosclerotic patient by his addition of three lipolytic agents (choline, inositol, and methionine) to the IV treatment with the EDTA. Dr Edwards believes this treatment might be thought of as "lipid stripping" enhanced chelation. He feels that the primary benefits of EDTA is related to its primary metal-binding activity, and thus arteriosclerosis with its higher calcium content should be expected to have better results than atherosclerosis where the lipid problem must be separately addressed. He tries to distinguish between atherosclerosis and arteriosclerosis by the use of either rapid CT scan or soft tissue extremity x-rays.

I believe that IV EDTA Chelation therapy for cardiovascular disease should never be employed without concurrent aggressive effective pharmacological and/or nutritional/natural product based therapy for all the newly recognized applicable cardiovascular risk factors. These include replenishment of deficient minerals that become relatively even more deficient in the face of the serious excesses of toxic metals in heart muscle cells. Furthermore it has now become essential to deal effectively with the infectious[xxxv] and resulting hypercoagulability[xxxvi] aspects reflected in the newer cardiovascular risk panels.[xxxvii]

It is now established that about 85% of sudden cardio- and cerebro-vascular deaths are due to rupture of vulnerable, non-calcified arterial plaque and subsequent clot formation.[28] This form of plaque, invisible by conventional angiography, initiates a terminal thrombo-embolic event superimposed on chronic vascular inflammation, hypercoagulation and metabolic derangement as in acquired homocysteinemia. Patients who choose I.V. chelation instead of by-pass surgery hope for more than symptomatic improvement, and when some learn that they still have seriously calcified coronary vessels on ultra high-speed cat scans, they are very disappointed. Some mistakenly opt for surgery at that time, even if they find they can easily

sustain a far higher level of physical activity following their "unsuccessful" chelation therapy. Unfortunately most patients are unaware of the new information about Vulnerable Plaque, the kind that is actually now believed to be involved in heart attacks, and they are not told that this truly life-threatening plaque is not readily seen on any currently widely available vascular tests, including angiograms. This failure has led me to consider the standard vascular tests relied on to sell by-pass and other invasive procedures to patients, as, at the very least, unreliable and misleading. Improved oxygenation of ischemic tissues is a reasonable goal of therapy and simple improvement in exercise tolerance testing is very useful in evaluating this.

I believe that most patients seldom are adequately informed regarding the severe limitations of all surgical approaches in the management of their vascular disease. In fact, since the vulnerable plaque involved in 85% of heart attacks and strokes cannot be seen with modern technology, their heart surgery is generally attacking the wrong plaque and thus is providing little, if any, long term benefit at great expense and risk. It is now widely believed that the underlying cause of death in heart attacks and strokes is from a blood clot related to vulnerable soft plaque due to an active infection in the arterial wall, often caused by herpes related cytomegalic virus or chlamydia pneumonia. Current research calls for treating the blood to prevent these life-threatening clots, not the blood vessel.[24]

I hope that wider dissemination of this new information will help lead to the end of the largely useless surgical attack on coronary vessels so rampant today. In fact, some believe that operating on infected tissue is poor medical practice, which happens frequently with unstable angina as shown by elevated C-reactive protein levels that standard medicine has such difficulty managing. In fact, Dr Terry Haws has informed me that using the cardioCRP test offered by Quest Labs, that the majority of his new patients are coming back reported as "at risk" (verbal communication). It appears that just as "safe" levels of cholesterol and homocysteine tests, over time, were moved lower and lower, the same can be anticipated with c-reactive protein testing as more data regarding "ideal" values is accumulated. The infection that apparently we all have in our vascular tissues causes hypercoagulability, resulting in local ischemia that is far better treated medically.[xxxviii] Of course, intravenous chelation always has a place in the management of any ischemic process. We all routinely expect to see improved circulation in 85% or more of our chelation patients[xxxix] and there are over thirty potential beneficial actions of EDTA to help explain this improved blood flow.

