HISTORICAL PERSPECTIVES ON THE DEVELOPMENT OF CHELATION THERAPIES

An Extended Compendium
Prepared for the Advanced Training Seminar on
Heavy Metal Toxicology
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In studying this material, pay particular attention to DATES that have been printed in BOLD face type; also, pay attention to references on EDTA that are printed in BOLD face type. These materials are especially important for your understanding and are covered on the written and oral examinations.

This syllabus is much more than a review of dates and places. It is written in such a way for you to review chelation chemistry, nutrition, cardiovascular physiology, and other critical topics that you must integrate into effective patient treatment plans. Enjoy reading this casually – study the areas that interest you most.

To make best use of this extensive summary, use it often when discussing chelation treatments with your patients. Show them that scientific studies have been done on medical conditions similar to their own. Trace for them the history of our understanding of chelation. Reassure them that a long and rich scientific history precedes their entry into this treatment program.

In following this outline, be mindful of the following abbreviations:

CHEM = regarding chemical theory, structure, application

EDTA = ethylenediaminetetraacetic acid [Endrate*, Edetate*, Versene*, other brand names]
BAL = British Anti-Lewisite (dimercaprol, dimercaptopropanol) [BAL in Oil*]
DMSA = dimercaptosuccinic acid [Chemet*]
DMPS = dimercaptopropanesulfonite [Dimaval*][Unithiol*]
DFO = desferoxamine B methanesulphonate [Desferal*]
PCA = D-penicillamine [DePen*, Cuprimine*]

ABCT = American Board of Chelation Therapy
ACAM = American College for Advancement in Medicine
AAMP = American Academy for Medical Preventics (changed to ACAM)
APMA = American Preventive Medical Association
GLACM= Great Lakes Association of Clinical Medicine (changed to GLCCM)
GLCCM= Great Lakes College of Clinical Medicine
IBOM = International Bio-Oxidation Medicine Foundation
ISCT = International Society of Chelation Technicians

*** = generally denotes a registered trademark or brand name**

Key individuals in early EDTA chelation history:
Bersworth = Frederick C. Bersworth
Rubin = Martin Rubin, Ph. D., Professor Emeritus, Georgetown University School of Medicine, Washington, D. C.
Clarke = Norman E. Clarke, Sr., M. D., Providence Hospital, Detroit, Michigan

Some comments on the early history of EDTA have been quoted directly from personal communications with Professor Martin Rubin, for whose kind assistance I am most grateful.

The "Chronological History of EDTA Chelation Therapy," prepared in October 1994 by Charles H. Farr, M. D., Ph. D., Robert L. White, P. A.-C., Ph. D., and Michael Schachter, M. D., provided source material for a number of the references and incidents cited. This excellent summary is available from the ACAM office.

Some general introductory definitions (along with historical details) have been borrowed directly from B. W. Halstead, The Scientific Bases of EDTA Chelation Therapy, published in 1979. The second edition of this fine volume, by Bruce W. Halstead and Theodore C. Rozema, was published in 1997 and is available from TRC Publishing, 1000 East Rutherford Road, Landrum, South Carolina 29356 (phone 864-457-4141, fax 864-457-4144).

CHELATION = the incorporation of a metal ion into a heterocyclic ring structure; this binding process provides the bio-inorganic chemical basis for therapeutic applications.

In the case of the ethylenediamine molecule, the presence of two complexing groups results in the metal ion being incorporated into a ring structure. When this process takes place, the metal is said to be "chelated" and the ethylenediamine is termed a "chelating agent."

Thus, chelation may be more completely defined as an equilibrium reaction between a metal ion and a complexing agent, characterized by the formation of more than one bond between the metal and a molecule of the complexing agent, resulting in the formation of a ring structure incorporating the metal ion.

Chlorophyll is a chelate of magnesium; hemoglobin, cytochrome C, catalase, and peroxidase are chelates of iron. Many successful drugs used in the treatment of disease depend upon chelation processes for their therapeutic properties.

ION = a charged particle

CATION = a positively charged particle (example Ca++); metals are positively charged cations

ANION = a negatively charged particle (example Cl-)

COORDINATION NUMBER = a statement of the maximum number of coordination bonds that can be formed by negative ions or molecules that coordinate or complex with a metal ion (for most of the common metals, the number is 4, 5, or 6)

REACTIVE SITES = the centers of activity of the metal ion, where coordination bonds can be formed; the reactions caused by free metal ions in solution are generally due to these reactive sites

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HISTORICAL EVENTS

1893 -- CHEMISTRY/PHYSIOLOGY

Alfred Werner (Swiss Nobel Laureate, 1866-1919) propounded revolutionary theory of metal ligand binding as a RING formation, providing foundation for modern coordination chemistry.

1893 -- CHEMISTRY/PHYSIOLOGY

As Werner described his concept .....

"If we think of the metal atom as at the center of the whole system, then we can most simply place the molecules bound to it at the corners of an octahedron."

This led to new developments in concept of valency and concept of ring formation, a complete break with his contemporaries.

Werner had introduced the field that later would become known as chelation chemistry -- or complexion chemistry, for the complexes that are formed.

1898 -- CHEMISTRY/PHYSIOLOGY

F. Blau -- structural studies of complexes

1904 -- CHEMISTRY/PHYSIOLOGY

H. Ley -- structural studies of complexes

G. Bruni and Fornara -- structural studies of complexes

1920 -- CHEMISTRY/PHYSIOLOGY

Morgan and Drew first introduced and defined the term "chelation." (G. T. Morgan and H. D. K. Drew, "Researches on residual affinity and coordination. Pt. II. Acetylacetones of selenium and tellurium," J Chem Soc (London) 117:1456-1465, 1920)

"CHELE" is the Greek word for "claw" or "pincer," bringing to mind the picture of "pinching" a marble (ion) between the thumb and forefinger.

“CHELATION” = the incorporation of a metal ion into a heterocyclic ring structure; this binding process provides the bio-inorganic chemical basis for therapeutic applications.

Known chelators other than EDTA include D-penicillamine, BAL, desferoxamine, aspirin, and numerous antibiotics (especially tetracycline, which chelates zinc in the cell wall of bacteria and inhibits reproduction. Journal of Chemical Society (London) 117:1456-1465, 19XX.

1927 -- CHEMISTRY/PHYSIOLOGY

Sidgewick -- structural studies of complexes

1930s -- CHEMISTRY/PHYSIOLOGY

Quantum mechanics applied to problem of molecular structure, greatly enhancing the theory of the development of the full chemical bond

Investigations included the valence bond technique of Heitler, London, Slater, and Pauling; the molecular orbital techniques of Hund, Bloch, Mulliken, Lennar-Jones, and Huokel

mid-1930s -- EDTA

F. Munz at Hochst, Farbwerke, Frankfurt, (Nazi) Germany (a member company of the I. B. Farbenindustrie) first synthesized EDTA as part of an attempt by the Nazi German government to reduce chemical imports. The problem he was assigned was to find a substitute for citric acid, then imported and used in considerable quantities in the printing textile industry as an additive to prevent the formation of stains due to calcium from hard water, which reacted with certain mordant (fixed, permanent, non-fading) dyes.

1935 -- EDTA

The first patent for EDTA was filed in Germany, with EDTA marketed as a sequestering agent under the name TRILON B. Trilon A (sodium or potassium salt

of NTA = nitrile-triacetic acid) was also marketed then.

Munz had noticed the similar formulas of citric acid and nitrile-triacetic acid (NTA), a compound known since 1862. NTA was even more effective than citric acid in removing calcium. NTA was subsequently called Trilon A. This initial success led to synthesis of other polyaminocarboxylic acids, the chemical class for EDTA (later called Trilon B, by which it is sometimes referred to in the medical literature) and similar chelators, many able to sequester calcium.

Interestingly, citric acid's "chelating effect" was explored in 1941 as a clinical treatment for lead poisoning, reported by S. S. Kety and T. V. Letnoff in the Proceedings of the Society for Experimental Biology and Medicine 46:476-477, 1941 ("Treatment of lead poisoning with sodium citrate") -- predating the similar use of EDTA by 11 years!

1930s -- EDTA

Frederick C. Bersworth and William H. Warren, at Clark University, Worcester, Massachusetts, about 1933 began studies leading to later synthesis of EDTA in the United States of America.

Bersworth synthesized EDTA by formaldehyde and cyanide process, providing patent base for first commercial production of EDTA in the USA. This was later marketed as Versene.

1937 -- EDTA

Apparently earliest literature references appeared in Chemisches Zentralblatt 2:2050, 1937; 1:2996, 1938; 1:2100, 1940. Articles referred to the patents for application of polyaminocarboxylic acids in general, used to prevent precipitation of alkaline earth compounds (any of a group of [soluble salts of] metallic elements in natural waters and arid soils, especially containing calcium, strontium, barium, beryllium, magnesium, radium) during washing processes, photographic processes, and textile treatment.

The early German synthesis of EDTA used ethylenediamine in combination with chloracetic acid. The later process produced EDTA from formaldehyde and sodium cyanide neutralized with sulfuric acid to yield the cyanomethyl derivative of ethylenediamine, with the resulting tetranitrile then hydrolized with sodium

hydroxide to give the tetrasodium salt of EDTA.

1940s -- CHEMISTRY/PHYSIOLOGY

Investigations included the crystal field studies of Bethe, Kramers, and Van Vleik; the complexion coordination studies of Brintzinger, Pfeiffer, and Schwarzenbach and their coworkers

Schwarzenbach and his coworkers did fundamental studies of complexion ability of alpha-amino acids, in which a carboxymethyl group was bound to a nitrogen atom and at least one -N(CH2COOH)2 group was present. Studies allowed development of a sound theory based on values of the ionization constants of the acids and the stability constants of the complexes which they form. [Pertinent work referenced in Schwarzenbach's 1955 reference, Die Komplexometrische Titration, Enke, Stuttgart]

1941 -- EDTA

Berswerth filed his first patent application for the commercial production of EDTA on July 3, 1941 -- it was finally approved by the U. S. Patent Office (No. 2,387,735) on October 30, 1945. Berswerth designated his EDTA product as VERSENE. A second patent (No. 2,407,645) was filed on June 21, 1943, and was granted on September 17, 1946.

A most significant historical problem arises at this point -- patent expired in late-1960s, before EDTA clinical research had advanced very far.

1940s -- EDTA

Although Berswerth was the first to develop an economical process that formed EDTA directly, his product was not as pure as the one originally synthesized in Germany. John J. Singer, a former employee of Berswerth, developed a process for reaction of ethylenediamine with formaldehyde and hydrogen cyanide to produce tetranitrile and then EDTA. This process continues to be used today in commercial production of EDTA in the USA.

1950s -- EDTA

In the 1950s, Abbott marketed EDTA for medical use as the trademark product "ENDRATE."

early 1940s -- CHEMISTRY/PHYSIOLOGY

World War II and the fear of use of arsenical nerve gases -- such as Lewisite, used in WWI -- stimulated a search for effective antidotes.

Arsenic is a highly poisonous metallic element having three alloptropic forms, yellow, black, or gray. Brittle crystalline gray is the most common. Arsenic and its compounds are now used in insecticides and weed killers. Arsine (AsH3) is a colorless, flammable, very poisonous gas used as the military poison gas.

Previous studies showed arsenic had a strong affinity for -SH (sulfhydryl) groups, such as found in the amino acid cysteine and the compound glutathione. Administration of extra amounts of these natural compounds, cysteine and glutathione, showed a protective action against organic arsenicals, presumably by binding the toxic arsenic to their -SH groups.

Soviets made use of this effect of -SH groups in the 1970s, using a compound called Unithiol as a chelation agent -- we now know that chemical as DMPS (dimercaptopropanesufonite).

The scope of chemical weapons during WWI raised a fearsome spectre of man's inhumanity: fully 1.3 million combatants had been either killed or incapacitated by poison gas in 3 short years. The Germans loosed chlorine gas upon the Allies' muddy trenches at Ypres, Belgium, in 1915. A good dose caused lasting lung damage. The Allies retaliated. Mustard gas followed. Its effects were, if anything, even worse.

Mustard gas is an oily, volatile liquid used as a gaseous blistering agent. Its name comes from its mustardlike odor. The formula is (ClCH2CH2)2S.

In 1926, a Geneva protocol banning use of chemical weapons in wartime was adopted. Italy used poison gas in Ethiopa in 1935 and Japan used it in China in the late 1930s. However, none of the belligerents reportedly used it during WWII.

1945 -- BAL

R. A. Peters, L. A. Stocken, and R. H. S. Thompson contributed largely to development of the chelating agent BAL, British Anti-Lewisite, chemically known as 2,3-dimercapto-propanol (Dimercaprol).

1945 -- CHEMISTRY/PHYSIOLOGY

Of key significance: a drug had been developed that was an effective antidote for heavy metal intoxications, marking the acknowledged beginning of chelation therapy as a pharmaceutical medical treatment. "British Anti-Lewisite (BAL)," Nature 156(3969):616-619, 1945.

1946 -- BAL

Treatment of metal toxicity with chelating agents became clearly established as World War II ended. H. Eagle, "The systemic treatment of arsenic poisoning with BAL (2,3-dimercapto-propanol)," American Journal of Syphilis, Gonorrhea, and Venereal Diseases, 27:114-21, May 1946; H. Eagle and H. J. Magnuson, "The systemic treatment of 227 cases of arsenic poisoning (encephalitis, dermatitis, blood dyscrasias, jaundice, fever) with 2,3-dimercaptopropanol (BAL)," American Journal of Syphilis, Gonorrhea, and Venereal Diseases, 30(5):420-41, September 1946; Supplement to the Journal of Pharmacology and Experimental Therapeutics (entire publication), 87(4), August 1946 (The William and Wilkins Company, Baltimore, Maryland).

1940s + 1950s -- CHEMISTRY/PHYSIOLOGY

The problem of atomic fission products that could result from future atomic warfare enhanced the scientific interest in metal-binding agents.

1940s -- EDTA

Frederick C. Berswerth, German-American chemist, established the Berswerth Chemical Company to manufacture chemicals, including EDTA, in a small plant in Massachusetts. To assist him, Dr. Berswerth retained Professor Arthur E. Martell of Clark University (presently at Texas A & M University in College Station) as his consultant to develop the chelate chemistry of EDTA and other compounds.

1940s + 1950s -- EDTA

Studies by Pfeiffer and Schwarzenbach on complexion properties of the polyaminocarboxylic (EDTA) series of compounds and the efforts of Bersworth, Rubin, and their associates led to introduction of EDTA chelation into the scientific medical arena.

1947 -- EDTA

Martin Rubin, Ph. D., a pathology faculty member at Georgetown University, had a graduate student, Peter Weiss, then working on the staff of the Food and Drug Administration. Weiss was aware of Bersworth's recent question to the FDA on the studies necessary to clear EDTA as nontoxic for use as a preservative in food.

Further, Weiss knew that Berswerth insisted that his "chelation" development would someday cure atherosclerosis and vascular calcification. At Weiss' request, Rubin hosted Berswerth at his Georgetown hospital office. Rubin had a natural interest in the chelation concept: 1) his doctoral thesis at Columbia in the mid-1930s had been on the synthesis of cardiac drugs as alternatives to digitalis, and (2) ongoing research at Georgetown included the development of therapeutic metal-organic compounds.

