Guest Editorial

Chelation Therapy for Cardiovascular Disease

Review and Commentary

Matthew R. Lewin

Two years ago, C. Richard Conti, in his capacity as editor-in-chief of *Clinical Cardiology*, wrote a brief editorial on chelation therapy for atherosclerosis.[1] His conclusion ("I counsel all patients who ask me about this therapy not to seek out individuals who prescribe it") was not startling, given the almost total absence of scientific evidence in support of the treatment. What did surprise me was the need for such an editorial in 1995, after the adoption of a dozen formal position statements by medical organizations* and the federal government. Dr. Conti acted, he explained, at the request of a cardiology colleague, and after having been asked by a number of his patients about the value of chelation therapy for coronary heart disease.

A surprisingly large number of people in the United States seek out unproven and potentially harmful alternative therapies. A 1993 study published in the *New England Journal of Medicine*[7] suggested that each year Americans make more than 400 million visits to providers of unconventional therapies, a number greater than the total number of visits to all primary care physicians. The annual out-of-pocket expenditure has been estimated to be $10 billion.[8]

In order to answer patients' questions about chelation therapy, a physician should know a few things about chelators: their history, their method of action, and their confirmed (and unconfirmed) medical applications.

Background

Chelation therapy usually involves a series of slow-drip, intravenous infusions of the synthetic amino acid EDTA (ethylenediamine tetraacetic acid).** For many years, EDTA has been approved by the Food and Drug Administration for use in the treatment of some types of heavy metal poisoning (e.g., inorganic lead); and it was used in the treatment of digitalis poisoning until antibody fragments took its place. The term chelate was coined by analytical chemist G.T. Morgan in 1920;[10] it comes from the Greek *chela*, or "claw," which refers to the claw-like chemical structure of the compound (Fig. 1). In chelation, a metallic ion is sequestered and firmly bound into a ring within the chelating molecule. Alfred Werner was awarded the 1913 Nobel Prize in chemistry for developing this concept.[11]

Natural Chelators. Naturally occurring chelating agents, such as citrate, were among the 1st used in medicine. According to Jones,[12] the 1st modern medical exploitation of the properties of chelation occurred in 1917, with the use of tartrate[12]—and then, in 1925, of tiron[13]—to reduce the toxicity of antimonial-based antiparasitic agents used against diseases such as schistosomiasis.[13] In a 1938 publication, *Health Hazards in the Plating Shop: Some Suggestions for Their Elimination*,[14] F.M. Carlsen proposed the empiric use of "fruit juices" for the treatment of nickel-induced eczema. In 1943, Kety and Letonoff[15] explored the use of sodium citrate to reduce the lead burden in human beings.

Synthetic Chelators. Synthetic chelators are abundant and serve as useful analytical and biochemical tools. By the time chemist Ferdinand Münz, at the Ger-

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Key words: *Alternative medicine/utilization; atherosclerosis/drug therapy; chelation therapy; chelating agents; edetic acid/administration & dosage; edetic acid/adverse effects; edetic acid/therapeutic use; history of medicine, modern; Versene*

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*There have been, for example, statements (advising against chelation therapy for cardiovascular disease) by the American Medical Association (1984),[2] the American College of Cardiology (1984),[3] the American Heart Association (1985),[4] the American Osteopathic Association (1990),[5] and the American Academy of Family Physicians (1993).[6]

**Also called Versene (or calcium disodium versenate[9]).

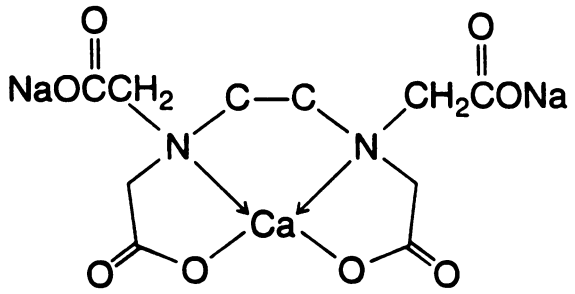


Fig. 1 *Ethylenediamine tetraacetic acid effectively binds di- and trivalent cations, forming a stable ring. Here it has bound calcium, to form edetate calcium disodium.*