I believe that with our improved understanding regarding the need for effective control of hypercoagulability in virtually all ill patients[xl], it may be beneficial to routinely add a more therapeutic level of intravenous or subcutaneous Heparin[xli], along with more aggressive therapeutic levels of intravenous Vitamin C, in our efforts to manage this newly identified epidemic of hypercoaguability/infection related problems. 4,000 to 6,000 units of Heparin, based on weight, administered subcutaneously b.i.d. are safe, for a therapeutic trial of several weeks, without doing specialized coagulation studies in patients without a history of serious bleeding disorder (personal communication with David Berg, May 3, 2000). Longer term use of oral enzymes[xlii] or daily heparin injections to decrease fibrinogen concentrations and soluble fibrin monomers appear to greatly facilitate the treatment of any chronic infectious process[36].

Appropriate enteric-coated oral enzymes containing bromalain and/or heparin injections decrease fibrinogen concentrations and soluble fibrin monomers to facilitate the treatment of any infectious process. A safe approach in helping to combat infection can be with colostrum and colostrum-based transfer factor[xliii,xliv,xlv,xlvi] and other immune enhancing and cardiovascular supporting nutritional supplements[xlvii,xlviii,xlix,l,li]. All are now better supported with a new, non-acidic, neutral pH, well-tolerated form of oral Vitamin C, and/or Vitamin C infusions. The already high efficacy of combinations of these natural approaches in dealing with any infectious process

has recently been significantly enhanced by an effective extract of gram-positive bacteria known as muramyl polysaccharide glycan complex. This has been found to enhance immunity against all infections, and even shows anti-tumor activity[lii].

We no longer have to rely on the long-term use of largely ineffective antibiotics alone for the control of chronic and often resistant infections now recognized in the hypercoagulability problem. Antibiotics alone have been shown to be inadequate for long-term control of chlamydia, although currently some experts are recommending a full year of azithromycin,[35] or the other chronic hidden infections found in the vascular wall that is now clearly implicated in deaths from vascular disease[liii].

I believe that the optimal use of EDTA in clinical practice needs to be totally repositioned, probably as an adjunct to most other therapies, providing improved management of most chronic diseases, since its primary function is eliminating excessive levels of metals. I fear negative outcomes from currently proposed and/or ongoing chelation cardiovascular studies where removal of the wrong plaque is the focus and the ethical dilemma in blinding any study may seriously jeopardize any studies.[liv] If, on the other hand, trace element studies are done to document the significant detoxification benefits seen with chelating agents, and long-term outcomes and quality of life data are compared to standard therapies, the combination of this data should offset any detected failure to simply remove plaque. Combined with safe, effective, natural treatment of all the newly recognized risk factors, such a comprehensive chelation protocol, I believe, would produce exceptional results. Since we have now entered the age of Einsteinian, molecular-based cardiology, nothing but the elimination of most by-pass surgery, a Newtonian concept, should be the goal.

Generally, the toxic metals removed by intravenous EDTA chelation simply start to re-accumulate once the treatment is discontinued. Thus, a number of oral chelators, including ascorbic, malic and lactic acids[lv], may help maintain chelation benefits more cost effectively over a lifetime. Another approach is to reduce the biologic availability of heavy metals. For example, selenium binds mercury, markedly diminishing its potential for biologic harm, and many naturally occurring substances such as rutin and lactoferrin have been shown to have chelating properties. There is however, no single chelator available today that can effectively deal with the wide spectrum of potentially toxic metals that have been implicated in the degenerative diseases associated with aging. Thus, I believe that a broad spectrum of natural and/or pharmacological agents with chelating ability would be predictably more effective. My experience is that a comprehensive preventive approach can be effective even in high-risk patients, i.e. those with documented hi-grade involvement of two or three vessels.

For example, eicosapentaenoic acid supplementation[lvi,lvii] augmented with garlic[lviii], ginkgo, EDTA activated polysaccharides, bromelain and rutin can all be effectively employed synergistically in such a comprehensive broadly based protection program.

There is no critical need for monitoring with bleeding or clotting tests patients maintained on such a program since there is no significant risk of pathologic bleeding. It is, however, important to emphasize to the patient that this protection must be continuously maintained. Aspirin and NSAID's reportedly contribute to over 16,000 deaths each year[lix], largely as a result of induced G.I. bleeding. The benefits from aspirin and Coumadin are seriously limited[24]. The use of modern platelet aggregation and fibrinogen studies can show patients just how incomplete their standard drug protection is. By later repeating these tests after initiating a comprehensive natural product based anticoagulant program, patients can generally see the remarkably improved level of protection they now enjoy with little or no side effects.