The Bersworth Chemical Company provided a research grant to Georgetown University, enabling Rubin and associates to investigate biological effects of EDTA. Initial studies centered on the capability of EDTA to chelate calcium.

The established role of Ca++ as an essential constituent in the complex coagulation cascade suggested that its chelation by EDTA could interrupt the clotting process. Experimental confirmation lead to the worldwide acceptance of EDTA as an in-vitro anticoagulant ("lavender-top tubes"). (M. A. Klapheke and M. Rubin, "Na2EDTA as an anticoagulant for routine laboratory procedures" Bulletin Georgetown University Medical Center 5:33 1951)

1947 -- EDTA

Charles Geschickter, M. D., at the Georgetown University Medical Center, in Washington, D. C., a clinical colleague of Rubin, was the first to administer EDTA

to a human being. The presumed anti-cancer effect of nickel complexes was being studied in chemotherapy and the patient -- suffering with advanced adenocarcinoma of the breast -- was treated with nickel in the form of nickel-EDTA. Neither therapeutic nor toxic effects were observed; nickel-EDTA was excreted in the urine unchanged. (Citation?? 19XX)

1947 -- EDTA

Physicians at the Walter Reed Army Medical Center in Bethesda, Maryland, attempted to use EDTA to dissolve kidney and bladder stones. (Citation?? 19XX)

1950 -- EDTA

Rubin and coworkers established (in animals) that intravenous EDTA would chelate plasma calcium with resulting hypocalcemia and urinary excretion of CaEDTA. (A. Popovici, C. F. Geschickter, A. Reinovsky, and M. Rubin, "Experimental control of serum calcium levels in vivo" Proc Soc Exp Biol Med 74:415-417, 1950; M. Rubin, "Chelating agents in the study of calcium metabolism" Josiah Macy Foundation 355-368, 1953). Mice, rats, and rabbits were used as animal subjects during early EDTA investigations.

1951 -- EDTA

Discussions with Prof. Martell suggested to Rubin that weakly bound magnesium in its EDTA chelate would exchange with plasma calcium in vivo. Not only was this confirmed, but also the released Mg++ had a significantly enhanced hypotensive action in the presence of hypocalcemia resulting from EDTA.

Oral hypotensive drugs were under study at Georgetown; unfortunately, clinical colleagues expressed no interest in study of a compound that had to be administered by slow intravenous infusion. (A. Popovici, C. F. Geschickter, M. Rubin, "The treatment of essential hypertension by magnesium chelate solution" Bulletin Georgetown University Medical Center 5:108-116, 1951)

1951 -- BAL

D. Denny-Brown and H. Porter published "The effect of BAL (2,3-dimercaptopropanol) on hepatolenticular degeneration (Wilson's disease)," N

Engl J Med 245:917-25, Dec 13, 1951.

1951 -- CHEMISTRY/PHYSIOLOGY

C. Soprana documented the "Effect of sodium disulfonate-pyrocatechol on enteric elimination of lead in experimental intoxication," Folia med 34:456-460, Sep 1951.

1952 -- EDTA

In vitro chemistry studies of CaEDTA showed that the addition of soluble Pb++ would rapidly form Pb-EDTA with release of Ca++. Animal studies showed the same result, with urinary excretion of Pb-EDTA. At this time, one of Rubin's clinical colleagues, Dr. S. P. Bessman, had a patient with acute lead poisoning at Children's Hospital in Washington, D. C. Treatment performed with Ca-EDTA resulted in massive urinary lead excretion and significant clinical improvement. (S. P. Bessman, H. Reid, and M. Rubin, "Treatment of lead encephalopathy with calcium disodium Versenate, report of a case," Medical Annals, District of Columbia, 21:312-315, 1952)

Confirmation and extension of this original study followed rapidly .....

E. L. Belknap described the use of "EDTA in the treatment of lead poisoning," confirming previous reports of Norman Clarke. Industr Med Surg 21(6):305-306, June 1952.

A. M. Butler, "Use of calcium ethylenediaminetetraacetate in treating heavy-metal poisoning," Arch Indust Hyg Occupat Med 7:136-147, 1952.

H. A. Agerty, "Lead poisoning in children," Medical Clinics of North America, (36):1587-XXXX, 1952.

H. Foreman, H. L. Hardy, T. L. Shipman, and E. L. Belknap, "Use of ethylenediaminetetraacetate in cases of lead intoxication," AMA Arch Indust Hyg and Occup Med 7:148-151, Feb 1953.

M. Rubin, S. Gignac, S. P. Bessman, and E. L. Belknap, "Enhancement of lead excretion in humans by Na2CaEDTA (Versenate)," Science 117:659-660, June 12, 1953.

Rubin noted in personal communication 40 years later: "Since that time, CaEDTA has been used to treat lead poisoning throughout the world. I well remember my presentation of the first case to a distinguished group of lead poisoning experts. The first question and comment was: 'Since it is not possible to remove lead from the body once it enters, are you sure your analytical data are correct?'"

*ADVERSE*

R. O. Bauer, F. R. Rullo, C. Spooner, and E. Woodman reported the acute and subacute toxicity problems using EDTA. Their studies were done following chelation therapy that included an iv push of 10 grams EDTA or with frequent treatments given without vitamin/mineral supplementation. This was the FIRST negative report on EDTA treatments. "Acute and subacute toxicity of ethylene diaminetetraacetic acid (EDTA) salts," Fed Proc 11:321-327, 1952.

1950s -- EDTA

Elderly patients treated with EDTA for lead poisoning showed dramatic improvements in their coexisting atherosclerotic circulatory disorders.

1950s -- EDTA

The 1950s were an exciting era for clinical studies with EDTA chelation therapy.

In 1952, Herta Spencer first described treating hypercalcemia.

In 1956, Clarke, Clarke, and Mosher described the disappearance of angina symptoms.

In late 1950s, Surawicz described EDTA as an effective treatment for cardiac arrhythmias associated with digitalis toxicity.

1952 -- EDTA

Treatment of hypercalcemia (in man) with Na2-EDTA first described by Herta Spencer (with V. Vankinscott, I. Lewin, et alia, "Removal of calcium in man by ethylenediamine tetra-acetic acid: a metabolic study," J Clin Invest 31:1023-1027, 1952).

1952 -- BAL

R. C. Giannattasio, M. J. Pirozzi, A. V. Bedo, and K. G. Jennings published "BAL therapy in chronic lead poisoning," Pediatrics 10(5):603-11, Nov 1952 .....

..... then published "Lead poisoning, observations in fourteen cases," American Journal of Diseases of Children 84:316-21, Sep 1952

..... An abstract, "Dimercaprol in acute lead encephalopathy," soon followed in J Am Med Assoc 152(13):1272-3, July 25, 1953.

S. Moeschlin and L. Schnecterman reviewed "Comparative studies on therapeutic effect of dimercaprol or sodium citrate on experimental (lead) poisoning" in Schweiz med Wchnschr 82:1164-1165, Nov 8, 1952.

1952 -- CHEMISTRY/PHYSIOLOGY

D. O. Shiels reported on "Treatment of (lead) poisoning by intravenous administration of sodium thoisulfate" in M J Australia 1:879-882, June 28, 1952.

1953 -- EDTA

F. E. Karpinski, Jr., with F. Rieders and L. S. Girsh, reported on "Calcium sodium Versenate in therapy of lead encephalopathy" in J Pediat 42:687-699, June 1953.

J. B. Sidbury, Jr., J. C. Bynum, and L. L. Fetz published their observations on "Effect of chelating agent (calcium Versenate) on urinary lead excretion; comparison of oral and intravenous administration," Proc Soc Exp Biol Med 82:226-228, Feb 1953.

S. H. Cohen, J. K. Gong, and M. C. Fishler reported on "Ethylenediaminetetraacetic acid (EDTA) treatment of internal radioactivecontamination," Nucleonics 1953, suggesting it to be the most effective method of treating acute radiation poisoning. Later reviews disputed the effectiveness of EDTA, certainly in comparison to other chelators (such as DTPA). (Nucleonics 11(1):56-XX, 1953)

H. Foreman described "The use of chelating agents for accelerating excretion of radioelements," J Am Pharm A (Scientific edition) 42:629-632, Oct 1953.

H. Hart and D. Lazlo described "Modification of the distribution and excretion of radioisotopes by chelating agents," Science 11:56-61, 1953.

H. S. M. Uhl, H. H. Brown, A. Zlatkis, et alia reported on the lowering "Effect of ethylenediamine tetraacetic acid on cholesterol in rabbits." Am J Clin Path 23:1226-1233, 1953.

F. L. Leitch and J. F. Haley described "The effect of ethylene-diamine-tetraacetic acid and other chelating agents on the isolated mammalian heart," Arch Int Pharmacodyn 95:234-XXX, 1953.

1953 -- BAL

G. E. Deane, F. J. Heldrich, Jr., and J. E. Bradley reported on the "Use of BAL (2,3-dimercaptopropanol) in treatment of acute lead encephalopathy," J Pediat 42:409-413, April 1953.

1954 -- EDTA

Rubin published on the effects of EDTA on calcium hemostasis. (M. Rubin, "Chelating agents in the study of calcium metabolism" Josiah Macy Foundation 355-368 (1953)).

S. P. Bessman, M. Rubin, and S. Leikin, "The treatment of lead encephalopathy -- a method for the removal of lead in the acute stage," Pediatrics 14:201-208, 1954.

H. Foreman and T. Trujillo described the intermediate metabolism of EDTA, using labeled *C14 in humans. He reported that the EDTA molecule was excreted unchanged from the body, other than being excreted in combination with a divalent or trivalent metal ion. "Metabolism of carbon-14 labeled ethylenediaminetetraacetic acid in human beings," J Lab and Clin Med 43:566-571, 1954.

H. Foreman, P. A. Fuqua, and W. D. Norwood reported on "Experimental

administration of EDTA in plutonium poisoning" in AMA Arch Indust Hyg 10:226-231, Sept 1954.

N. Sapeika described "Antagonism of digitalis action by ethylenediamine-tetraacetic acid," Arch Int Pharmacodyn 97:373-xxx, 1954.

L. W. Holm reported on "The use of calcium disodium salt of Versene in heavy-metal poisoning of livestock," Proc Am Vet Med Assoc 48:33-xx, 1954.

*ADVERSE*
Marjorie B. Zucker, Ph. D., published her observations on "Some effects of disodium ethylenediamine tetraacetate on blood coagulation," Am J Clin Pathol 24:39-41, 1954. She observed that clotting time of EDTA plasma after optimal recalcification is longer than that of oxalated plasma -- which might be due to an effect of EDTA on the thrombin-fibrinogen reaction (the final stage of clotting).

1950s - EDTA

Various trade names have been used to designate the commercial products of EDTA compounded as the disodium or tetrasodium salt, such as Cheladrate*, Disodium Edetate*, Edathamil*, Endrate*, Trilon B*, Versene (Versenate), and so on, with "edetate" being used as the generic name. ENDRATE* (supplied by Abbott) was among the most commonly used in chelation therapy in the field of medicine.

The Na2 salt of EDTA is generally used in medicine because it increases the solubility of the chelating agent.

1950s - EDTA

Much of the early work on EDTA chelation therapy for atherosclerosis and related disorders was performed at Providence Hospital, Detroit, Michigan, under Director of Research Norman E. Clarke Sr., a cardiologist.

Clarke had reasoned that (1) soft tissue calcification was part of the atherosclerotic plaque, and (2) EDTA seemed to chelate calcium, then (3) EDTA chelation might help patients suffering from atherosclerotic cardiovascular disease. He found immediate and sometimes startling improvements with many patients and continued in this line of investigation.

1950s - 1960s -- EDTA

With his several reports published in major peer-reviewed American medical journals, Clarke was later called "the Father of EDTA Chelation Therapy in America." Research proceeded elsewhere in the USA as well.

Harper and Gordon in 1976 published a review article containing references to many of the early articles on EDTA chelation therapy. "EDTA Treatment for Atherosclerosis: History and Mechanisms of Action," Osteopathic Annals 4:38-62, 1976.

1954 -- CHEMISTRY/PHYSIOLOGY

E. Friedheim, J. R. DaSilva, and A. V. Martins published "Treatment of schistosomiasis mansoni with antimony a,a'-dimercapto-potassium succinate (TWSb)" Am J Trop Med Hyg 1954;3:714-27, demonstrating a 90% cure rate within 3 days of intramuscular or intravenous injection with limited side effects.

1955 -- EDTA

N. E. Clarke, C. N. Clarke, and R. E. Mosher were the first to publish research showing the effectiveness of EDTA in "The in vivo dissolution of metastatic calcium, an approach to atherosclerosis" (Am J Med Sci 229:142-149, 1955).

They did not find effects on the fibrous tissue. They wisely speculated that safe removal of "metastatic calcium" might allow for subsequent removal of interrelated cholesterol deposits from arterial walls. They also speculated on homeostatic activation of parathyroid hormone. They made anecdotal report of marked improvement of roentgenogram findings in a patient with bilateral renal calcinosis, while localized Paget's disease changes seen in the left hip bone was not influenced by the EDTA treatment.

H. M. Perry and H. A. Schroeder reported on "Depression of cholesterol levels in human plasma following ethylenediamine tetraacetate and hydralazine," J Chr Dis 2:520-523, 1955.

P. D. Smith and E. H. Grinnell noted the "Effect of dipotassium ethylene-diamine tetraacetic acid on digitalis-produced cardiac arrhythmia," Fed Proc 14:387-XXX, 1955.

ADVERSE

H. R. Dudley, M. D., A. C. Ritchie, M. D., A. Schilling, M. D., and W. H. Baker, M. D., described various "Pathologic changes associated with the use of sodium ethylene diamine tetra-acetate in the treatment of hypercalcemia: Report of 2 cases with autopsy findings," N Engl J Med 252:331-337, Mar 3 1955. "Because of the paucity of reports of toxic reactions to the drug, 2 cases of hypercalcemia [a woman dying with osteolytic metastases, the other a child with hypercalcemia after vitamin D therapy] treated by intravenous administration of large doses of sodium EDTA are here recorded. In each, in addition to the lesions expected, there were three unexpected pathological findings: the renal tubules, especially the proximal convoluted tubules, were severely damaged; the reticuloendothelial cells were enlarged and contained coarse eosinophilic granules; and internal hemorrhages were extensive."

ADVERSE

"Case 40361, Case Records of the Massachusetts General Hospital: Weekly Clinicopathological Exercises," N Eng J Med 251(11):442-448, Sep 9 1954. This is the detailed case report of the child described in the Dudley article (above).

1955 -- CHEMISTRY/PHYSIOLOGY

Johann Bjorksten published a speculative article, "Cross-linking -- key to aging?" in Chemical and Engineering News 33:1957-XXXX, 1955.