man company General Aniline, received the U.S. patent for the structure, synthesis, and application of EDTA in 1938 (Fig. 2),[16] there was already a rich tradition in analytical chemistry surrounding chelating compounds. Synthetic methods such as the ones developed by Münz[16] in the 1930s and Bersworth[17,18] in the 1940s ameliorated the chief disadvantages of earlier synthetic methods, i.e., low yields and the release of free hydrogen cyanide.[19] Applications for chelating compounds already considered or in use by the late 1930s included the study of metal ions in biochemical systems such as chlorophyll and hemoglobin. Such compounds helped settle questions related to stereochemistry in organic systems, to the theory and practice of mordant dyeing, and to pharmaceutical preparations.[20]

Medical Applications of Chelation. A synthetic compound, dimercaprol (Fig. 3), better known as British antilewisite (BAL), was introduced in 1945 by Peters and coworkers[21] as a remedy for military arsenical blisters and systemic arsenic poisoning from the war gas lewisite.[21,22] It was soon found to be useful against other heavy metal poisonings, such as that caused by mercury. The introduction of EDTA-based chelating agents to combat heavy metal poisoning was a tremendous advance in toxicology. To put the impact of this new technology in perspective, one has only to remember that the 1st edition of Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, published in 1941, states the following objective in the treatment of lead poisoning: "the main objective . . . is to drive the lead from the circulation and deposit it in the bones. . . ."[23]

In the 1950s and 1960s, there was an explosion of publications on the effects of various chelating agents in animals and human beings. By 1951, EDTA was being used for the treatment of inorganic lead poisoning[24,25] and was under investigation as a tool to treat hypercalcemia[26-28] and even radiation poisoning from plutonium.[29] Contemporary discoveries in the field of cancer chemotherapy spawned an immense body of investigation (over 600 papers[30]) on the potential of chelation-based therapies, including EDTA.

Two new areas in which chelating agents are of interest in the medical community today are cerebrovascular physiology and neurobiology. The invention of membrane-permeant analogs of EDTA and related compounds (e.g., BAPTA-AM and EGTA-AM*) has opened new frontiers in these areas of research. First synthesized in 1975 by Roger Tsien[31] as an analytical reagent, BAPTA-AM has since been studied by Tymianski and coworkers to determine the mechanisms by which calcium ion chelators reduce early excitotoxic and ischemic neuronal injury in vitro and in vivo.[32,33] As in the past, EDTA-based chelating agents are interesting and powerful analytical and research tools. Applications for cell-permeant analogs of calcium ion chelators may in the future have a major impact on a wide range of medical specialties, including neurosurgery, trauma care, cardiology, and (especially) cardiovascular surgery. I anticipate that a significant application for membrane-permeant calcium chelators will be prophylactic reduction in the activity of calcium-dependent enzymes thought to be important in post-ischemic pathology, especially iatrogenic types. These hypotheses will need to be tested rigorously, in a controlled scientific setting.

Cardiovascular Applications of EDTA

This brings us to the cardiovascular applications of chelators. At present, the clinically proven applications are few. Over 3 decades ago, EDTA was examined as a tool to treat certain arrhythmias and digitalis poisoning. By 1964, there was widespread agreement that EDTA was useful in the management of digitalis poisoning and in the suppression of ventricular premature contractions in the emergency setting.[34-36]

In 1955, Clarke, Clarke, and Mosher introduced the possibility that EDTA could be used as a treatment for atherosclerotic heart disease.[37] Twenty-two patients were treated with EDTA for a variety of reasons; these included several patients who were receiving EDTA experimentally in an effort to determine its effects on serum calcium. Particular attention was given to the case history of 1 patient under treatment for progressively worsening bilateral nephrocalcinosis. The apparent salutary effects of EDTA on this patient included improved hearing and improvement of digestive symptoms. The authors presented radiographic evidence of improvement in this