The Homeopathic Medical Board of Arizona Chelation Peer review committee that I chair has currently advised physicians in Arizona that all chelation informed consent procedures for cardiovascular disease should specifically spell out the important caution that, even though patients may enjoy tremendous symptomatic improvement, actual (regular or visible) plaque reversal as measured and relied on today for prescribing life-threatening vascular surgery, may not be occurring.

BLOOD CLOTTING

Berg[38] has shown that a coagulation panel that is more sensitive than hitherto available is capable of distinguishing healthy from unhealthy subjects with over 95% accuracy. In fact, hypercoagulability is associated with a large number of chronic diseases.[39]

Since EDTA prevents clotting in blood collection tubes used daily, I believe more sensitive tests may show some subtle reduction of hypercoagulability. Possibly lowering the number of adhesion molecules, or soluble fibrin monomers, may be one of its subtler, but life saving benefits. The combination of a polluted environment, stressful life style and chronic low-grade infection leading to hypercoagulability, initially called the AntiPhospholipid antibody syndrome, has now more recently been renamed "immune system activation of coagulation" (ISAC). It appears to be surprisingly common and those at risk need long-term effective but safe lifelong anticoagulation treatment. Aspirin alone is too weak and too dangerous to handle this epidemic of hypercoagulability. It has also recently been reported to be too dangerous for men with hypertension to take on a regular basis[lx]. Effective aspirin substitutes include pancreatic enzymes (Wobenzym™)[lxi] and properly stabilized bromelain supplements, preferably used in combination with garlic, Ginkgo, and salmon oil. A polysaccharide/ chelation based product, containing EDTA, also acts as an effective aspirin substitute and affordably helps to meet this nearly universal need[lxii].

ORAL EDTA

Chelating agents are routinely added to our food supply so that EDTA, for example, is added to foods for its ability to bind with the transition metals, particularly iron and copper[lxiii]. These agents inhibit rancidity in substances such as oils[lxiv,lxv]. This has led me to consider the potential benefits from the non-absorbed fraction of orally ingested EDTA, which, I believe, may help prevent oxidative degradation within the intestinal tract, just as phytic acid has been reported useful in chelating iron, which acts as a catalyst in the development of colorectal cancer[lxvi]. Many oral-chelating agents, including EDTA, might provide long-term protection, including helping to prevent potential intravascular coagulation[lxvii,lxviii,lxix,lxx]. Remarkable responses have been attributed to various chelating agents, including DMPS, Penicillamine, Desferoxamine, as utilized by Paul Cutler (personal conversation, October 7, 2000) in the treatment of diabetes, infections and cancer and EDTA[lxxi,lxxii]in an extremely diverse number of conditions.[lxxiii,lxxiv,lxxv]

There are, in fact, over 300 references to the use of oral EDTA[3]. Nonetheless, there are many knowledgeable clinicians who are very negative about the oral ingestion of EDTA and who raise questions about its long-term safety. Recently published research has more than adequately rebutted those concerns.[63, 64,lxxvi] I believe that the benefits of lowered levels of toxic metals and diminished availability of transition metals more than offsets any theoretical concerns about potential essential trace mineral depletion, about which I believe we have adequate knowledge to monitor and treat.[lxxvii,lxxviii] and some research suggests that minerals become more bioavailable.[lxxix] Since only 5% of orally ingested EDTA is absorbed, taking 1200

mg for a year would provide at least some of the benefits seen from receiving 10 intravenous therapies of 3gm each a year.[lxxx,lxxxi]

I am totally convinced that there are significant benefits from oral chelation for patients unable to undergo a more complete program of intravenous therapy, and further that oral EDTA helps provide for an effective maintenance program even for those who are concurrently undergoing a series of intravenous chelation treatments[lxxxii]. Oral EDTA for the treatment of asymptomatic lead toxicity was FDA approved for the indication "to increase the excretion of lead." This is described in the Physicians' Desk Reference (PDR) through 1976, with obvious supporting references in the FDA files, complete copies of which we are still attempting to obtain. We, as licensed physicians, specializing in Chelation Therapy, I believe are fully responsible and probably legally liable to become adequately informed about the pro and con of all forms of chelation therapy, if we are to adequately discuss all of the available choices with our prospective chelation patients. This would seem essential if we hope to obtain a totally informed consent before prescribing chelation therapy for any reason, to our patients.