1955 -- CHEMISTRY/PHYSIOLOGY

Denham Harman, M. D., first proposed his free radical theories in a brief paper from the University of California/Berkeley, Donner Laboratory of Biophysics and Medical Physics, printed for the U. S. Atomic Energy Commission ("Aging: A Theory Based on Free Radical and Radiation Chemistry," July 14, 1955, UCRS-3078, Unclassified Health and Biology, Contract No. W-7405-eng-48):

"The universality of this phenomenon [of aging: growth, decline, and death] suggests that the reactions which cause it are basically the same in all living things. Viewing this process, which in essence is cellular degeneration, in the light of present day free radical and radiation chemistry and of radiobiology it seems possible that one factor in aging may be related to deleterious side attacks of free radicals (which are normally produced in the course of cellular metabolism) on cell

constituents.

.....

"The most likely source of OH and HO2 radicals, at least in the animal cell, would be the interaction of the respiratory enzymes involved in the direct utilization of molecular oxygen, particularly those containing iron, and by the action of catalase on hydrogen peroxide. ...

.....

"Thus, although the evidence is indirect, there are good reasons for assuming that the changes produced by irradiation and those which arise spontaneously in the living cell have a common source -- the OH and HO2 radicals. ...

" ... In this manner the functional efficiency and reproductive ability of the cell could eventually be impaired. In addition, since genes would be expected to be attacked occasionally it would be anticipated that mutations and cancer would result every now and then.

.....

"This theory is suggestive of chemical means of prolonging effective life."

This paper was reprinted, same title, in J Gerontol 11:298-300, 1956.

Harman followed this initial speculation with a study in mice with Ehrlich ascites tumor, demonstrating "Reducing Compounds as Chemotherapeutic Agents in Cancer," Clin Res Proc 4:54-55, 1956:

" ... According to a recently proposed theory of aging, which relates aging to the deleterious side reactions of active free radicals produced in the normal course of metabolism, an increased concentration of compounds capable of reacting rapidly with free radicals (i.e., reducing agents) should slow down the aging process and hence ameliorate the systemic effects of cancer."

1957 -- CHEMISTRY/PHYSIOLOGY

Harman extended his thinking with publication of "Atherosclerosis: A Hypothesis Concerning the Initiating Steps in Pathogenesis," J Gerontol 12(2):199-202, 1957:

"The rate of progression of atherosclerosis as manifested by coronary artery disease is correlated with the serum levels of low density lipoproteins. What may be the basis for this relationship? ...

.....

"It has been shown that atherosclerotic aortae contain lipoperoxides and that the content of the peroxides parallels the degree of severity of the atherosclerosis while normal aortae are free of lipoperoxides. Such peroxides are produced in the oxidation of fats. ...

.....

"Compounds that can act as oxidation inhibitors, such as ascorbic acid, thiamine, iodine, and thyroxine, in the diet of rabbits being fed cholesterol, decreases the severity of the cholesterol-induced atherosclerosis. Further, a mixture of vitamin A palmitate and alpha-tocopherol acetate, fed orally, very significantly reduced plaque formation, aortic total fat, and free and esterified cholesterol in chickens on a regular diet.

.....

"Thus, it would seem that both the type of molecule entering the arterial wall and the length of time it stays there are involved in the development of atherosclerosis. ...

.....

"Thus, atherosclerosis appears to be the result of three primary processes: 1) Oxidative-polymerization of constituents of serum lipoproteins; 2) Anchoring of the oxidized material in the arterial wall; 3) An inflammatory reaction induced in the arterial wall by these oxidation products. With increasing age the contributions of the first two processes increase while that of the latter decreases. ...

"This concept of the pathogenesis of atherosclerosis is suggestive of means to slow down the process. One of the most obvious is to decrease the chain length of the oxidative-polymerization reactions by increasing the serum concentration of compounds capable of acting as oxidative inhibitors. ..."

Another article, "Atherosclerosis: effect of an antioxidant -- cysteine," furthered these ideas (Clin Res Proc 6:50-51, 1958).

Harman pushed the limits of his theories in looking at "Prolongation of the Normal Life Span by Radiation Protection Chemicals," Clin Res Proc 5:46, 1957:

"The theory has been advanced that aging may be due in part to the deleterious side effects of free radicals normally produced in metabolism. On the basis of this theory it would be anticipated that raising the concentration in the organism of compounds capable of reacting rapidly with free radicals would tend to slow down the aging process and thus lead to an extension of the normal life span. This possibility has been tested [in two] short-lived strains of mice ...

.....

"AKR mice on cysteine hydrochloride (1%), 2-mercaptoethylamine

hydrochloride (1%), and 2,2'-diaminodiethyl disulfide dihydrochloride (0.5%) had a half life span (10 months) approximately 20% greater than the controls (8 months) ... the prolongation of life by these chemicals was significant at a P value of 0.01 or less."

Seven years before the American Heart Association endorsed the dietary incorporation of highly-unsaturated fats, Harman used his theories to speculate that such a measure might be unwise ("Atherosclerosis: Possible Ill-Effects of the Use of Highly Unsaturated Fats to Lower Serum-Cholesterol Levels," Letter to the Editor of Lancet 2:1116-1117, Nov 30, 1957):

"At present there is an increasing interest in the clinical use of such unsaturated acids as linoleic acid to lower serum-cholesterol levels, and thus presumably to slow down the rate of progression of atherosclerosis. Unfortunately, the use of highly unsaturated fats in the diet may lead to side-effects that would outweigh any benefit they have in atherosclerosis.

"In general, the more unsaturated a fat is, the more readily it is oxidised -- peroxides and compounds of higher molecular weight are among the products. Thus, increasing the degree of unsaturation of dietary fats -- particularly of those containing two or more double bonds -- will increase the intake of fat oxidation products.

.....

" ... Oxidised fatty acids have been shown to have an adverse effect on a number of oxidative enzymes.

"Unsaturated fatty acids increase the body's demand for vitamin E. ...

"The deleterious action of fatty acid peroxides on the body is probably related to the fact that they are strong oxidising agents; many important enzymes and vitamins are easily oxidised. ...

.....

"Further, one of the initiating steps in atherosclerosis may be the oxidative polymerisation of some of the constituents of the lipoproteins. If this is true, an increase in the degree of unsaturation of the dietary fats may, over the long term, actually increase the severity of atherosclerosis."

1956 -- EDTA

N. E. Clarke, C. N. Clarke, and R. E. Mosher published on "Treatment of angina pectoris with disodium ethylene diamine tetraacetic acid" (Am J Med Sci

232:654-666, Dec 1956), detailing experiences with 20 patients with documented angina whose symptoms showed consistent decrease or disappearance -- along with, in some cases, disappearance of EKG abnormalities consistently present during the 2 years preceding treatment.

In describing side effects encountered in over 4,000 infusions of 5 grams EDTA given close together, they noted mild gastrointestinal symptoms to be common -- apparently reduced by 25 - 75 mg of pyridoxine (B6) given daily.

AS WE GO THROUGH THE NEXT 15 YEARS ..... take note of the number of references published in recognized, peer-reviewed journals.

J. F. Saunders, J. V. Princiotto, and M. Rubin reported on the lowering "Effect of calcium disodium ethylenediamine tetraacetate on hypercholesterolemic rabbits (22374)," Soc Exp Biol Med 92:29-31, 1956.

R. H. Rosenman and M. K. Smith reported on beneficial effects in rats, "The effect of certain chelating substances (EDTA) upon cholesterol metabolism in the rat," J Clin Invest 35:11-19, 1956.

Herta Spencer, J. Greenberg, E. Berger, et alia published "Studies on the effect of ethylenediaminetetraacetate in hypercalcemia" in J Lab & Clin Med 47:29-41, Jan 1956.

*ADVERSE*
Jack T. Bechtel, M. D., Jefferson E. White, M. D., and E. Harvey Estes, Jr., M. D., documented "The electrocardiographic effects of hypocalcemia induced in normal subjects with edathamil disodium," Circulation 13:837-842, June 1956. "The major changes in the electrocardiogram with the induction of hypocalcemia were shortening of the R-R interval, prolongation of the RS-T and Q-T intervals, all of which were proportional to the degree of hypocalcemia. No change in the spatial P, QRS and T vectors, no T wave flattening or inversion and no elevation or depression of the RS-T segment appeared with hypocalcemia."

1956 -- EDTA

*ADVERSE*
In 1956, Harry Foreman, M. D., Camile Finnegan, B. S., and Clarence C. Lushbaugh, M. D., first reported that there was a "Nephrotoxic hazard from

uncontrolled edathamil calcium-disodium therapy." J Am Med Assoc 160:1042-1046, 1956.

Their case report was similar to that reported by Bauer (see 1952) in using larger doses of EDTA: a 40-year-old female chemical technician who had accumulated a small body burden of plutonium was given 2-1/2 grams of calcium disodium EDTA TWICE daily by intravenous drip over a half-hour period each time. The first treatment period was for 4 days and was followed by 2 days of rest; in the second period, the drug was administered for 12 consecutive days, on the final two days of which the patient complained of nocturia, frequency, urgency, burning on urination, as well as worsening mental dullness, lassitude, nausea, nasal stuffiness, and low back pain. Urinalysis showed 2+ albumin, renal parenchymal cells, fine granular casts, and occasional red and white blood cells. By the fifth day after cessation of treatment, the urine was clear and the patient appeared entirely recovered.

Spurred by this case, they conducted experimental studies on Sprague-Dawley rats and defined a dose-response curve for renal toxic effects. In animals treated with lower doses of EDTA (62.5 and 125 mg/kg), pathological changes were limited to the proximal convoluted tubules. With increasing dosages (250 mg/kg), occasional loops of the tubule adjacent to a glomerulus showed nuclear pyknosis and huge intracytoplasmic vacuoles with destruction of cell walls; then severe hydropic degeneration extended to about half of each proximal convoluted tubule, with the rest of the tubular system showing fine droplet degeneration (at 500 mg/kg). Higher doses (1,000 mg/kg) showed hydropic degeneration of almost the entire proximal convoluted portion of the renal tubular system, including formation of huge vacuoles and even rupture of cell walls. Still higher doses (3,000 mg/kg) produced the most severe changes, with some areas showing only basement membranes and no signs of preexisting cells -- further, they noted parenchymatous degeneration of the distal convoluted tubules, with nuclear pyknosis and chromatolysis and granular amorphous intratubular debris. No lesions were seen in the other organs examined. This was the first study to demonstrate that EDTA "is a potentially hazardous drug, since, on repeated administration of moderately large doses, it produced nephrosis."

"The results of these experiments should promote caution in the use of the drug. The reversibility of the lesions and the prolonged administration of large doses of the drug required to produce lesions offer an obvious means of using the drug safely. It is suggested that the drug be used in doses of approximately 50 mg per kilogram per day, given for five days, and followed by two days of rest before the regimen is repeated." NOTE: Current usage in humans limits exposure for each day to no more than 50 mg/kg EDTA, adjusted downward for significant decrements of measured renal function.

1957 -- EDTA

R. S. Gubner and H. Kallman published their findings on "Treatment of digitalis toxicity by chelation of serum calcium," Am J Med Sci 234:136-XXX, 1957.

..... BUT credit is usually given to Surawicz, who published extensively in 1959 - 1961 on his experience in treating digitalis toxicity with concurrent improvement with cardiac arrhythmias.

late 1950s -- EDTA

The late 1950s were fertile years for research into mechanisms of action and results obtained with chelation therapy.

1957 -- EDTA

A. J. Boyle demonstrated the reversal of atherosclerosis in man using EDTA. Bull Schweitz Akad Med Wess 13:408-XXX, 1957.

H. M. Perry described "Lesions resembling vitamin B-complex deficiency and urinary loss of zinc produced by ethylenediamine tetraacetate," in patients given chelation therapy without appropriate supplementation. Amer J Med 22:168-172, 1957.

ADVERSE

W. Vogt and H. Cottier reported "A case of necrotizing nephrosis after treating a man for chronic lead poisoning with large doses of EDTA," (Nekrotisierende Nephrose nach Behandlung einer subakut-chronischen Bleivergiftung mit Versenaat in hohen Dosen) Dosen Schweiz Med Wchnschr 87:665-667, Jun 1 1957. They reported clinical and autopsy findings of a 38-year-old man with chronic lead poisoning who mistakenly received 600 mg of CaEDTA per kilogram of body weight daily for four days (10 times the intended dosage). On the fifth day, anuria and uremia were noted; CaEDTA was discontinued, and the patient died the next night. At autopsy, there was an extensive necrotizing nephrosis involving the proximal convoluted tubules and loops of Henle. The lumina, particularly of the proximal tubules, were dilated and the epithelial cells were necrotic, flattened or desquamated, or showed minimal regeneration in several areas. The endothelial

cells of the glomeruli were frequently swollen, and there were homogeneous or finely granular eosinophilic masses in Bowman's space.

1957 -- EDTA

*ADVERSE*
S. Moeschlin reported two instances of nephrosis resulting from the treatment of lead intoxication from CaEDTA, but autopsy findings were not included. One case was that of a 60-year-old lead factory worker with acute poisoning who received 4 g of iv therapy daily for 4 days. Then 2.1 g were given orally each day for 4 weeks, followed by 5 g iv given for 2 days, then a 4 day interval, and 5 g iv for 2 more days. There was albuminuria, uremia, coma, and death in 2 days from severe toxic nephrosis. After each infusion, there was transient headache, nausea, stomach cramps, and diarrhea. The second case was a 53-year-old painter with chronic intoxication who developed anuria and uremia and died 4 days after CaEDTA treatment was discontinued. Therapy consisted of 2 g given iv for 1 day, 4 g for 2 days, and 2 g for 1 day. Another case was a 52-year-old man who developed uremia after 6 days therapy of 2 g administered iv daily and who died 14 days later. Autopsy disclosed a severe necrotizing nephrosis with lipid in the tubules. Hyaline casts were noted in the dilated tubules. "Zur Klinik und Therapie der Bleivergiftung mit Bericht uber eine todliche toxische Nephrose durch CaEDTA (Calciumversenat)," Schweiz med Wchnschr 87:1091-1096, Aug 24, 1957.

1958 -- EDTA

H. A. Peters, P. Eichman, and H. Reese described their experience with "Therapy of acute, chronic and mixed hepatic porphyria patients with chelating agents," Neurol 8:621-625, 1958.

H. A. Peters, S. Woods, P. L. Eichman, and H. H. Reese published on "The treatment of acute *porphyria* with chelating agents: A report of 21 cases," Amer Intern Med 47:889-XXX, 1957.

B. Kabakow and M. J. Brothers published their observations on "The effects of induced hypocalcemia on myocardial irritability and conductivity," A. M. A. Arch Int Med 101:1029-XXXX, 1958.

*ADVERSE*
E. Weinig and W. Schwerd reported the case of a 59-year-old factory worker who

received 3 g of CaEDTA ... for one day with a 2-day interval followed by 4 days more of therapy for chronic lead poisoning. He developed uremia along with prolonged bleeding and clotting time and died 2 days after administration of the last dose. At autopsy, the proximal convoluted tubules were minimally dilated and lined by both flattened necrotic and regenerating cells and sloughed cells filled with lumina. There were fine-sized to middle-sized droplets of fat within the epithelial cells. Frequent protein casts were present in the collecting tubules. Both chemical and histochemical studies disclosed lead in the kidney. "Nil nocerel Gefahren bei der Behandlung der Bleiintoxikation mit Calciumversenat ("Mosatil Komplexon")," Munchen med Wchnschhr 100:1788-1789, Nov 14 1958.