* 1,2-bis-(2-amino-phenoxy)ethane-N,N,N′N′-tetraacetic acid acetoxymethyl ester (BAPTA-AM) and ethylene glycol-bis(beta-aminoethyl ether)-N,N,N′,N′-tetraacetic acid acetoxymethyl ester (EGTA-AM)

Patented Sept. 20, 1938 **2,130,505**

UNITED STATES PATENT OFFICE

2,130,505

POLYAMINO CARBOXYLIC ACIDS AND PROCESS OF MAKING SAME

Ferdinand Münz, Frankfort-on-the-Main, Germany, assignor to General Aniline Works, Inc., New York, N. Y., a corporation of Delaware

No Drawing. Original application October 22, 1936, Serial No. 107,020. Divided and this application April 3, 1937, Serial No. 134,737. In Germany October 30, 1935

2 Claims. (Cl. 260—534)

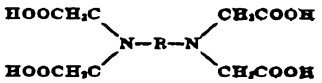
This application is a division of my copending application Ser. No. 107,020, filed October 22, 1936, which relates to the use of amino polycarboxylic acids for avoiding and rendering harmless the precipitates of water-insoluble metal salts, particularly formed owing to the hardness of water.

My present invention relates to polyamino carboxylic acids and a process of making same.

They are obtainable by acting with monochloro acetic acid on a polyamine.

As a polyamine from which the carboxylic acids are derived, there may be mentioned particularly ethylene diamine.

In this manner polyamino-polycarboxylic acids are obtained which correspond to the general formula:

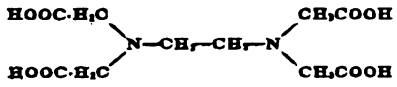


wherein R stands for a lower alkylene radicle.

The following example will further illustrate how the said invention may be carried out in practice, but the invention is not restricted to this example. The parts are by weight.

Example

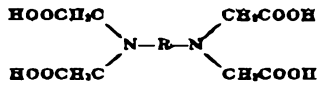
60 parts of ethylene diamine in an aqueous solution of 10% strength are mixed with 466 parts of the sodium salt of monochloracetic acid and 212 parts of sodium carbonate and the mixture is heated at 90 to 95° C. for 8 to 10 hours. Then 470 parts of a hydrochloric acid of 20° Bé. are added. When cool an acid of the formula:



precipitates, which is scarcely soluble in water and may be recrystallized from water.

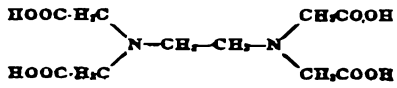
I claim:

1. Polyamino polycarboxylic acids corresponding to the formula:



wherein R stands for a lower alkylene radicle.

2. A polycarboxylic acid of the formula:



which is scarcely soluble in water and may be recrystallized from water.

FERDINAND MÜNZ.

Fig. 2 *United States patent for ethylenediamine tetraacetic acid.*

patient's kidney stones and implied that this was direct evidence of the removal of metastatic calcium. Their protocol included intravenous administration of 5 grams of EDTA in 500 cc of normal saline or 5% glucose over a period of 4 hours. Each patient was given 12 to 20 infusions over a 2- or 3-week period. The authors anticipated a mechanism by which EDTA might preferentially remove metastatic calcium, and their discussion focused on the possible interrelationship between the calcium and the cholesterol found in atheromatous plaques. They concluded that EDTA was worthy of further study and mentioned that they were investigating the effect of EDTA on angina pectoris in some patients from this same group and in additional patients. These results would be published later.

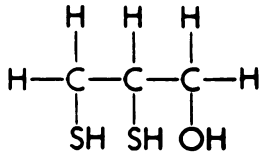


Fig. 3 *Structure of the metal complexing agent dimercaprol (BAL).*

Indeed, in "Treatment of Angina Pectoris with Disodium EDTA" (1956),[38] Clarke, Clarke, and Mosher reported that anginal symptoms, following treatment in accordance with their EDTA protocol, improved in 19 of 20 patients with coronary artery and peripheral occlusive disease. They cited 2 chest radiographs (1 showing mitral valve calcification) as evidence in support of their hypothesis, but they did not publish the radiographic images. At physiologic

pH, the sodium salt of EDTA is an effective chelator of calcium. It was this observation, and the observation by others that calcium and cholesterol are associated in the structure of atherosclerotic plaques, that led Clarke, Clarke, and Mosher to hypothesize that EDTA could dissolve disease-causing plaques in the coronary systems of human beings.[38]