Oral EDTA probably exerts some anticoagulant and antiplatelet effects partially by the effect of chelating calcium ions[lxxxiii,lxxxiv]. It has also been shown to prolong prothrombin time[lxxxv,lxxxvi] and has effects on platelets[lxxxvii,lxxxviii] and other blood components[lxxxix,xc] cell membranes[xci] and has cholesterol-lowering potential.[xcii] EDTA has also has been the subject of a US patent[xciii] because some therapeutic substances, especially sulfated polysaccharides, like heparin, which previously were only effective when given parenterally, became orally effective in the presence of EDTA.[61] Oral EDTA therapy was discussed in the *Waukegan News-Sun*, because a soap manufacturer, Neil Purdy, was supplying EDTA powder to anyone who contacted him.[xciv] A physician, Dr. James Mercer of Lenexa, Kansas, was favorably disposed to recommend this treatment to his cardiovascular patients. Dr. Mercer received a letter because of the improvement seen in a shared patient, from Dr. Sawyer, Professor of Surgery, State University of New York (written communication November 9, 1971) as well as a letter of support from Loren Parks, Director of Parks Electronics Laboratory, Cardiovascular Instrumentation of Beaverton, Oregon (written communication June 13, 2000). The oral EDTA therapy program recommended to those patients involved taking 3gm of sodium EDTA given in 6 ounces of preferably grapefruit juice or a Vitamin C drink. Additional mineral supplementation was advised for the patients. Dr. Mercer also reported a consistent lowering of cholesterol and triglycerides in the over 100 patients he treated with this regimen.

Studies have been published measuring urinary and fecal lead excretion induced by oral EDTA.[xcv] However, the use of EDTA in the treatment of lead-poisoned workers fell into disfavor because of abuse by industrial-based physicians, who ignored the basic axiom of good medical practice, which is to remove as much as possible the source of exposure, rather than concentrating on the less expensive prescribing of oral EDTA tablets to lead workers.[xcvi] In spite of this, the PDR through 1976 under Riker continued to list calcium disodium Versenate tablets with the only approved indication, to increase the excretion of lead.[xcvii]

The body has many metal binding substances, including albumin, metalothioneins, ferritin, ceruloplasmin, transferin, and others. A reasonable hypothesis may be that additional chelators further support our health by enhancing our body's ability to handle free metal catalyzed reactions. The reason that EDTA is routinely added to the food supply today is to help prevent the oxidative degradation of nutrients by chelating the transition metals. Our individual consumption of EDTA from food sources is estimated to average between 15mg-50mg per day. There has been concern raised that the widespread use of EDTA in our food may have an adverse effect on the environment because EDTA was non-biodegradable and may have increased the solubilization of heavy metals, particularly cadmium.[xcviii] Increasing low levels of EDTA in the environment may lead to the enhanced uptake of heavy metals, particularly cadmium, in living tissues. Fortunately, I believe we can neutralize this concern because cadmium had been shown to respond to adequate therapeutic administration of oral EDTA.[xcix,c,ci] EDTA has a 40-year history of oral use in asymptomatic patients with laboratory evidence of lead accumulation and can safely be given continuously in doses of up to 1gm a day to adults. Concomitant administration of essential trace elements, especially zinc, is

obligatory. Its safety seems to be firmly established, and the potential of mineral depletion seems to be minimal.[63,cii]

In fact, at the NIH/ODS Bioavailability Conference the ENVIRON International Corporation report on mineral absorption listed EDTA as a dietary factor enhancing absorption and bioavailability of zinc along with protein, cysteine, citrate and methionine.[ciii]

In a recent recorded and published interview by ACAM member and Diplomate of ABCT, Ron Kennedy, MD, of Santa Rosa, California, on the subject of oral chelation,[civ] I provided more of the historical background to further assist others in understanding some of the potential clinical applications of oral chelation.