1959 -- EDTA

H. M. Perry found that many of the trace minerals are removed by administration of EDTA. The amount of trace mineral removed was determined by the concentration of the particular element, its stability constant with EDTA, and the presence and concentration of other minerals. "Normal concentrations of some trace metals in human urine: changes produced by EDTA," J Clin Invest 38(8):1452-1463, Aug 1959 (pages 1452-1455?). This report predated by 30 years the similar review by Elmer Cranton, M. D., in the Journal of Advancement in Medicine special issue, volume 2, numbers 1/2, Spring/Summer 1989.

S. Jick and R. Karsh reported on "The effect of calcium chelation on cardiac arrhythmias and conduction disturbances," Am J Cardiol 4:287-293, 1959.

Borys Surawicz, M. G. MacDonald, V. Kaljot, et alia reported on "Treatment of cardiac arrhythmias with salts of ethylenediamine tetraacetic acid (EDTA)," Am Heart J 58:493-503, 1959, subsequently publishing also in several other journals and in Seven's 1960 monograph, Metals Binding in Medicine (see below).

B. D. Cohen, N. Spritz, G. D. Lubash, and A. L. Rubin noted observations on the "Use of a calcium chelating agent (NaEDTA) in cardiac arrhythmias," Circulation 19:918-XXX, 1959.

K. I. Sivjakov presented data on rats given EDTA treatment for acute intoxication with selenium, cadmium, and tungsten. Toxicology and Applied Pharmacology 1:602-608, 1959.

ADVERSE

Heinrich G. Brugsch, M. D., reported fatal cases involving treatment with EDTA (Edathamil) for lead poisoning. AMA Arch Indust Health 20:285-292, 1959. "The LD50 dose for edathamil in rats, as established by ... Bersin and Bauer, et al, ranges from 500 mg per kilogram to several thousand milligrams per kilogram, according to the mode and length of application. ..... Altogether there is now considerable clinical evidence on record to suggest that lead, like other heavy metals, such as mercury or cadmium, damages the tubular system of the kidneys. ..... Practically all chelated lead reaches the kidney within five hours after a three-hour infusion ..... Edathamil should be given only with proper evaluation of the patient's renal status before, during, and after therapy."

1960 -- EDTA

Marvin J. Seven (with L. Audrey Johnson) edited a seminal monograph entitled Metal-Binding in Medicine: Proceedings of a Symposium held in 1959, sponsored by Hahnemann Medical College and Hospital of Philadelphia, published by J. B. Lippincott Company (Philadelphia), 1960. [QV290, H148M, 1959]

Marvin J. Seven reported on "Observations on the toxicity of intravenous chelating agents," in Seven, M. J. (editor), Metal-Binding in Medicine, J. B. Lippincott Company (Philadelphia), 1960, pages 95-103.

1960 -- EDTA

Seven hosted his second symposium in September 1960.

The future scientific acceptance of EDTA chelation therapy into mainstream medical practice was unfortunately delayed (probably by decades) by Dr. Seven's untimely death shortly thereafter. A 31-year-old physician associated with the National Institutes of Health, Seven died in an automobile accident in 1961.

Seven's second Symposium, in September 1960, did not appear in book form (likely due to his death), but is covered extensively in over 200 pages of Supplement 10 to the Federation Proceedings in 1961 -- "Proceedings of a Conference on Biological Aspects of Metal Binding". (Fed Proc 20(Suppl 10), 1961)

H. M. Perry and G. H. Camel reported on "Some effects of calcium disodium EDTA on plasma cholesterol and urinary zinc in man," in Seven, M. J. (editor), Metal-Binding in Medicine, J. B. Lippincott Company (Philadelphia), 1960, pages 209-215.

M. D. Reuber, M. D., and J. Edmund Bradley, M. D., reported a case of acute kidney nephrosis as the result of treating lead poisoning with EDTA. Toxic reactions in the kidney appeared secondary to LEAD nephrosis rather than changes induced by EDTA itself. When large amounts of lead are removed quickly from the body (by chelation or by mass effect), the kidneys may be damaged. "CaEDTA is a valuable drug in the treatment of lead intoxication, however, it should be recognized that it can produce acute tubular necrosis. ... The dosage should be calculated carefully and should not exceed 75 mg. per kilogram of body weight." "Acute Versenate nephrosis as a result of treatment of lead intoxication," J Am Med Assoc 174:263-269, Sep 17, 1960.

As noted earlier, treatment of digitalis toxicity and relief of cardiac arrhythmias with Na2 EDTA was first described by Borys Surawicz, M.G. MacDonald, V. Kaljot, E. Lepeschkin, and C. Bettinger (in Metal-Binding in Medicine, edited by M. J. Seven, 1960, "The effect of intravenous administration of disodium and dipotassium EDTA on cardiac arrhythmias"; in Prog Cardiovasc Dis 6:432-443, 1960, [Surawicz] "Use of the chelating agent, ethylene diamine tetraacetic acid, in digitalis intoxication and cardiac arrhythmias"; in Am Heart J 58:493-523, 1959, [Surawicz, MacDonald, Kaljot, and Bettinger] "Treatment of cardiac arrhythmias with salts of ethylenediaminetetraacetic acid (EDTA)"; and in [authorship?] "The effect of hypocalcemia induced by intravenous administration of disodium versenate on ectopic beats and rhythms," Proc New Eng Cardiovasc Soc 116(22):1957-1958, 19XX). "Review of the literature to date discloses that hypocalcemia without a concomitant change in serum potassium concentration has been induced in 86 patients with cardiac arrhythmias. An effective antiarrhythmic action was found in patients with ventricular tachycardia, in whom this arrhythmia was apparently precipitated by digitalis toxicity. Supraventricular and ventricular premature beats were suppressed in approximately 50 per cent of the patients. ... The antiarrhythmic action of induced hypocalcemia can probably be attributed to the prolongation of refractory period of myocardium."

J. L. Rosenbaum and M. J. Seven reported the reversal of digitalis intoxication using EDTA. "EDTA affects the complexing of digitalis with the Ca++ molecule," Am J Med Sci 240:77-84, 1960.

J. L. Rosenbaum, D. Mason, and M. J. Seven reported further on "The effect of disodium EDTA on digitalis intoxication," Am J Med Sci 240:111-118, 1960.

A. Soffer, T. Toribara, D. Moore-Jones, and D. Weber described "Clinical applications and untoward reactions of chelation in cardiac arrhythmias", AMA Arch Intern Med 106:824-834, 1960.

Herta Spencer summarized "Studies of the effect of chelating agents in man," Ann N Y Acad Sci 88:435-439, 1960.

1950s - 1960s - EDTA

H. Ray Evers, M. D., and others had began extensive clinical treatment programs in private hospital settings. As summarized later by Dr. Evers,

"From our experience in treating these approximately 3,000 patients with varying degrees of calcinosis (arteriosclerosis, atherosclerosis, etc.), we will unequivocally state that it is our opinion that every patient with this disease in any part of the body should be given a therapeutic trial before any type of vascular surgery is performed."

(H. Ray Evers, M. D., private communication, as published in the Reprints of Medical Literature on Chelation binder collection available from ACAM)

In another paper, "Chelation of Vascular Atheromatous Disease," privately circulated after presentation at professional meetings in the 1970s, Evers stated: "We find [in a review of a six year period where chelation therapy treatments were given to about 3,000 patients by the Staff of Columbia General Hospital that results are,] in all cases of angina, characterized by the patient having no need for vasodilators after about the fifth infusion ... and that ninety per cent of these problems in the lower extremities make significant gains including regaining ability to walk long distances comfortably, freedom from claudication, and evidence of improved distal circulation."

1960 -- EDTA

N. E. Clarke Sr. reported on a series of 283 patients with occlusive atherosclerotic vascular disease, treated between 1956 and 1960, with 87% showing improvement, despite the fact that minerals and trace elements depleted by EDTA were not replaced and risk factors (such as diet and tobacco use) were not modified. (with N. E. Clarke, Jr., and R. E. Mosher "Treatment of occlusive vascular disease with disodium ethylene diamine tetraacetic acid (EDTA)," Am J Med Sci 239:732-744, Jun 1960; and "Atherosclerosis, occlusive vascular disease and EDTA," Am J Cardiol 6:233-236, Aug 1960.

1960 -- EDTA

Lawrence E. Meltzer, M. E. Ural, and J. R. Kitchell studied chelation therapy for ischemic coronary artery disease because "it is not who has atherosclerosis but who has more and who has less. The current management of this disease is hardly more than a program of watchful waiting and palliation." In their study of 10 male patients with angina pectoris, therapy was discontinued after several treatments given over 2 to 3 months "because of disappointing results." Each patient received between 57 and 163.5 grams of EDTA, given intravenously, and none had shown improvement. Three months later, reevaluation showed that 9 of 10 had significant reductions in number and severity of anginal attacks, 5 of 9 showed EKG improvements, and all 3 patients with cardiomegaly showed a reduction in heart size -- with no significant toxicity encountered.

This completely positive and enthusiastic summary was entirely consistent with the data given in the body of the report. ("The treatment of coronary artery disease with disodium EDTA," pages 132-136, published in Metal-Binding in Medicine, edited by M. J. Seven, 1960, J. B. Lippincott Company)

This article and the reappraisal article (see 1963) published by the same authors are extremely important in the history of EDTA chelation therapy for cardiovascular disease. The reappraisal article is the main reference used by chelation opponents to support their contention that "it doesn't work." However, a careful reading of the two articles (which study the same patient cohort) leads the unbiased physician to exactly the opposite conclusion -- in other words, despite their stated conclusion, their data clearly show EDTA to be an effective treatment for cardiovascular disease.

1960 -- BAL

H. N. MacFarland published "The use of dimercaprol (BAL) in the treatment of cadmium oxide fume poisoning," Archives of Environmental Health 1:487-96, December 1960.

1961 -- EDTA

L. E. Meltzer, J. R. Kitchell, and F. Palmon, Jr. published a comprehensive clinical toxicity study involving EDTA, concluding no serious side effects when administered

as they described (3-gram dose as 0.5% solution over 2-1/2 to 3 hours). Their conclusion was based on "Two thousand consecutive infusions of disodium EDTA ... given to 81 subjects in a study ... of ... coronary artery disease during a 2-year period. ..... It is therefore our opinion that the drug can be used without danger over prolonged periods." ("The long term use, side effects, and toxicity of disodium ethylene diamine tetraacetic acid," Am J Med Sci 242:51-57, 1961)

J. R. Kitchell, L. E. Meltzer, and M. J. Seven described the "Potential uses of chelation methods in the treatment of cardiovascular diseases," Prog Cardiovasc Dis 3:338-349, Jan 1961.

A. J. Boyle, N. E. Clarke, R. E. Mosher, et alia noted the beneficial effects of "Chelation therapy in circulatory and other sclerosing diseases, such as scleroderma and rheumatoid arthritis. Fed Proc 20 (Part II Supp) 10:243-251, 1961.

A. Soffer documented "Changes in serum and spinal fluid calcium affected by disodium ethylenediamine tetraacetate," J Lab Clin Med 58:542-547, 1961.

A. Soffer, T. Toribana, and A. Sayman documented "Myocardial responses to chelation," Br Heart J 23:690-694, 1961.

H. Foreman reviewed the "Use of chelation agents in treatment of metal poisoning (with special emphasis on lead)," Fed Proc 20 (Part II Supp) 10:191-196, 1961.

R. A. Kehoe similarly reviewed "Value of calcium disodium ethylenediaminetetraacetate and British Antilewisite in therapy of lead poisoning," Fed Proc 20 (Part II Supp) 10:196-199, 1961.

H. L. Hardy reported on "Clinical experience with the use of calcium disodium ethylenediaminetetraacetate in the therapy of lead poisoning," Fed Proc 20 (Part II Supp) 10:199-202, 1961.

R. S. Eliot and S. G. Blount, Jr., described their experience with "Calcium, chelates, and digitalis, a clinical study," Am Heart J 62:7-21, 1961.

H. A. Peters noted his experience with "Trace minerals, chelating agents and the porphyrias," Fed Proc 20 (Part II Supp) 10:227-234, 1961.

H. M. Perry, Jr., offered a discussion of "Chelation therapy in circulatory and sclerosing diseases," Fed Proc 20 (Part II Supp) 10:793-795, 1961.

S. M. Woods, H. A. Peters, and S. A. M. Johnson described "Chelation therapy in

cutaneous porphyria," Arch Dermatol ??:84-89, 1961.

1961 -- EDTA

H. Foreman is credited with describing hypoglycemia as a result of EDTA chelation therapy. That report on toxic side effects, however, appears to have been published in 1963 and is referenced later in this document. Foreman offered summary remarks by the chairman at the second conference on biological aspects of metal-binding, and comments on hypoglycemia might be found there (Fed Proc 20(Suppl 20):257-XXX, 1961).

ADVERSE

Lawrence E. Meltzer, M. D., Florentino P. Palmon, Jr., M. D., and J. Roderick Kitchell, M. D., described the "Hypoglycaemia induced by disodium ethylenediamine tetra-acetic acid," Lancet 2:637-638, Sep 16, 1961. "The hypoglycaemic response seems to be related to alteration in trace-metal content induced by the chelation. ..... Since hypoglycaemia occurred only in insulin-treated subjects we suggest that EDTA chelated the zinc of this exogenous hormone ..., producing rapid solubility and, in turn, hypoglycaemia. Probably protamine (or other proteins) also complexed with insulin are similarly affected, which would increase the release of insulin. Unexplained is the gradual reduction in insulin requirements following long-continued chelation therapy."

1961 -- CHEMISTRY/PHYSIOLOGY

J. Shubert described "Radioelement removal by chelating agents: application of mass action laws and other factors," Fed Proc 20 (Part II Supp) 10:219-222, 1961.

A. Catsch reviewed the effectiveness of various chelating agents against various radioactive metals, noting that EDTA had a very limited application for radionuclides. Indeed, EDTA could not prevent the accumulation of radium, radiostrontium, or radiobarium in the skeleton -- indeed, EDTA could lead to an increased deposition by inhibiting radionuclide urinary excretion. Results showed promising effectiveness of DTPA (diethylenetriaminepentaacetic acid), possibly related to its penetration into the intracellular space to some extent (in contrast to EDTA). ("Radioactive Metal Mobilization," Fed Proc 20 (Part II Supp) 10:206-218, Sep 1961)

1962 -- EDTA

L. W. Wilder, L. R. DeJode, S. W. Milstein, and J. M. Howard at Hahnemann Medical College's Department of Surgery in Philadelphia, Pennsylvania, undertook to determine whether the in vitro perfusion of human atherosclerotic arteries with EDTA solutions could mobilize calcium independent of physiologic responses. "The use of EDTA in the treatment of atherosclerosis has been given clinical validity by the symptomatic improvement of such conditions as intermittent claudication and angina pectoris. It is assumed that a significant part of the clinical improvement is due to the mobilization of calcium from the atherosclerotic vessels."