The 1st controlled clinical trial of EDTA chelation therapy for cardiovascular disease, conducted by Kitchell and associates in 1963,[39] was subtitled "A Reappraisal," in reference to their earlier (1961) work with EDTA in human subjects.[40] In 1961, they had examined 10 patients with angina and reported subjective improvement of anginal symptoms in 9 patients. In the 1963 clinical study, the authors performed follow-up on 28 patients with angina who received EDTA for at least 20 treatments. Nine other patients were in a double-blinded, cross-over wing of the study. Of these 9, 4 were treated with EDTA and 2 of the treated patients reported subjective improvement of their symptoms after 3 months. After 18 months, 7 (25%) of the 28 patients receiving EDTA were dead, 2 (7%) were "worse," 6 (22%) were "the same," and the remaining 13 (46%) were "improved." They concluded, "At present we believe that chelation as used in this study did not benefit patients more than other commonly used therapeutic methods. It is not a useful clinical tool in the treatment of coronary heart disease at the present time."

To date, in the English-language medical literature, there has been only 1 other controlled clinical trial evaluating the efficacy of EDTA in cardiovascular disease. The trial conducted by Guldager and colleagues[41] is the only placebo-controlled, double-blind study with random patient allocation. One of the endpoints studied was symptomatic relief of stable, intermittent claudication. Other endpoints were pain-free walking distance on the treadmill and maximum walking distance. One hundred fifty-three patients who averaged 65 ± 9 years in age were randomized to receive 20 infusions of EDTA over a 5- to 9-week period, in accordance with a regimen similar to those used by Clarke's group and others[38,39] in the 1950s and 1960s. No difference between the placebo and treatment groups was noted in any category investigated.

Although there has been a paucity of controlled clinical trials, case-report series are abundant, and there have been 2 open-label longitudinal studies and 1 open-label clinical trial. I surveyed 12 consecutive case reports[38-40,42-50] that specifically examined the apparent effect of EDTA on the symptoms and signs of peripheral vascular disease, coronary artery disease, or both. There were a total of 2,217 patients treated with EDTA. Improvement was reported for 2,060 (93%) of patients. Of these, the most notable is the open-label clinical trial published by Olszewer and Carter[47] in 1988. This study enrolled 1,974 consecutive patients and reported its results in qualitative terms, such as "marked" or "good" improvement. Ninety-four percent of patients with ischemic heart disease treated with EDTA chelation therapy had marked or good improvement (77% and 17%, respectively), and 97% with peripheral vascular disease had marked or good improvement (91% and 6%, respectively). An excellent, detailed review of all case reports and trials was published by Grier and Meyers in 1993.[51]

Common criticisms of the data that appear to support EDTA chelation therapy for cardiovascular disease have included: small sample sizes, open-label formats, and the qualitative rather than quantitative means by which most studies have evaluated treatment outcomes. In addition, while there have been relatively few fatalities directly attributable to EDTA infusions,[51] other adverse effects have been many and varied.[9] The most commonly reported adverse effect is pain or burning at the site of infusion.[41] Moreover, EDTA has been reported to have toxic effects on the kidney,[9,51,52] sometimes causing proximal tubule damage, and has been associated with hypoglycemia, malaise, gastrointestinal symptoms, T-wave inversion, dermatitis, and hypocalcemic symptoms such as tetany.[9,41,51]

The 1963 clinical trial by Kitchell[39] was the 1st published study that was critical of the EDTA protocol for atherosclerosis. In fact, other than the Kitchell study, there appears to have been little enthusiasm or interest in this experimental therapeutic modality in the 1960s, when only 2 small case report series were published (by Lamar, in 1964 and 1966).[44,45] By the early 1970s, interest in EDTA chelation therapy for cardiovascular disease had pretty much faded among most members of the medical and scientific community.