The central role of iron in catalyzing free radical pathology, and consequently upon health span and longevity, belies the common clinical perception that iron saturation is preferable to the risk of deficiency. Epidemiological studies show that iron stores, as measured by serum ferritin, accumulate four times faster in males than pre-menopausal females and that cardiovascular disease is also four times more likely in age-matched men. Monthly menstrual iron losses may thus mitigate cardiovascular risks in a manner analogous with the chelation of excess free iron, inasmuch as hysterectomy, even with intact ovarian function, abolishes the protective effect[cv]. Similarly, regular blood donors show decreased incidence of myocardial infarction and cancer, recalling the Swiss experience with regular EDTA rapid IV injections of Calcium Disodium EDTA in carefully monitored patients over almost two decades. For example, the level of lead has now been shown to relate directly to IQ.[cvi] This suggests that it would be prudent to offer some form of oral chelation to every student, recognizing the cost and importance of education in our society.

CHELATION AND HEAVY METALS

Chelation therapy benefits may still however be primarily the result of the obvious heavy metal detoxification. Blumer[cvii] showed dramatic long-term benefits from parenterally administered calcium disodium edetate that clearly support the concept that we all may live far longer and healthier lives by simply decreasing our body burdens of lead. Occult lead intoxication has been documented to be a cause of hypertension and renal failure[cviii], and the disappearance of immune deposits in a patient with renal impairment due to low-level lead toxicity has now been demonstrated by renal biopsy before and after EDTA chelation[cix]. It has also been reported in one study that 4 out of 6 patients being treated for renal failure who developed gout *de novo* had underlying plumbism[cx].

The future of combined chelation agents appears promising and largely understudied. The combined use of EDTA and DMSA shows clear advantages if the primary focus of therapy is identified- namely to reduce body burden of heavy metals such as lead[cxi]. With lead toxicity still being an epidemic in the US, there is still no standardization in its therapy. Less than one-third of responding lead clinics report utilizing oral chelation as the agents of choice even though the 1984 consensus statements fully describe the use of penicillamine. Oral DMSA also appears to be safe and effective for the treatment of childhood lead poisoning. There is still no consensus regarding the use of provocative testing or protocols for treatment[cxii].

Olwin[cxiii] was one of the earliest investigators to recognize that blood flow improvement in vascular disease patients from EDTA chelation was very probably due to removal of lead. At that time, over twenty years ago, most experts were unwilling to accept this all too obvious explanation. This was partly due to our lack of understanding regarding the subtle adverse effects we are all suffering from as a result of the over 1000-fold increase in lead levels in average bone tissues today over pre-industrial levels. Since then, we have become much more knowledgeable about the magnitude of these increases in average lead levels and the

adverse health effects associated with them.[cxiv,cxv,cxvi,cxvii,cxviii] Research to document whether or not most chelation benefits are primarily from deleading effects alone, however, is complex and expensive. Furthermore, we cannot readily find a "control group" that is not significantly lead-burdened anywhere on our planet today. Experts now generally agree that there is no safe level of lead[cxix,cxx,cxxi,cxxii]. This may make proving what chelation really does as complicated as that involved in documenting the adverse effects of second-hand smoke, from which virtually no one was truly escaping. Since everyone had some of the adverse exposure it was not simple to prove the long-term benefits of a smoke free, or in this case, a low lead internal environment[cxxiii].

Over the past twenty years, the so-called "safe levels" of all potentially toxic metals have gradually been lowered to the point that I believe that no one is escaping at least some of their adverse effects[cxxiv,cxxv,cxxvi,cxxvii]. This would suggest that everyone would have better health and respond better to the management of any disease process if we could safely and cost effectively assist them in controlling some of these toxic metals now seen in all living tissues. Therapeutic assistance might be either through simply increasing the capacity of the body to bind free metals safely, or by effectively removing them through some form of chelation therapy. We need to establish some standards for the responsible use of chelating agents. There are millions of children in the world suffering from sub-optimal health because of toxic metal overload[cxxviii]. Upon finding at least a doubling of the excretion of a known toxic metal in a provoked urine specimen, compared to baseline tests, it would be reasonable to suggest some form of chelation, preferably oral.