This report, "Mobilization of atherosclerotic plaque calcium with EDTA using the isolation-perfusion principle" (Surgery 52(5):793-795, Nov 1962), showed that calcium released into perfusate across atherosclerotic arteries was proportional to the preperfusion estimate of the degree of atherosclerosis present. Undoubtedly these results contributed to the now-discredited "Roto-Rooter" theory of action of EDTA. However, a "direct effect" might still contribute to observed therapeutic results, complementing what is now known to be parathyroid hormone-induced mobilization of available ionic calcium.

Since calcium was removed from fresh cadaveric atherosclerotic iliac arteries by a 5% EDTA perfusate, Wilder and coworkers suggested that researchers explore further the adaptation of the regional (isolated limb) approach utilized by Creech and his colleagues in the treatment of cancer. No report of such an attempt has been located in the medical literature.

R. E. Birk and C. E. Rupe reported on treatment of "Systemic sclerosis" in Henry Ford Hospital Med Bull 10:522-523, 1962.

K. E. Nelder, R. K. Winkelmann, and H. Perry reported on their experience treating "Scleroderma," Arch Dermatol 86:95-99, 1962.

ADVERSE

J. Altmann, K. G. Wakim, and R. K. Winkelmann described the "Effects of edathamil disodium on the kidney, J Invest Dermatol 38:215-218, 1962. These effects were later identified as PINOCYTOSIS rather than tubular damage from vacuolization.

1963 -- EDTA

ADVERSE

H. Foreman reported on "Toxic side effects of ethylenediamine-tetraacetic acid," such as hypoglycemia. Reactions apparently are due to the formation of metalloenzyme complexes with EDTA, which cause an aberration of gluconeogenesis and other insulin-related enzymatic activities. "Reports on chemical experiences with EDTA over the past ten years indicate that unexpected side effects have been associated with its intravenous administration. The most significant of these is renal irritation. Apparently injudicious use of the drug can lead to death in individuals already severely ill from other causes. A variety of discomforting symptoms, ranging from lightheadedness, dizziness, vertigo and nausea to headache, vomiting, abdominal cramps, chest pain, muscle pains and joint pains have occurred singly or together in a relatively high proportion of patients after single doses. Seven suggests that these fall into a pattern which he terms 'excessive chelation syndrome,' the severity of which is apparently related to the size of dose of the drug and the rate at which it is administered. Mucocutaneous lesions have appeared after prolonged administration. There are occasional reports of glucosuria. There is no definitive explanation as to how the administration of the drug results in the development of these side effects. Trace mineral depletion may be involved but this is not certain at the present time. Zinc is the trace metal whose urinary excretion is most consistently affected by administration of chelating agent. Iron and manganese excretion is affected to a lesser extent and the excretion of other trace metals apparently is not altered at all." J Chr Dis 16:319-323, 1963.

L. E. Meltzer, F. Palmon, and J. R. Kitchell, during 1961, had published observations consistent with Foreman's descriptions in 1963 and Lamar's 1964 note of hypoglycemic response, in "Hypoglycemia induced by disodium ethylendiamine tetra-acetic acid," Lancet 2:637-638, Sep 16, 1961.

1963 -- EDTA

ADVERSE

J. Roderick Kitchell, F. Palmon, N. Aytan, and L. E. Meltzer published "The treatment of coronary artery disease with disodium EDTA, a reappraisal" in the American Journal of Cardiology (11:501-506, 1963):

"At the end of four years of treatment in 10 patients and after one and a half to three years in 28 others [added to the original cohort reported in 1961], a re-appraisal of the effect of EDTA therapy on arteriosclerotic coronary disease is reported. Whereas after three months of treatment, 66 per cent of these 38 patients exhibited improved anginal patterns ... and 40 per cent showed improved electrocardiographic patterns, none of these effects were lasting. At the time of this

report 12 of the 38 were dead of their original disease (32%) and only 40 per cent remained clinically improved. ... 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 disease at the present time."

Of striking interest is the dramatic reversal that these authors made over the two years (from 1961 to 1963) with regard to the effectiveness of "other commonly used therapeutic methods" available for this deadly disease.

A later in-depth review of this and their 1960 article was done by Elmer M. Cranton and James P. Frackelton -- "Current Status of EDTA Chelation Therapy in Occlusive Arterial Disease," J Adv Med 2:107-119, 1989) -- showing many unusual errors of interpretation. A thorough data review (as well as their lack of follow-up maintenance treatments to preserve the clear initial benefits) have suggested to some that the reversed conclusions found in the "reappraisal" might have been prompted by other-than-scientific considerations.

Analysis of their data reveals that their patients were extremely high-risk coronary patients in which no form of therapy had helped. The majority of these patients were reported to have improved and to have maintained improvement following conclusion of therapy. After 18 months with NO further therapy -- and with no stated dietary or risk factor modification -- 46 per cent of a group of 28 patients remained improved [ECG improvement in 46 per cent, in addition to improvement by subjective report in 64 per cent of subjects and increased exercise tolerance in 64 per cent]. These desperately ill patients had remained improved, despite most having previously suffered one or more myocardial infarctions and thus being at high risk for cardiac complications or death. Most of the patient had improved after only 20 EDTA infusions.

As Cranton and Frackelton stated in their 1989 review article: "These results were very impressive and did not support the authors' negative conclusions. In retrospect, it appears that the authors' summary in the 're-appraisal article' was, to a great extent, responsible for the lack of funding and for cessation of clinical trials with EDTA chelation therapy for occlusive arterial disease."

Kitchell later was criticized by the medical community for his support of an early form of the internal mammary artery bypass, which proved to be of little value in the treatment of coronary artery disease.

Interestingly, after issuing a negative "reappraisal" in 1963, Kitchell, Meltzer, and Rutman went on just 2 years later to cite the beneficial results in vascular disease

and diabetes, in their basic science article "Effects of ions on in vitro gluconeogenesis in rat kidney cortex slices" Am J Physiol 208:841-846, 1965.

B. T. Emerson wrote about using EDTA to diagnose chronic toxicity, particularly in kidney disease caused by lead. Toxic reactions were actually due to increased levels of lead being excreted rather than toxicity of EDTA. Australian Annals of Medicine 12:310-324.

A. J. Boyle, R. E. Mosher, and D. S. McCann described "Some in vivo effects of chelation -- I. Rheumatoid Arthritis" J Chronic Dis 16:325-328, 1963.

D. M. Aronov reported his experience in "The treatment of atherosclerotic patients with calcification of the arteries with Trilon B (disodium salt of EDTA)," (Russ, Moscow) Klin Med 41:19-23, 1963. This paper's title has also been referenced as "First experience with the treatment of atherosclerosis patients with calcinosis of the arteries with Trilon-B (disodium salt of EDTA)."

P. Szekely and N. A. Wynne reported on the "Effects of calcium chelation of digitalis-induced cardiac arrhythmias," Brit Heart J 25:589-594, 1963.

1963 -- BAL

J. Julian Chisolm, Jr., published "The use of edathamil calcium disodium (EDTA) and 2,3-dimercaptopropanol (BAL) in combination for the treatments of acute lead encephalopathy," American Pediatric Society 63(4-part 2):843-4, October 1963.

OF SIGNIFICANCE: This was the first note of a combination of chelation agents in clinical use.

1964 -- EDTA

Albert Soffer edited a superb monograph entitled Chelation Therapy, published by Charles C. Thomas (Springfield, Illinois, 1964), detailing effects of EDTA in cardiovascular diseases, as reported by several authors. Soffer later recanted his endorsement of chelation treatment for these conditions, though he never recanted his data. He subsequently became editor of the journal Chest, and wrote several critiques of chelation practice -- example: J Am Med Assoc 233 (1975).

Soffer had authored a number of positive articles on EDTA chelation, including these:

(with T. Toribara, D. Moore-Jones, and D. Weber) "Clinical Applications and Untoward Reactions of Chelation in Cardiac Arrhythmias," AMA Arch Int Med 106:524-534, 1960.

(with T. Toribara and A. Sayman) "Myocardial Response to Chelation," Br Heart J 23:690-694, 1961.

(with T. Toribara) "Changes in Serum and Spinal Fluid Calcium Affected by Disodium Ethylenediamine Tetraacetic Acid (EDTA)," J Lab Clin Med 58:542-547, 1961.

In the 1964 Soffer monograph, Rubin summarized recent years' research into disordered iron metabolism. (M. Rubin, "The significance of chelation for clinical problems of iron metabolism," pages 66-122)

(See also an earlier paper: M. Rubin, J. Houlihan, and J. V. P. Princiotto, "Chelation and iron metabolism: relative iron binding of chelating agents and siderophilin in serum," Proc Soc Exp Biol Med 103,663-6 (1960)).

These papers (and almost a dozen others) pointed to the competitive potential of EDTA in plasma to chelate and then excrete incoming iron. These data assumed much greater significance in the mid-1980s, with the clear-cut demonstration of the role of iron (and copper, as another transition metal) to dramatically accelerate the free radical-associated oxidation of LDL and other lipids, critical in the progression of atherosclerotic disease. Rubin and coworkers had already established that EDTA chelation therapy could interdict the first step in this progression.

1964 -- EDTA

Carlos P. Lamar coined the term "chemical endarterectomy" in his study of 15 diabetic patients suffering from severe vascular complications, all of whom were relieved of their peripheral vascular insufficiency. His 3 cases of diabetic retinopathy all showed dramatic subjective and objective benefits. He also noted hypoglycemic responses in some diabetic patients treated with EDTA and also receiving long-acting insulin (zinc-containing) daily. Seven of 15 diabetics showed persistent improvement with reduction of insulin needs after EDTA.

Lamar's studies suggested that patients suffering with progressive atheromatous degeneration excrete lower than normal urinary calcium -- and that they increase their calciuria with EDTA treatment. He maintained that patients seemed to respond better and faster to EDTA infusions given daily with occasional rest periods rather than infusions given only 2 or 3 times per week -- and claimed that 5 consecutive daily treatments as periodic boosters were more effective in the maintenance follow-up. Further, he described increases in BUN (to 30 mg/dl) and uric acid (to 10 mg/dl) with precipitation of gouty attacks during EDTA treatments, with levels of BUN and UA maintaining low normal levels subsequent to treatment periods. He also described anecdotal improvements in osteoarthritis, calcified tenosynovitis, and benign prostatic calcinosis.

In his review of side effects, he noted a significant frequency of burning and pain at the injection site and along the course of the infused vein (3 g EDTA in 500 ml of NS or D5W or 10 per cent levulose for diabetics). He also described mild hypotension, mild hypoglycemia (transiently in 2 patients with prior history of reactive hypoglycemia), mild hypocalcemia, and rarely dermatitis (?induced pyridoxine deficiency), nausea, vomiting, abdominal cramps or pain. Even more rarely seen were systemic reactions (fever, anorexia, malaise, headache, fatigue), histamine-like reactions (sneezing, lacrimation, nasal congestion), hematopoietic changes, glycosuria, hyperglycemia.

See his various reports .....

"Chelation therapy of occlusive arteriosclerosis in diabetic patients," Angiology 15:379-394, 1964.

"Chelation endarterectomy for occlusive atherosclerosis," J Amer Geriatric Soc 14(3):272-294, 1966.

"Calcium chelation in atherosclerosis -- 9 Years Clinical Experience -- New Modus Operandi," presented to the American College of Angiology, 1968.

1964 -- EDTA

C. R. Angle and M. S. McIntire investigated "Lead poisoning during pregnancy: Fetal tolerance of calcium disodium edetate," Am J Dis Child 108:436, 1964.

T. M. Batchelor, M. McCall, and R. M. Mosher described "Potassium diuresis induced by edathamil disodium," J Am Med Assoc 187:305-XXX, 1964.

1964 -- BAL

H. D. Smith published "Pediatric lead poisoning," Archives of Environmental Health, 8:256-61, Feb 1964.

1964 -- CHEMISTRY/PHYSIOLOGY

D. H. Blankenhorn described the derivation of "Calcium deposits in the plaque" in Evolution of the Atherosclerotic Plaque, edited by R. J. Jones, University of Chicago Press, 1964, pages 297-314.

A. L. Aronson and P. B. Hammond detailed the "Effect of two chelating agents on the distribution of lead," J Pharmacol Exp Ther 146:241-251, 1964.

1964 -- DFO

Extensive research into iron chelation was summarized in an excellent paper from CIBA Research Laboratories, Basle, Switzerland, when H. Keberle published "The biochemistry of desferoxamine and its relation to iron metabolism" in Ann NY Acad Sci 119(2):758-768, 1964.

1965 -- EDTA

W. Friedel, F. H. Schultz, and L. Schroder wrote about the treatment of atherosclerosis through the use of mucopolysaccharides and EDTA. Deutsch Gesundh 20:1566-1570, 1965.

1965 -- CHEMISTRY/PHYSIOLOGY

E. D. Willis published on the mechanisms of lipid peroxide formation in tissues. "Role of metals and hematin proteins in the catalysis of the oxidation of unsaturated fatty acids," Biochem Biophys Acta 98:946-951, 1965.

1966 -- EDTA

S. L. Schwartz, J. R. Hayes, R. S. Ide, et alia first reported the effects of EDTA on the kidneys were relative to dosage and rate of administration. "Studies of the nephrotoxicity of ethylenediamine tetraacetic acid," Biochem Pharmacol 15:377-389, 1966.

R. E. Birk and C. E. Rupe presented studies on the "Treatment of systemic sclerosis with ethylene diamine tetraacetic acid, pyridoxine, and reserpine," Henry Ford Hospital Bulletin 14:109-118, 1966. (pages 109-139??)

R. E. Birk reviewed experience in "Treatment of systemic sclerosis," Modern Treatment 3:1286-1301, 1966.

late 1960s -- EDTA

The late 1960s showed a renewed research interest into the mechanisms of action of EDTA .....

1967 -- EDTA

A. Wartman, T. L. Lempe, D. S. McCann, and A. J. Boyle published data on "Plaque reversal with magnesium EDTA in experimental atherosclerosis, elastin and collagen metabolism," J Atheroscler Res 7:331, 1967.

P. Doolan and S. L. Schwartz described the effects of EDTA on the kidneys and the normal physiological role of pinocytosis in the elimination of EDTA from the body. They concluded that EDTA ALONE is NOT NEPHROTOXIC -- refuting earlier studies on possible drug toxicity. Toxicol Applied Pharm 10:481-500, 1967.

S. L. Schwartz, C. B. Johnson, J. R. Hayes, and P. D. Doolan reported on the "Subcellular localization of EDTA in the proximal tubular cell of the rat kidney," Biochem Pharmacol 16:2413-2419, 1967.

1967 -- EDTA

In 1967, A. J. Boyle and D. S. McCann described "New concept relating parathyroids to atherosclerotic plaque reversal," Circulation 5 (Supp 2):35-36,

1967. (As we saw earlier, Clarke had already suggested parathormone to plaque reversal.)