In 1973, however, the American College for Advancement in Medicine (ACAM) was founded with the purpose, in part, of promoting chelation therapy.[53] This group, which comprises about 750 licensed physicians, sponsors certification programs and publishes the *Journal of Advancement in Medicine*. It also has an easily accessible web site on the Internet. The ACAM organization has published protocols for the administration of EDTA, which call for infusions of 50 mg per kilogram of body weight. This is similar to doses used in early studies.[37,38] However, ACAM has made many modifications and additions. These include the use of heparin, B-complex vitamins, and megadoses of vitamin C and other vitamin and mineral supplements. Infusions are given several times per week, and a complete course of therapy can include 20 to 40 trips to the doctor at a cost ranging from $1,600 to $4,000, or $80 to $100 dollars per treatment. These are not covered by any

insurance companies. Additionally, lifestyle- and diet-modification programs (not dissimilar to those developed, published, and validated by Dean Ornish, Larry Scherwitz, and Lance Gould and coworkers during the last 2 decades) are encouraged to complete this therapy.[54,55]

Claims regarding the benefits of EDTA have grown since the 1950s and 1960s. Dozens of books have been published by proponents of chelation therapy. These claims include, but are not limited to, the treatment and prevention of atherosclerosis, coronary heart disease, angina, and peripheral vascular disease, the reduction of blood viscosity and free-radical formation, and the slowing of the aging process. Claims also include "increased" sexual function,[56,57] improved mental and other nervous system function, and relief of all types of arthritis and even lupus.[56] Seldom are there claims of directly antineoplastic activities.

Proposed Mechanisms of Action. Since the introduction of EDTA as a potential treatment for cardiovascular disease, proponents of this therapy have put forward several hypotheses to explain its mechanism of action. Among the earliest was the concept that if calcium were removed from the atherosclerotic plaque, the plaque would disintegrate, thus improving the patency of the arteries. In *The Chelation Answer* (1982)[58] and *The Chelation Way* (1990),[59] Morton Walker explains that parathyroid dysfunction causes precipitation of calcium into the vasculature and other tissue. Chelation removes this calcium. Leading chelation therapy proponent Elmer Cranton proposes in his 1990 book, *Bypassing Bypass*,[60] that EDTA blocks the generation of free radicals implicated both in lipid peroxidation and in the chain of events leading to atherogenesis. Because free radicals have been implicated as a final common pathway in so many pathological processes, the expansion of claims regarding EDTA's applications has been dramatic.

Commentary

None of the claims listed above has been published in peer-reviewed scientific literature, but they are legion in books and flyers published by the alternative medicine community (Table I). Moreover, a cursory search of World Wide Web sites on any of several servers will pull up several hundred chelation therapy web sites. Of the hundred or so that I visited (Table II), only 2 sites were for skeptics and 1 was a statement from the American Heart Association (Fig. 4). Indeed many of the sources that I reviewed have a common complaint: the existence of a conspiracy to suppress EDTA-based treatments. Many cite the lack of financial incentive for pharmaceutical companies to produce EDTA, since the patent on the compound ran out in the 1940s.[51] (In fact, there are several thousand patents on the medical and pharmaceutical uses of EDTA.) Other proponents accuse surgeons of suppressing chelation therapy in order to keep their wards filled with revenue-generating bypass patients. The Internet has become an efficient and cheap way for practitioners of alternative medicine to promote their therapies with no regulation.

In 1954, Irvine H. Page[61] outlined several methods of combating atherogenesis that he deemed worthy of further investigation. He described most others as "tentative thrusts into the unknown, some capable of being built upon, most too weak to support a superstructure." He followed with a warning about the growing open market for preventive health products: "none are of proved value and few have even any semblance of experimental evidence to support their use as a treatment or prophylactic in atherosclerosis. Their recommendation is based on the philosophy that they do no harm and might do good. This is an expensive and elusive philosophy, seldom contributing to the advancement of sound therapeutics, and greatly contributing to logical delinquency in the minds of the prescribing physician. . . ." His words were prophetic.