We know that there are numerous published papers describing adverse effects with cadmium[cxxix,cxxx,cxxxi,cxxxii], aluminum[cxxxiii,cxxxiv,cxxxv,cxxxvi,cxxxvii], mercury[cxxxviii,cxxxix,cxl,cxli,cxlii], iron and copper[cxliii]. Crapper-McLachlan[cxliv,cxlv,cxlvi,cxlvii] has done extensive studies relating aluminum to the aging process. The mercury issue, thanks primarily to dental fillings, continues to wreak havoc on our health[cxlviii,cxlix,cl]. With the public's interest in anti-aging and detoxification, it appears reasonable that many will choose to detoxify themselves with whatever non-prescription chelators with which they become aware. We should be able to augment their efforts with knowledge and therapies they cannot self-administer.

Whenever possible, it makes good sense to remove the patient from a lead or other metal contaminated environment, but this is frequently not possible. Abuse of this principle by physicians working for the lead industry resulted in subsequent confusion regarding the benefits from the use of oral EDTA[cli]. They failed to follow the simple and basic principles of ethical medicine since nothing was done to clean up the workers' environment. They chose instead to administer the inexpensive tablets of oral EDTA to the workers in order to maintain their blood lead levels in acceptable ranges, so they could continue working. Therefore, workers remained at risk on the job. This led to the American Medical Association condemning the use of oral EDTA in lead poisoned workers, although the tablets were FDA approved for treating asymptomatic lead poisoning, with the recommended dose of 1000 mg per 35 pounds body weight.

With increasing research documenting the danger of elevated iron levels, and the life-prolonging benefits associated with regular donation of blood, it is beginning to become quite clear that it may become malpractice to prescribe iron to patients without documenting their need. Many believe that it is the lower levels of iron that is primarily responsible for the increased life span of women over men. Research on a new oral iron-chelating agent under study shows dramatic benefits including protection against skin cancers, skin aging, ultraviolet protection and significant neural protection in trauma.

The initial observation of symptomatic improvement in chest pain in patients receiving EDTA for lead poisoning was coincidental.[clii,cliii,cliv] This led to many years of research on the effect of various chelating agents, whether administered orally or intravenously.

The many potential benefits from the chelating effects of toxic and transition metals have already been mentioned and we may come to realize that we have seriously under-utilized all forms of chelating agents in medical practice today due to our lack of appreciation of the tremendous increases in total metal burden we all face as a part of today's environmental degradation[clv]. Current research regarding the adverse effects from our increased lead burden and the more recently recognized iron overload problem[clvi,clvii,clviii,clix,clx] warrants every physician

becoming knowledgeable in the appropriate use of oral and parenteral chelators and/or metal binding substances. It may not be necessary to completely remove a toxic or transition metal to obtain significant clinical benefits, as simply binding it, thus making it less available, may markedly diminish its potential for harm.

Experts in chelation chemistry (bio-inorganic chemists) such as David R. Williams[clxi] have suggested that most health problem can be shown to involve a deficiency or excess of trace minerals at some level. The fact that Dimethylpropanyl sulfate (DMPS) was used by Russian investigators[clxii] in the treatment of atherosclerosis and they reported and measured improved circulation I believe further suggests that the primary beneficial action from chelating agents is from reduction of our ubiquitous toxic metal burden, although life-extension benefits may be more directly related to the associated reduction in free radical pathology.

CALCIUM AND CHELATION

One of the paradoxes of aging is the occurrence of osteopenia in conjunction with vascular and soft tissue calcification, the precise cause of which is unknown. A deficiency of Vitamin K is an integral part of this undesirable pathologic calcification process[clxiii,clxiv]. This is a complex process since coronary calcification is markedly increased in hostile young adults[clxv].

Nearly 90 percent of young dialysis patients have coronary calcification 2.5 to 5 times more than normal, raising serious questions about the current practice of aggressive calcium supplementation to offset the disturbed phosphorus metabolism in these patients. Those consuming the highest intakes of calcium revealed the most calcified vessels. Some of the worst levels were seen with associated elevations of c-terminal parathyroid hormone and this was also related to lower bone density[clxvi,clxvii,clxviii].