G. W. Bates, C. Billups, and P. Saltman presented data on "The kinetics and mechanism of iron(III) exchange between chelates and transferrin: II. The presentation and removal with ethylene diamine tetraacetate," J Biol Chem 242:2816-XXXX, 1967.

1968 -- EDTA

J. H. Olwin and J. L. Koppel reported on "Reduction of elevated plasma lipid levels in atherosclerosis following EDTA therapy," Proc Soc Exp Biol Med 128(1):1137-1145, 1968. "In 34 patients exhibiting various clinical manifestations of atherosclerosis, 14 diabetic, 20 nondiabetic, abnormally high plasma lipid levels were observed to be depressed, in many instances to normal range, following the intravenous administration of EDTA."

*ADVERSE*
F. A. Ahrens and A. L. Aronson reported on "Toxicity of calcium ethylenediaminetetraacetate XXXX," Am Soc Exp Biol 27:1401-XXXX, 1968. (CITATION NEEDS CORRECTION)

A. L. Aronson, P. B. Hammond, and A. C. Strafuss reported on "Studies with calcium ethylenediaminetetraacetate in calves; toxicity and use in bovine lead poisoning," Toxicol Appl Pharmacol 12:337-349, 1968.

1968 -- BAL

J. Julian Chisolm Jr. published "The use of chelating agents in the treatment of acute and chronic lead intoxication in childhood," J Pediatrics 73(1):1-38, July 1968.

1969 -- EDTA

Langhof et alia reported "EDTA [chelation] treatment in 12 patients with arteriosclerosis was performed. An intravenous infusion ... gave good results after 6 to 8 weeks without side effects or complications. Blood serum cholesterol levels were decreased ....." Metab Parietis Vasorum, Papers Intern Congr Angiol, 5th,

Prague, 1969.

1969 -- EDTA

Abbott's patent on EDTA (Endrate*) expired.

Thus, the three major blows to the professional acceptance of EDTA chelation therapy for cardiovascular disease were .....

(1) the accidental death of Dr. Marvin Seven in 1961,
(2) the aberrated conclusions expressed by Kitchell and Meltzer in their re-appraisal article in 1963, and
(3) the expiration of Abbott's patent (and thus, their interest in commercial support of further research) in 1969.

1970 -- EDTA

L. J. Leipzig, A. J. Boyle, and D. S. McCann published on successful "Case histories of rheumatoid arthritis treated with sodium or magnesium EDTA" J Chronic Dis 22:553-563, 1970.

S. L. Schwartz, C. B. Johnson, and P. D. Doolan provided further data in their "Study of the mechanism of renal vasculogenesis induced in the rat by ethylenediaminetetraacetate," Molecular Pharmacol 6:54-60, 1970.

1971 -- EDTA

Helene Swenerton and Lucille S. Hurley reported their observations on "Teratogenic effects of a chelating agent [EDTA] and their prevention by zinc," Science 173:62-64 (1971). Injection of EDTA into pregnant has resulted in congenital malformations in the young, as reported in 1956. "The present study suggests but does not prove that the congenital anomalies caused by EDTA [in rats] are due to specifically to zinc deficiency. ..... Because of the ubiquitous presence of zinc in plants and animals, deficiencies of this essential trace element have been considered rare in man. However, increases in environmental levels of metal-binding substances (such as EDTA) or zinc antagonists (such as cadmium) may induce zinc deficiency and interfere with the fundamental processes in which the trace element plays an essential role."

*ADVERSE*

F. A. Ahrens and A. L. Aronson reported their findings in "A comparative study of the toxic effects of calcium and chromium chelates of ethylenediaminetetraacetate in the dog," Toxic Appl Pharmac 18:10-XX, 1971.

*ADVERSE*

F. A. Ahrens and A. L. Aronson published their "Comparative study of the toxic effects of calcium chelates of etheylenediamine tetraacetate in the dog," Toxic Appl Pharmocol 18:1-XX, 1971. (Citation needs verification)

A. L. Aronson and F. A. Ahrens reported on "The mechanism of renal transport and excretion of ethylenediaminetetraacetate with interspecies comparison," Toxic Appl Pharmacol 18:1-XX, 1971. (Citation needs verification)

1971 -- BAL

J. M. Arena published "Treatment of mercury poisoning," Modern Treatment 8(3):619-25, August 1971, Hoeber Medical Division, Harper & Row, Publishers.

J. Julian Chisolm published "Treatment of lead poisoning," Modern Treatment 8(3):593-611, August 1971, Hoeber Medical Division, Harper & Row, Publishers.

1972 -- EDTA

With the exception of occasional papers by Carlos Lamar ("Chelation endarterectomy for occlusive atherosclorosis" J Am Geriatr Soc 14:272-, 1966) and presented in 1968 (14th annual meeting of the American College of Angiology, San Juan, Puerto Rico, December 8, 1968: "Calcium chelation of atherosclorosis -- Nine years clinical experience") -- EDTA chelation therapy and clinical research virtually came to a standstill in the late 1960s. Thus, it was left to other countries to pick up and develop the concept. The transcript of his presentation is available from ACAM -- dial 1-800-LEAD-OUT.

T. G. Brien and J. A. Fay reported a new method of using "51-Cr-EDTA biological half-life as an index of renal function," J Nucl Med 13(5):339-340, 1972.

E. K. Nikitina and Abramova reported positive clinical results in the "Treatment of atherosclerosis with trilon B [EDTA]," Kardiologica 12(11):137, Nov 1972. "The purpose of the present study is the study of the effect of Trilone-B on patients with

stenosed forms of atherosclerosis of the coronary [25 patients], cerebral [8 patients], and peripheral vessels [7 patients]. ... During treatment with Trilone, the general condition of all patients improved significantly."

O. Brucknerova and J. Tulacek published on successful use of "Chelates in the treatment of occlusive atherosclerosis" Vnitrlek Lekarstri 18:729-736, Aug 1972, perhaps presaging the work of Zechmeister (Czechoslovakia) in the mid-1980s. "The treatment with [EDTA chelation therapy] is considered as a method of choice in both states of claudication and in the [advanced stages] of occlusive atherosclerosis of arteries of the lower extremity."

1972 -- BAL

F. W. Oehme published "British Anti-Lewisite (BAL), the classic heavy metal antidote," Clinical Toxicology 5(2):215-222, 1972.

A. A. Browder, M. M. Joselow, and D. B. Louria published "The problem of lead poisoning," Medicine 51(2):121-139, 1973.

1973 -- DMPS

V. N. Kurliandchikoc reported on "Treatment of patients with coronary atherosclerosis with Unithiol in combination with Decamevit)," (Russian) Vrach Delo 6:8-12, June 1973.

Kurliandchikoc had also investigated and reported on .....

"Use of Unithiol, its combination with polyvitamin preparations and cetamiphen in the treatment of patients with cerebral atherosclerosis," (Russian) Vrach Delo 9:24-28, Sep 1972.

"Complex treatment of hypertensive disease with Decamevit and Unithiol under the condition of biotron," (Russian) Vrach Delo (7):25-29, 1974.

"Electrical activity of the brain in patients with the cerebral form of hypertension under the effect of combined Unithiol and Dekamevit treatment under biotron conditions," (Russian) Vrach Delo (1):35-39, Jan 1974.

"Use of Decamevit and Unithiol in the treatment of patients with cerebral form of

hypertensive disease under usual conditions and in the biotron," (Russian) Vrach Delo (1):38-41, Jan 1975.

V. I. Zapacnick, with V. N. Kurliandchikoc, et alia, described the "Pharmacological activity of Unithiol and its use in clinical practice," (Russian) Vrach Delo 8:122-125, Aug 1973.
Zapacnick had also investigated and reported on .....

"Normalization of metabolic and functional disturbances in aging with drugs," (Russian) Vrach Delo 9:5-8, Sep 1968.

"Decamevit -- an effective geriatric agent," (Russian) Klin Med (Mosk) 49(5):50-54, May 1971.

(with Kurliandchikoc) "Urinary excretion of sulfur compounds and certain microelements in patients with hypertensive disease treated by combination of Unithiol and Decamevit under biotron conditions," (Russian) Vrach Delo (12):26-28, Dec 1974.

"Means of reactivation of the processes of regeneration in the aged organism," (Russian) Vestn Akad Med Nauk SSSR (12):40-42, 1975.

1973 -- PCA

H. Vasken Aposhian reviewed "Penicillamine and analogous chelating agents," Ann N Y Acad Sci 179:481-486, Jul 6 1971. CONFIRM DATE -- 1973?? 1971?? XXXX

1973 -- CHEMISTRY/PHYSIOLOGY

B. T. Emerson reported on "Chronic lead nephropathy," J Kidney Int 4:1-XX, 1973.

1973 -- CHEMISTRY/PHYSIOLOGY

Harry B. Demopoulos, M. D., published seminal articles in Federation Proceedings: "The basis of free radical pathology" (32:1859-1861) and "Control of free radicals in the biologic systems" (32:1903-1908). ..... based on the theories of free radical activities in biological systems first advanced by Denham Harman in 1955.

Demopoulous' work was given some interesting perspectives in a July 1975 article by A. Sincock -- "Life extension in the rotifer by application of chelating agents" -- showing a 50% increase in lifespan of rotifers [simple marine life] treated every other day with EDTA. J Gerontol 30:289-293, 1975.

1973 -- ORGANIZATION

A small group of physicians meeting in Southern California decided to form the American Academy of Medical Preventics, to help educate physicians and to promote the use of EDTA chelation therapy for cardiovascular disease. IAPM (International Academy of Preventive Medicine) had refused to become involved with chelation therapy, so several of its members decided to form the new group, including Charles Farr, M. D., Ph. D., Garry Gordon, M. D., Ross Gordon, M. D., Robert Vance, D. O., Yiwen Tang, M. D., David Edwards, M. D., and Harold Harper, M.D. Encouragement and financial assistance was provided by vendor Claire Smith, soon thereafter joined by vendor Bob Davies. Harold Harper, M. D., was chosen as first president.

1974 -- EDTA

J. Julian Chisolm, Jr., M. D., published his observations on "Chelation therapy in children with subclinical plumbism [lead poisoning]," Pediatrics 53(3):441-443, Mar 1974. "The three chelating agents used to treat plumbism in the United States are ... CaEDTA, ... BAL, and d-penicillamine (PCA). ... PCA was appreciably inferior to [the others] in terms of the quantity of lead mobilized and excreted. ... For all three drugs, the vast bulk of lead mobilized was derived from osseous tissue, presumably marrow, and the portion of lead loosely bound to bone."

T. N. James researched "Selective experimental chelation of calcium in the sinus node," J Mol and Cell Cardiol 6:493-504, 1974.

Paul A. Huff presented a paper on "The Origin, History, Chemistry, and Uses of EDTA" to the American Academy of Medical Preventics (AAMP). Text published in Reprints of Medical Literature on EDTA Chelation Therapy, ACAM:594-608.

G. Wong reported on "The Chemistry of EDTA" to the American Academy of Medical Preventics. Text published in Reprints of Medical Literature on EDTA Chelation Therapy, ACAM:403-425.

1975 -- EDTA

A. Sincock documents "Life extension in the rotifer by application of chelating agents" -- showing a 50% increase in lifespan of rotifers [simple marine life] treated every other day with EDTA. J Gerontol 30:289-293, 1975.

*ADVERSE*
A. Soffer published a negative commentary (without offering any original data) on "Chelation therapy for arteriosclerosis" in J Am Med Assoc 233(11):1206-1207, Sep 15 1975.

*ADVERSE*
A. Soffer issued a second critique, "Editorial -- Chihuahuas and laetrile, chelation therapy, and honey from Boulder, Colorado" in Arch Int Med 136(8):865-866, Aug 1975.

*ADVERSE*
P. C. Craven and H. F. Morelli wrote a negative opinion statement, "Chelation therapy," in Western J Med 122:277-278, 1975. "No well designed, controlled studies with blindly read, objective results have been reported. Because of the risk of severe renal toxicity, and the lack of objective evidence suggesting therapeutic benefit from EDTA therapy for atherosclerotic disease, such therapy should be regarded as investigational and conducted under carefully controlled conditions in an academic institution by experienced investigators."

*ADVERSE*
The California Medical Association issued warnings against the use of chelation therapy. CMA News, September 12, 1975.

1975 -- EDUCATIONAL

H. W. Harper and G. F. Gordon published "Reprints of Medical Literature on Chelation Therapy," Los Angeles: American Academy of Medical Preventics, 1975.

Bruce W. Halstead, M. D., published in 1975 his first summary volume, Chelation Therapy, later revised in 1976, and finally expanded into the reference text, The Scientific Bases of EDTA Chelation Therapy, published in 1979 by Golden Quill Publishers, Box 1278, Coulton, California 92329.

"... [The] crude clinical data based on the experience of hundreds of physicians over a period of almost two decades involving more than 100,000 patients and upwards of 2 million treatments indicate that a positive response with good to excellent results occurs in about 75 per cent of the cases. An additional 15 per cent show mild improvement, and 10 per cent of cases show no clinical evidence of improvement. ..... Chelation therapy with EDTA should be considered in any disease in which there are abnormal deposits of free ionic calcium present in the skin, joints, or in which there is impairment of the circulation."

1976 -- CHEMISTRY/PHYSIOLOGY

W. A. Pryor edited several volumes, Free Radicals in Biology, published by the Academic Press.

1976 -- EDTA

Garry B. Gordon and Robert B. Vance published a summary paper, "EDTA Treatment for Atherosclerosis: History and Mechanisms of Action," in Osteopathic Annals 4(2):38-62, 1976.

1976 -- EDTA

In 1976, G. Tamburino, C. E. Flore, and A. Petralito reported their "Comparison of effects of EDTA (Versenate) infusion on plasma calcitonin levels in senile osteoporotic and aged matched healthy subjects," IRCS Med Sci Libr Compend 4:362, 1976. Effects secondary to EDTA administration were an induced PTH response and concomitant increase in osteoblastic/osteoclastic activity in bones. Osteoporosis, usually a post-menopausal resorption of calcium from the bones into soft tissues, is reversed by EDTA, which initiates deposition of new bone matrix.

B. M. Altura and B. T. Altura described "Magnesium withdrawal and contraction of arterial smooth muscle: effects of EDTA, EGTA, and divalent cations," Proc Soc Exp Biol Med 151(4):752-755, 1976. They demonstrated the restoration of electromagnetic potential across cell membranes, critical for the maintenance of cell integrity and biochemical functions. Their findings lend support to the view that magnesium ions either play an important role in regulating membrane permeability to calcium or occupy membrane sites that are exchangeable with membrane-bound calcium in certain types of arterial smooth muscle.

1977 -- EDTA

C. F. Peng, J. J. Kane, M. L. Murphy, and K. D. Straub reported data showing that "Abnormal mitochondrial oxidative phosphorylation of ischemic myocardium reversed by calcium chelating agents," J Mol Chem Cardiol 9:897-908, 1977.

(ON THIS SAME SLIDE: Walker showed that EDTA removes calcium from arteriosclerotic plaque in rabbits.)