TABLE I. Excerpts from a Popular Booklet on Chelation Therapy[56]

A Partial List of the Benefits of Chelation Therapy

Improves liver function	Removes excessive iron deposits
Lowers blood cholesterol	Heals poor circulation ulcers
Lowers blood fats	Reduces leg cramps
Reduces blood pressure	Improves vision
Improves coronary circulation	Improves varicose veins, pigmentation
Reduces heart irritability	
Reduces strong heart beats	Relieves angina pectoris
Relieves signs of senility	

Diseases Aided by Chelation Therapy

Angina pectoris	Scleroderma
Coronary arteriosclerosis	Hypoglycemia
Psoriasis	Cerebral degeneration
Thrombophlebitis	Lupus
Venom bites	Diabetic gangrene
Parkinson's disease	Arteriosclerosis
Lead toxicity	

[The inside front cover, however, bears the following caveat: "This booklet is intended only for informational purposes. It only advises people to question and learn for themselves that there are other treatments and methods available. The author and publisher make no medical claim direct or implied. The reader should consult a licensed physician for any condition that requires his services."[56]]

TABLE II. This is a sample of the web sites available simply by typing "chelation therapy" when using any of the more common Internet search engines, such as Alta Vista, Yahoo, or Web Crawler.

http://www.pathwaysdc.com/9-96baer.html	http://www.newagemall.com/prac/WA/yelm.html
http://www.macontel.com/data/health/thera817.htm	http://www.envprevhealthctratl.com/chelther.htm
http://www.coos.or.us/~signal/chel2.htm	http://www.acam.org/biblio.html
http://www.acam.org/cict.html	http://www.vitawise.com/chethe.htm
http://www.abchealth.com/chelatio.htm	http://www.acam.org/pospaper.html
http://www.idsweb.com/ahma/josephs/therapy.htm	http://www.acam.org/edtapapr.html
http://www.adcomtek.com/veins/chelo.htm	http://www.acam.org/schedule.html
http://www.chelation.com/	http://mel.lib.mi.us/health/health-chelation.html
http://www.hrt.org/wellfac3.html	http://www.amhrt.org/hs96/chelate.html
http://www.ssnow.com/med2life/chelation.htm	http://wheel.ucdavis.edu/~btcarrol/skeptic/chelate.html
http://www.eurohost.com/docwelln/chelat.html	http://www.quackwatch.com/01QuackeryRelatedTopics/
http://healthy.net/clinic/therapy/chelat/intro/	chelation.html

Chelation therapy for cardiovascular disease has been embraced by the alternative medicine community for over 30 years, despite its lack of support by clinical evidence or by logic. Grier and Meyers[51] point out that almost all clinical studies of chelation therapy are subjective and do not apply measurements of endpoints uniformly. Nor are there any controls. Such criticisms do not intimidate the proponents of chelation. In *The Chelation Way*,[59] Walker cites 2 authorities, H. Richard Casdorph, MD, PhD, and Elmer Cranton, MD, both of whom contend that double-blind studies are unnecessary, "since each patient legitimately receiving chelation therapy serves as his own control."

There are many reasons for believing that the logic of chelation therapy for atherosclerotic disease is flawed. Calcification of plaques is a late manifestation of the disease process. Moreover, the plaque is an integral part of the arterial wall and cannot be reached by EDTA, which is water soluble and does not pass freely through cell membranes. The target ion for chelation therapy, Ca^{2+}, is not the ion most strongly bound by EDTA, which has a much greater affinity for heavier metal ions. Although EDTA does increase the urinary excretion of calcium, there are sources of calcium much more abundant than atherosclerotic plaques—the 2 most obvious being bone and serum.

Then there is the newer claim that EDTA chelation therapy prevents the generation of free radicals and, thereby, lipid peroxidation. This also does not make sense, unless chelation is combined with the administration of antioxidant vitamins such as ascorbic acid. Even chelated, ferric iron has 2 free electrons available to help catalyze the formation of free radicals by participating in oxidation-reduction chemical reactions. At best, this treatment might do no harm; but at worst, it might actually generate a greater quantity of free radicals.[53] (This has not been substantiated either way.) These are but a few reasons, in addition to the absence of supporting clinical data, that chelation therapy with EDTA has faced such skepticism.