Until effective prevention of this process becomes more widely available, the anti-aging benefits of chelation to reduce calcium content in vascular tissues remains highly desirable. However, it is clearly not a routinely predictable outcome. It should always be employed in association with the therapeutic modalities already discussed. After reviewing hundreds of radiograms before and after IV EDTA chelation, it is clear that grossly visible pathologic calcification is generally reduced, [clxix] as I have seen on hundreds of before and after radiograms from the practice of Dr. Ray Evers (Gordon GF. Unpublished observation) even in nephrocalcinosis, calcinosis universalis[clxx,clxxi] and Mönckeberg's sclerosis.[clxxii] Extensive calcification of arteries was seen in radiographs of the 5,000–year-old "Ice Man" and in Egyptian mummies. Therefore, calcification of arteries is not a new disease. Sudden death from heart attack I believe is a modern, separate new, problem. The current research on hypercoagulation due to chronic inflammation may be a plausible explanation for how this is superimposed on arteriosclerosis.

AGING, LEAD AND OTHER HEAVY METALS

Davies[clxxiii] showed that aging was associated with a gradual decrease in the levels of essential trace elements and a gradual increase in the levels of potentially toxic metals. Thus, chelation of heavy metals[clxxiv], together with replacement of essential elements is a logical step in the control of aging[clxxv].

In considering the phenomena associated with aging, Tyler found that EDTA increased the life span of sea urchin sperm cells significantly by adding it to the seawater medium. The same kinds of results were observed in cells from roosters and steers[clxxvi]. The decline of

hormone levels with aging has been the subject of considerable interest, and much attention has focused on exogenous replacement strategies or attempts to re-stimulate endogenous secretion and release. Another potential benefit is suggested by the finding that lead lowers brain energy levels.[clxxvii] Energy is essential for optimal health and the achievement of our maximum useful lifespan. Furthermore, Low-level lead exposure has recently been shown to speed up brain aging.[clxxviii] Also the immune system has been shown to be more vulnerable to low levels of lead than other organ systems, leading to increased incidence of infectious disease and neoplasia.[clxxix] The ability of EDTA to remove low levels of lead and other toxic metals, which we might then expect to favorably influence immune, metabolic and endocrine function, appears to be worthy of further study. Oral DMSA has been found to chelate mercuric residues, and urinary recovery of mercury was shown to correlate with increased human growth hormone levels[clxxx]. The role of EDTA in the reversal of cross-linkages as a potential mechanism for the correction of biological aging was carefully reviewed by Carpenter[clxxxi]. The dramatic life-span prolongation following EDTA exposure in prokaryotes and eukaryotic germ cells deserves further study[clxxxii,clxxxiii,clxxxiv] as is the apparent improvement of general health commonly observed in humans from exposure to intravenous EDTA that may be partially explained by preventing or reversing the pathologic calcium accumulation seen in the aging of all mammalian cells[clxxxv].

Research indicates that a combination of several chelating agents offers significant anti-aging potential and EDTA may still find a major role in longevity medicine.

CONCLUSION

The potential contribution of chelating agents such as EDTA to the health of mankind can be greatly augmented as we begin to appreciate the wider implications of their basic detoxifying activity[clxxxvi]. We now have the unparalleled history of over 40 years of extensive and safe use of EDTA, with studies showing increasing life span in research models. Oral EDTA in our toxic world may become as essential for health as an essential nutrient, and it appears to offer potential benefits as diverse as those seen with some essential nutrients, suggesting we all carry a greater burden of toxic metals than is in our best interest for achieving either optimal health or our maximum intended useful lifespan. The completed human genome project will help us better appreciate human biochemical individuality so someday we may even know in advance which patients will have the more dramatic clinical improvements and apparent age-reversal that we have all seen in some of our patients with EDTA.

It is my belief that virtually everyone could benefit from the continuous lifetime ingestion of EDTA, and/or other chelators, to help offset the increasing burden of toxic and free metals coming from our degraded environment. By contrast, it has been proposed that 50 percent of the American public should be on lipid lowering drugs[clxxxvii] and the Pharmaceutical industry is seriously proposing that such medications become available over-the-counter[clxxxviii] so that the public can self prescribe these clearly not innocuous lipid lowering drugs. We must move toward evidence-based medicine. The skyrocketing costs of largely ineffective and soon unaffordable orthodox cardiovascular health care have been outlined in detail[clxxxix]. I suggest that over-all health benefits from lowering toxic metals in everyone would far exceed those from administering statins to one-half of our population, with less risk, and less cost, since oral EDTA costs little more than vitamin C, and when combined with garlic[cxc] would provide a broader spectrum of affordable chelation activity.[22]

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