C. F. Peng, J. J. Kane, J. K. Bisset, et alia described "Improvement of oxidative phosphorylation by EDTA in mitochondria from acutely ischemic myocardium which has been reperfused," Clin Res 25(3):244A, 1977.

M. G. Konradi reported "Use of the disodium ethylene diamine tetraacetate for diagnosing latent forms of hypoparathyroidism. Probl Endokrinol (Russ.) 23(3):46-50, 1977.

P. Brachet and C. Klein described "Cell response to CAMP during aggregation phase of Dictyostelium discoideum. Comparison of the inhibitory effects of progesterone and the stimulatory action of EDTA and ionophore A23187," Differentiation 8(1):1-XX, 1977.

Charles Farr reported a study of skin tissue biopsies before and after EDTA chelation therapy to a meeting of the American Academy of Medical Preventics (AAMP). These studies showed "metastatic ionic calcium" in the skin and underlying subcutaneous tissues was reduced by an estimated 30 to 50 per cent after completion of a chelation treatment series. The reduction of calcium was directly related to the loss of wrinkles and increase in elasticity of the skin. Farr proposed the elasticity of arterioles is increased, accounting in part for the improved vascular functions of a patient treated with EDTA chelation therapy.

R. L. Kaman, Charles J. Rudolph, and J. Galewaler described "Mineral excretion patterns during EDTA chelation therapy," J Amer Osteopath Assoc 76(6):471, 1977.

1977 -- DFO

A series of detailed reports were published in Chelation Therapy in Iron Overload, edited by E. C. Zaino and R. H. Roberts, published by Symposia Specialists, Medical Books, Miami, Florida. Included was "The use of desferoxamine and 'the

pump'" (referring to sc continuous infiltration), by R. D. Propper and D. G. Nathan.

1977 -- CHEMISTRY/PHYSIOLOGY

Johann Bjorksten published on "Pathways to the decisive extension of the human specific lifespan," J Am Geriat Soc 25(9):xxx-xxx, 1977.

E. P. Benditt published "The origin of atherosclerosis" in Scientific American 236(2):74-85, Feb 1977. He explained his monoclonal theory of atherosclerosis in which mutagenic changes in smooth muscles cells results in the proliferation of these cells and subsequent development of plaques. Free radical pathology plays a major role.

See also Benditt's other articles:

"Implications of the monoclonal character of human atherosclerotic plaques," Beitr Pathol 158(4):405-416, Sep 1976; same article name, Ann N Y Acad Sci 275:96-100, 1976; same article name, Am J Pathol 86(3):693-702, Mar 1977.

S. Piomelli published "Lead poisoning -- its detection and treatment," Drug Therapy (Hosp), pp. 19-26, Sep 1977.

K. I. Shine, A. M. Fogelman, A. A. Kattus, G. D. Buckberg, and J. H. Tillisch published on the "Pathophysiology of myocardial infarction," Ann Int Med 87(1):75-85, Jul 1977. "Cellular defects of cholesterol metabolism may be more significant markers than serum lipid levels for the identification and treatment of atherosclerotic risk. Coronary spasm has been shown to be an important cause of ischemia in the presence and absence of atherosclerotic lesions." (See Fogelman's more extensive reports in 1994 and 1995)

1978 -- EDTA

V. A. Kozlov reported on the "Ca++-dependent immunosuppressive effect of EDTA," Zh Mikrobiol Epidemiol Immunobiol (1):69-72, Jan 1978.

F. Walker, C. Wilson, III, and R. L. Kaman published on "The effects of EDTA chelation therapy on plaque composition and serum lipoproteins in atherosclerotic rabbits," J Am Osteopath Assoc 78(2):144, 1978.

1978 -- CHEMISTRY/PHYSIOLOGY

J. B. Butterfield described the theory of "free radical pathology" as it related to chronic disease processes. Stroke 9:443-445, 1978.

M. B. Zurcker and R. A. Grant published their observations on the "Nonreversible loss of platelet aggregability induced by calcium deprivation," Blood 52(3);505-513, Sep 1978.

1978 -- EDUCATIONAL

Medical writer Stanley A. Leitner published Last Chance to Live, a book based on 15 years of actual clinical treatment by Dr. Ray Evers of more than 15,000 victims of virtually every type of chronic degenerative diseases, presenting many documented case histories and testimonials, Chesterfield, Missouri: Wade Allen Publishing, 1978.

1978 -- LEGAL/POLITICAL

H. Ray Evers, M. D., won a precedent-setting case clearly establishing the right of a physician to use a drug approved for one condition by the U. S. Food and Drug Administration in the treatment of another condition for which such usage has not been approved.

Unites States v. Evers, 453 F.Supp. 1141 (1978) -- Decision rendered June 27, 1978:

"In People v. Privitera, Cal.App., 141 Cal.Rptr. 764, 774 (1977), the court ... stated that,

'To require prior State approval before advising -- prescribing -- administering -- a new treatment modality for an informed consenting patient is to suppress innovation by the person best qualified to make medical progress. The treating doctor, the clinician, is at the cutting edge of medical knowledge.

'To require the doctor to use only orthodox "State sanctioned" methods of treatment under threat of criminal penalty for variance is to invite a repetition in California of the Soviet experience with Lysenkoism. The mention of a requirement that licensed doctors must prescribe, treat, "within State sanctioned alternatives" raises the spector of medical stagnation at the best, statism, paternalist big brother

at worst. It is by the alternatives to orthodoxy that medical progress has been made. A free, progressive society has an enormous stake in recognizing and protecting this right of the physician.'" (at 1150)

"Irrespective of the strong medical school of thought that chelation has not been clinically shown to help arteriosclerosis, the weight of the evidence submitted to this court is to the contrary." (at 1145)

"The problem for the physician, as in most serious cases, is to weigh the possible benefits of treatment against the possible risks." (at 1146)

"... [If] a new drug has been shipped in interstate commerce intended for its approved use, a physician is not required to file an application for a new drug plan if he prescribes the drug as part of the practice of medicine." (at 1148)

"... [The] physician must be free to use the drug for an indication not in the package insert when such usage is part of the practice of medicine and for the benefit of the patient." (at 1149)

"... [The] physician can ascertain from medical literature and from medical meetings new and interesting proposed uses for drugs marketed under package inserts not including the new proposed usages. ... New uses for drugs are often discovered, reported in medical journals and at medical meetings, and subsequently may be widely used by the medical profession." (at 1149)

"When physicians go beyond the directions given in the package insert it does not mean they are acting illegally or unethically and Congress did not interfere with medical practice by limiting the ability of physicians to prescribe according to their best judgment. See FDA Consumer, November 1975, page 7." (at 1150)

"The courts have rather uniformly recognized the patients' rights to receive medical care in accordance with their licensed physician's best judgment and the physician's rights to administer it as it may be derived therefrom. [cases cited]" (at 1150)

"[note the] Federal Register for August 15, 1972 (Vol. 37, No. 150, P. 16503). ... [Once] a drug is in a local pharmacy, after interstate shipment, a physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patients or may vary the dosage for his patients or may vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration. Congress did not intend the Food

and Drug Administration to interfere with medical practice as between the physician and the patient." (at 1149) [see also the case of F.T.C. v. Simeon Management Corporation, 9 Cir., 532 F.2d 708 (1976)]

"... [The] decision making power of a physician may involve a consideration of the possible curative value of not notifying a patient of all of the risks associated with the use of a drug or indicated on the package insert on the drug prescribed for that patient. In the opinion of this court, that decision must be a professional one made by the physician himself." (at 1144)

"The Court will keep in mind the well-known medical fact proved by several physicians in this proceeding that, of all patients treated by physicians, a large majority would recover no matter what treatment is provided therefor. However, this majority is obviously not applicable to those suffering from advanced arteriosclerosis wherein the patient may expect an early disabling resulting from stroke, hypertension, heart failure, or other related diseases or cardiovascular problems." (at 1144)

"This court is of the opinion that ... hair analysis, as well as urine and blood analysis, are tests which may be used to gain information as to the needed or harmful minerals in the body." (at 1145)

"One does not have true freedom until one is free to choose how he wishes to be treated medically." -- H. Ray Evers, M. D. (1913 -- 1990)

"If it is to be, it is up to me." -- plaque that used to sit on the desk of H. Ray Evers, M. D.

1979 -- EDTA

D. Stankovic and M. Keser-Stankovi reported on "Effects of EDTA on liver and kidneys and protective effects of EDTA on these organs in animals treated with lead," Folia Med 14:101-XXX, 1979.

L. A. Grumbles used radionuclides to show improvement of cerebral arterial blood flow after chelation therapy, presenting his findings to the American Academy of Medical Preventics (AAMP), 1979. "Radionuclide studies of cerebral and cardiac arteriography before and after chelation therapy," New Horizons in Holistic Health II (Symposium), Chicago, May 27, 1979.

F. M. Walker, C. W. Wilson III, and R. L. Kaman reported on "The effects of

EDTA chelation therapy on plaque calcium and plasma lipoproteins in atherosclerotic rabbits." Fed Proc 38(311) (No. 4335), 1979.

1979 -- CHEMISTRY/PHYSIOLOGY

Hollander et alia reported "In rabbits treated with EHDP [chelation therapy] ... the aorta had fewer gross lesions and contained significantly less cholesterol, collagen and elastin that did the aorta of the rabbits fed the [cholesterol limited] regression diet alone." Atherosclerosis, 1979.

1979 -- CHEMISTRY/PHYSIOLOGY and LEGAL

On September 11, 1979, H. Ray Evers, M. D., was granted United States Patent No. 4,167,562 for his novel "Method and Composition for Treating Arteriosclerosis." Having faced the FDA in a major confrontation over his use of EDTA, Dr. Evers sought and perfected an alternative approach to intravenous infusions and applied for his patent on August 28, 1978.

"ABSTRACT -- New compositions and their method of use for treating cardiovascular diseases primarily due to arteriosclerosis and atherosclerosis. These new compositions are prepared from a base Ringers injection to which is added a B-complex [methionine, cholinechloride, thiamine hydrochloride, niacinamide, riboflavin-5'-phosphate sodium, pyridoxine hydrocloride, d-pantothenyl alcohol], hydrochloric acid, sodium ascorbate, pyridoxine hydrochloride, magnesium sulfate, adrenal cortex, magnesium chloride, thiamine, heparin sodium, calcium gluconate and calcium d-saccharate. Additional embodiments of the solution composition are also disclosed containing niacin, vitamin B12, ether, algae and amino acids. The compositions are useful in removing plaques from the interior walls of the arteries and veins, thereby improving blood supply to body tissues."

"SUMMARY OF THE INVENTION -- ..... While the solution composition and method will be described in greater detail below, it should also be noted that the administration of adjunctive therapies has also been found to improve the patient's condition. These therapies consist of the administration of citric acid orally, as well as the administration of many natural minerals and vitamins to improve the general nutrition of the body in order to rebuild and bring the body chemistry into proper balance. As stated above, this invention actually removes the plaques and improves the blood supply to all the tissues and organs of the body. The beneficial results are attributed to the increased blood supply in combination with better nutrients in the blood stream and more oxygen being provided to the body's tissues."

1979 -- LEGAL/POLITICAL

AAMP physicians won a major victory over the California Medical Association in January. (Citation??)

1979 -- EDUCATIONAL

Chelation expert Bruce W. Halstead, M. D., published the first practical physician's treatise on EDTA chelation therapy: The Scientific Basis of EDTA Chelation Therapy (1979).

"Experimentation and usage of EDTA chelation therapy has resulted in the development of techniques for the successful treatment of the catastrophic effects of atherosclerosis involving coronary artery disease, stroke, senility, early gangrene, essential hypertension, peripheral vascular occlusive disease, osteoarthritis, and related disorders ..... Clinical studies ... have consistently shown a definite improvement in the circulation of the patient as evidenceD by improvement in skin color, improvement of arterial pulsation in the feet, return of normal temperature to the feet, regaining ability to walk long distances comfortably, elimination of anginal pain, improved brain function and improvement of muscle coordination. ... Chelation therapy generally results in a significant improvement in coronary circulation in most cases to the extent that the patient no longer requires the use of nitroglycerin or similar drugs. ... In a large number of cases chelation therapy has been found to improve kidney function, decrease the amount of insulin required by diabetics, and produce significant improvement in arthritis and some cases of Parkinson's disease." (page 14)

Chelation expert James J. Julian, M. D., published his first lay book on chelation therapy: Chelation Extends Life (1979).

1980 -- EDTA

Walter Blumer and T. Reich published findings from clinical study in Switzerland, showing a statistically significant 90% reduction in incidence of cancer in a group of 59 chelation patients studied over a 10-year follow-up, when compared to 231 control patients ("Leaded gasoline -- a cause of cancer," Environmental International 3:465-471, 1980).

Blumer and Cranton subsequently updated this report with an 18-year follow-up in 1989, showing that only 1 of 59 treated patients (1.7%) had died of cancer while 30 of 172 nontreated control subjects (17.6%) had died of cancer, reported in the Journal of Advancement in Medicine (2(1/2):183-8;Spring/Summer 1989).

1980 -- EDTA

In 1980, F. Walker published a Ph. D. thesis from the Texas State University entitled "The effects of EDTA chelation therapy on plaque, calcium, and mineral metabolism in arteriosclerotic rabbits" (University Microfilm International, Ann Arbor, Michigan 48016).

O. Brucknerova and V. Malinovska reported "The first clinical experience with combined chelation and glucagon in ischemic disease of the lower extremities" (Cas Lek Ces 119:814-815, 1980), suggesting a complementary effect with medications aimed at the calcification in the plaque and at the softer components as well.

1980 -- CHEMISTRY/PHYSIOLOGY

J. Bjorksten published two excellent papers in journal Rejuvenation: "The cross-linkage theory of aging as a predictive indicator" (8:59-66, 1980) and "Possibilities and limitations of chelation as a means for life extension" (8:67-72, 1980).

A. M. Fogelman, I. Shechter, J. Seager, M. Hokom, J. S. Child, and P. A. Edwards reported that "Malondialdehyde alteration of low density lipoproteins leads to cholesteryl ester accumulation in human monocyte-macrophages," Proc Nat Acad Sci 77(4):2214-2218, Apr 1980.

An editorial in Lancet reviewed "Atherosclerosis and auto-oxidation of cholesterol," ii:964-XXX, 1980.

1980 -- EDUCATIONAL

Medical writer Morton Walker, D. P. M., published the first popular lay book, Chelation Therapy: How to Prevent or Reverse Hardening Of The Arteries (1980).

1980 -- LEGAL/POLITICAL

Robert J. Rogers, M. D., pursued his case to the Florida Supreme Court, establishing his right to practice chelation therapy for cardiovascular disease.

In decision No. 56.096, rendered on September 4, 1980, in the matter of State Board of Medical Examiners of Florida, Appellant, vs. Robert J. Rogers, M. D., Appellee, the Supreme Court of Florida stated:

"...[We] affirm the result of the district court's decision because, under the particular facts of this case, it appears that the action of the Board of Medical Examiners restraining Dr. Rogers from further utilization of chelation treatment was an arbitrary and unreasonable exercise of the state's police power."