The overwhelming majority of chelation therapists promote their therapies as exceptionally safe, natural, and nontoxic. As we've already seen, this is (in the case of EDTA) patently untrue. However, the risks of serious harm from this therapy are relatively low when the drug is administered properly to a patient with healthy kidneys.[62] This has enhanced its appeal for promoters, who incur little liability by its use.

In 1993, Monaco and Green[63] noted that many promoters of unproven alternative therapies warn patients not to tell their regular doctors because "they won't understand" and will "interfere with your trust in our program." Moreover, these practitioners' liberal use of recognized (but little-understood) scientific and medical terms creates an aura of scientific expertise that is hard to resist.[63]

Dozens of physicians have been disciplined by state boards for using chelation therapy in unacceptable ways. In Texas, for example, an osteopath used chelation therapy in the treatment of Alzheimer's disease and was disciplined in 1990 for a "professional failure to practice medicine in an acceptable manner consistent with public health and welfare."* In Washington, DC, a medical doctor had his license revoked for using EDTA-based therapy to treat atherosclerosis and was told, "EDTA therapy is not an accepted treatment modality used by competent physicians. . . . the use of invalidated treatment modalities demonstrates a willful or careless disregard for the health, welfare and safety of patients. . . ."* Many of these censured doctors are considered martyrs in their professional circles.

* Personal communication, Saul Green, PhD, Zol Consultants, Inc. August 1996.

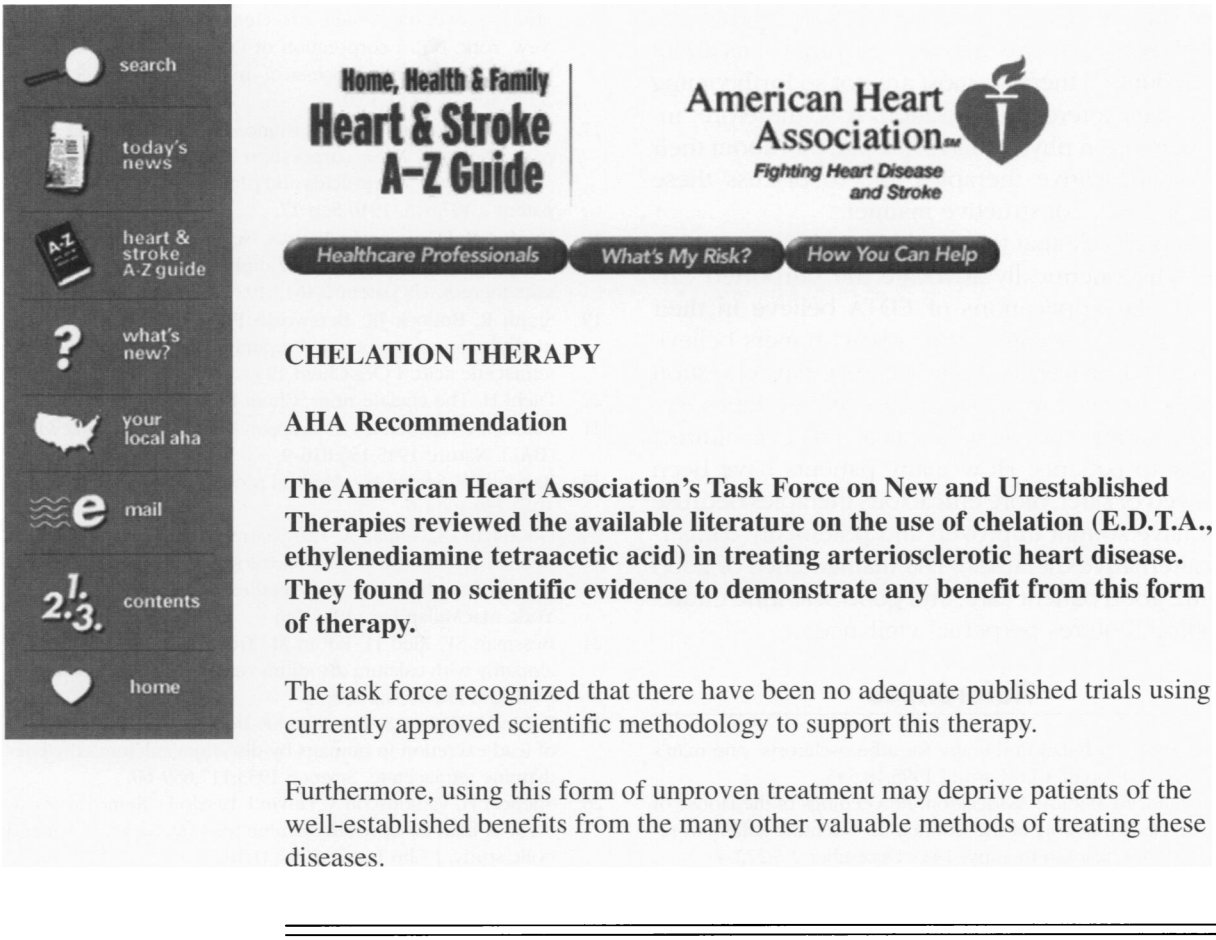


Fig. 4 *An excerpt from the American Heart Association's recommendation in regard to chelation for the treatment of arteriosclerotic heart disease, as it appears on the World Wide Web. Copyright © 1996 American Heart Association. Used by permission.*

The Appeal of Alternative Medicine. Unorthodox practitioners are not entirely to blame. The market for alternative medicine is a void that cries to be filled. In "Aequenimitas," his famous valedictory address at the University of Pennsylvania (1889), William Osler urged new graduates to ". . . restrain your indignation when you find your pet person has triturates of the 1000th potential in his pocket, or you discover a case of Warner's Safe Cure in the bedroom of your favorite patient. It must needs be that offenses of this kind come; expect them and do not be vexed." That the desperately ill will seek an alternative after conventional therapies have failed is clear. But contrary to the common belief of physicians in the United States, most seekers of alternative therapies are not terminally ill.[7,64] One reason, cited by Holohan,[64] for the proliferation of alternative therapies among the relatively healthy is the simple lack of professional vigilance among physicians: the absence of "clear, consistent, and active opposition to such approaches" is "perceived as at least tacit support of unorthodoxy." Perhaps even more significantly, people have sought alternative therapies because they have experienced costly and impersonal care by conventional practitioners.[7,65]

A New Zealand editorial[66] regarding medicine on the fringes commented that what is fringe to some is central to others and (again) cited William Osler: "A good doctor may have practice and no theory, art and no science." Certainly science has become a greater part of the medical equation than it was a century ago, but Osler's point should be considered seriously in attempting to understand why many people prefer alternatives to conventional medicine. Some unorthodox remedies have been found to be effective in controlled clinical trials,[66] either because of their inherent therapeutic qualities or because of their elaborate placebo effects, which can help patients alter their lifestyles in ways that are beneficial.

However, there are to date no scientific data to support the claims made by chelationists in regard to cardiovascular cures. Unfortunately, the sloppy science behind the original assumptions and observations—bolstered by the natural appeal of the hypothesis—has evolved step by step from good intention to the cascade of poor medicine and sci-

ence that envelops chelation therapy today. Although some patients do ask their physicians about this debunked therapy, most are not so forthcoming about their interest in chelation. It is, therefore, incumbent upon physicians to ask patients about their use of alternative therapies and to discuss these therapies in a constructive manner.

It is probable that the majority of chelation therapists who uncritically advocate the purported cardiovascular applications of EDTA believe in their practices, just as conventional practitioners believe in theirs. However, as it is practiced today, chelation therapy for cardiovascular disease at best defies recommendation and, at worst, is a direct or indirect danger to patients. How many patients have been deprived of safer, more efficacious therapies because they have sought unproven and potentially dangerous alternative therapies? The maintenance of good health, good patient care, and good scientific understanding requires perpetual vigilance.

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