.....

"Although the state has the power to regulate the practice of medicine for the benefit of the public health and welfare, this power is not unrestricted. The regulations imposed must be reasonably related to the public health and welfare and must not amount to an arbitrary or unreasonable interference with the right to practice one's profession which is a valuable property right protected by the due process clause. Doe v. Bolton, 410 US 179 (1973); Dent v. West Virginia, 129 US 114 (1889). ..... The record before us fails to evidence harmfulness as a reasonable basis for the Board's action in restricting use of this treatment. ... Furthermore, the evidence demonstrates that no fraud or deception was exercised by Dr. Rogers upon his patients who were fully informed of the nature of the procedure and the possibility of no improvement. Sanctions were imposed against Dr. Rogers because he used a modality not accepted by the Board as having been proven effective, not because the Board found that the treatment was harmful or that Dr. Rogers had defrauded his patients into believing that chelation treatment was a cure for their conditions. The Board's findings do not support a conclusion of quackery ..."

1981 -- EDTA

In the early 1980s, H. Richard Casdorph published in the Journal of Holistic Medicine the first two in a series of three studies on chelation therapy efficacy in arteriosclerotic heart disease, in brain disorders, and (with C. H. Farr) in peripheral arterial occlusion (5(1):3-15, 1983). Both of the 1981 studies showed significant improvement in arterial flow. Patients with coronary artery stenosis experienced an improvement in ejection fraction.

"EDTA chelation therapy: efficacy in arteriosclerotic heart disease," J Holist Med 3(1):53-59, 1981.

"EDTA chelation therapy, II: efficacy in brain disorders," J Holist Med 3(2):101-117, 1981.

1981 – CHEMISTRY/PHYSIOLOGY

J. L. Sullivan wrote a provocative series suggesting that excessive iron in the body could contribute to increased free radical formation and an increase in atherosclerosis, possibly explaining the different incidence and mortality between premenopausal women and their male counterparts in the same age group.

"Iron and the sex difference in heart disease risk," Lancet 1:1293-1294, 1981;

"The sex differences in ischemic heart disease," Perspectives in Biolog Med 26:657-671, 1983;

"Sex, iron, and heart disease," Lancet 2:1162, 1986; and

"The iron paradigm of ischemic heart disease," Am Heart J 117:1177-1188, 1989.

A. Suvorov and R. A. Marksoyan described "The mechanisms of action of EDTA on reducing platelet aggregation," J Mol Cell Cardiol 9:897-908, 1981. They reported also "Some mechanisms of EDTA effect on platelet aggregation," Byull Eksp Biol Med (USSR) 91(5):587-590, 1991.

1981 -- DMSA

K. Lenz, K. Hruby, W. Druml and coworkers published "2,3-dimercaptosuccinic acid in human arsenic poisoning," Arch Toxicol 1981;47:241-3.

1981 -- CHEMISTRY/PHYSIOLOGY

Crapper-McLaughlin presented his findings on "Aluminum toxicity in senile

dementia -- implications for treatment" to the American Academy of Medical Preventics convention. He suggested that chelation with desferoxamine might be helpful in treating certain dementias. (See D. K. Crapper, S. S. Krishman, and A. J. Dalton, "Brain aluminum distribution in Alzheimer's disease and experimental neurofibrillary degeneration," Science 180:511-XXX, 1973 -- Crapper reported increased aluminum in the brains of four patients with senile dementia when compared with normal controls; attempts by others to reproduce these results have been met with limited success ..... see D. P. Perl, "Pathologic associations of aluminum in Alzheimer's disease," pages 116-121, in B. Reisberg (ed): Alzheimer's Disease, New York: Macmillan, 1983.)

Schenk et alia reported in Rejuvenation, March 1981: "EDTA and other chelating agents rapidly removed the aluminum [on surface linings of the aorta] ... at levels approximating those used in clinical practice. ..... Methods for removal of accumulating aluminum ions from body tissues, especially aorta and brain gray matter, should prove beneficial in retarding aluminum cross-linked induced aging, including the aluminum-induced deterioration of the brain." (CITATION NEEDED) XXXXX

1981 -- EDUCATIONAL

Research scientist Johan Bjorksten, Ph. D., published Longevity: A Quest (1981), containing over 700 references relating to gerontology and the chemical/biochemical correlates of biological aging.

1982 -- EDTA

During the early 1980s through mid-1990s, a long series of clinical studies using EDTA was published in several medical journals by Edward W. McDonagh, Charles J. Rudolph, and Emanuel Cheraskin including these:

"The homeostatic effect of EDTA with supportive multivitamin trace mineral supplementation upon high-density lipoproteins (HDL)," J Osteopath Phys Surg California 8:34-xx, 1982;

"The effect of intravenous disodium ethylene diamine tetraacetic acid (EDTA) upon blood cholesterol levels in a private practice environment," J Internat Acad Prev Med 7:5-12, 1982. "The evidence [in 142 patients] indicates that, in a matter of approximately two to four weeks it is readily possible to reduce

hypercholesterolemia on the average about 14 per cent."

"The influence of EDTA salts plus multivitamin mineral therapy upon total serum cholesterol/high density lipoprotein cholesterol," Med Hypoth 9:643-646, 1982;

"An oculocerebrovasculometric analysis of the improvement in arterial stenosis following EDTA chelation therapy," J Holist Med 4(1):21-23, 1982. They evaluated 57 patients objectively for cerebral vascular occlusion pre- and post-treatment, with an average of 28 intravenous EDTA infusions. Arterial occlusion, measured noninvasively by oculocerebrovasculometric means, decreased from a mean of 28 per cent to a mean of 10 per cent following therapy ($p < 0.001$). Eighty-eight per cent of patients showed objective improvement in cerebrovascular flow.

"The effect of EDTA salts plus supportive multivitamins-trace mineral supplementation upon renal function: a study of serum creatinine," J Holist Med 4:146-151, 1982;

"The effect of EDTA chelation therapy plus supportive multivitamin-trace mineral supplementation upon renal function: A study in blood urea nitrogen (BUN)" J Holist Med 5(2):871-879, 1983;

"The effect of intravenous disodium ethylene diamine tetraacetic acid (EDTA) plus supportive multivitamin mineral supplementation upon fasting serum calcium," Med Hypoth 11:431-458, 1983;

"The glycohemoglobin (HbA1c) distribution in EDTA-chelation-eligible patients," J Orthomol Psychiat 12:72-74, 1983;

"The effect of EDTA chelation therapy with multivitamin/trace mineral supplementation upon reports of fatigue," J Orthomol Psychiat 113:1-3, 1984;

(E. Cheraskin, D. G. Wussow, E. W. McDonagh, et alia) "Effect of EDTA chelation and supportive multivitamin/trace mineral supplementation with and without physical activity on the heart rate," J Internat Acad Prev Med 8:5-9, 1984;

(E. W. McDonagh, C. J. Rudolph, E. Cheraskin, et alia) "The effect of EDTA chelation and supportive multivitamin/trace mineral supplementation with and without physical activity upon systolic blood pressure," J Orthomol Psychiat 13:1-9, 1984;

"The 'clinical change' in patients treated with EDTA chelation plus

multivitamin/trace mineral supplementation," J Orthomol Psychiat 14:61-65, 1985;

"The effect of EDTA chelation therapy plus multivitamin/trace mineral supplementation upon vascular dynamics: ankle/brachial Doppler systolic blood pressure ratio," J Holist Med 7:16-22, 1985;

(C. J. Rudolph, E. W. McDonagh, and D. G. Wussow) "The effect of intravenous disodium ethylenediaminetetraacetic acid (EDTA) upon bone density levels," J Adv Med 1:79-85, 1988. They showed that EDTA did not adversely affect bone density levels and might even increase bone density in low density individuals.

(C. J. Rudolph, E. W. McDonagh, and R. K. Barber) "Effect of EDTA chelation and supportive multivitamin/trace mineral supplementation on chronic lung disorders: a study of FVC and FEV1," J Adv Med, 2:553-561, 1989.

"The psychotherapeutic potential of EDTA chelation," J Orthomol Psychiat 14:214-217, 1985.

Elmer M. Cranton published "Kidney effects of ethylene diamine tetraacetic acid (EDTA): a literature review" (J Holistic Med 4:152-157, 1982), documenting the safety of EDTA administration with a proper dose delivered over a sufficient time period.

Elmer M. Cranton and James P. Frackelton described "The current status of EDTA in the treatment of occlusive arterial disease" (J Holist Med 4:24-33, 1982), including a scathing critique of the 1963 Kitchell and Meltzer "reappraisal" article. In spite of the number of positive results papers that were largely ignored by organized medicine, editorials and opinion papers had been published warning of the lack of efficacy and the dangers of EDTA chelation treatment -- relying largely on the only published article (by Kitchell and Meltzer) that concluded this therapy was not useful for atherosclerosis.

For the critical opinion articles, see Craven and Soffer articles in 1975; see Stevenson and Scott in 1982, Soffer in 1966, and Monaco in 1993.

K. Soiti, S. Juhasz-Nagy, V. Kacskemati, B. Czako, V. Nemeth, and V. Kekesi reported on the "Effect of the Ca++ chelators EDTA and EGTA on sinoatrial-node activity and heart irritability," Acta Phys Acad Sci Hung 60(3):155-164, 1982.

ADVERSE

J. G. Stevenson and T. R. Covington (West Virginia Drug Information Center)

offered their critical opinions in "Chelation therapy in atherosclerosis," Ann Int Med 5:89-90, 1982. "We would like to alert physicians and other health professionals to the misleading claims made by [AAMP] and clarify the status of EDTA chelation therapy. ..... Because of the lack of objective evidence of efficacy and the potentially dangerous nature of the treatments, EDTA chelation therapy for atherosclerosis and related disorders must be considered investigational and not without risk."

T. J. Baily Gibson wrote a favorable "Letter to the editor -- Chelation therapy," N Z Med J 95:54-55, Jan 27 1982. "After all, what is an 'effective' treatment? Is it one which brings the patient back to perfect health, or one which corrects the current problem, or is it one which only relieves the patient of the symptoms of which he complains? Most of us in general practice are very happy to control the symptoms of our patients' chronic degenerative disease. We do not really expect a 'cure.' Thus, anything which controls symptoms could be said to be effective."

ADVERSE

P. J. Scott published a negative editorial "Chelation therapy for degenerative vascular disease" in N Z Med J 95:538-539, Aug 11 1982. " ... [There] has been a resurgence of increasingly sophisticated successors to the old enemies of medical science, namely superstition, magic and outright quackery. These developments reflect a perceived failure of the medical profession and of medical science to deliver unremitting, progressively more spectacular series of miracles. Non-orthodox medical practice always thrives in situations where our profession can be depicted as arrogant, and lacking in compassion. ..... Despite claims to the contrary, the chelation movement is not a martyr to the inquisitorial prejudice and arrogance of the orthodox profession."

In response, T. J. Baily Gibson sent a "Letter to the editor -- Chelation therapy," N Z Med J 95:673-674, Sep 22 1982. "However, in my experience, the patients referred for chelation are usually the failure from such a regimen [of encouragement and exercise], as indeed are those who request surgery."

Sir Dove-Myer Robinson wrote a "Letter to the editor -- Chelation therapy," N Z Med J 95:750, Oct 1982, noting that studies published from the Soviet bloc suggested excellent clinical benefits and that chelation treatment should be investigated by the New Zealand Medical Association and/or the Department of Health.

ADVERSE

David S. Cole provided his critical comments in a "Letter to the editor -- Chelation therapy," N Z Med J 95:896, Dec 22 1982. ""In my capacity as chairman of the

scientific committee of the National Heart Foundation [Auckland], I would like to add that in response to many requests from both lay people and cardiologists, we have made an extensive search of the literature and corresponded both with colleagues in the United Kingdom and with the American Heart Association. We can find no satisfactory report in a journal which is regarded as 'respectable' in the English speaking language, giving any indication of an adequate trial."

*ADVERSE*
A highly biased critical note was offered by R. Magee, "EDTA chelation for arteriosclerosis" in Med J Australia 142:514-515, 1982.

T. W. Gibson noted "The benefits of EDTA chelation therapy for arteriosclerosis" in Med J Australia, 143:127, 1983.

*ADVERSE*
D. I. Moel and K. Kumar reported on "Reversible nephrotoxic reactions to a combined 2,3-demercapto-1-propanol and calcium disodium ethylenediaminetetraacetic acid regimen in asymptomatic children with elevated blood lead levels," Pediatrics 70:259-262, 1982. Doubling of baseline serum creatinine documented transient nephropathy in 13 per cent and acute oliguric failure developed in another 3 per cent of 130 children in New York City with combined chelation therapy for asymptomatic lead poisoning.

1982 - CHEMISTRY/PHYSIOLOGY

L. R. Cantilena Jr., and C. D. Klassen published "The effect of chelating agents on the excretion of endogenous metals," Toxicol Appl Pharmacol 1982;63:344-50.

M. L. Hess et alia offered details on "The involvement of free radicals in the pathophysiology of ischemic heart disease," Canada J Physiol/Pharmacol 60:1382-1389, 1982.

1982 -- CHEMISTRY/PHYSIOLOGY

J. M. Porter, B. S. Cutler, et alia reported on "Pentoxifylline (Trental) efficacy in the treatment of intermittent claudication," Am Heart J 1:104, 1982. This was a multicenter controlled double-blind trial with objective assessment of chronic occlusive arterial disease, showing approximately a 24 per cent increase over baseline in claudicatory walking distance with appropriate dosing of Trental.

G. Alfthan, J. Pikkarainen, J. K. Huttunen, and P. Puska reported their findings of "Association between cardiovascular death and myocardial infarction and serum selenium in a matched-pair longitudinal study," Lancet 2(8291):175-XXX, 1982.

1982 -- EDUCATIONAL

Medical writer Morton Walker, D. P. M., published the second popular lay book, this one in consultation with Garry Gordon, M. D.: The Chelation Answer: How To Prevent Hardening Of The Arteries And Rejuvenate Your Cardiovascular System (1982).

Research physician Lester Morrison, M. D., D. Sc., Director of the Institute for Arteriosclerosis Research at Loma Linda University School of Medicine (California), published for the lay public an excellent primer, Dr. Morrison's Heart-Saver Program: A Natural, Scientifically Tested Plan for the Prevention of Arteriosclerosis, Heart Attack, and Stroke (1982). This book describes the importance of nutritional compounds and mucopolysaccharides in preventing and treating cardiovascular diseases, as demonstrated by extensive research at the Institute. A companion volume for professionals, XXXX (citation needed), details the research in technical terms.

1983 -- EDTA

H. Richard Casdorph and Charles H. Farr documented profound results with EDTA in peripheral arterial occlusion, detailing the saving of four lower limbs that had been advised for amputation. "Treatment of peripheral arterial occlusion, an alternative to amputation," J Holist Med 5(1):3-15, 1983.

ADVERSE

Gerald R. Peterson, M. D., presented his opinions on "Adverse effects of chelation therapy," in a letter to the editor, J Am Med Assoc 250(21):2926, Dec 2 1983: "Within the past several months, I have seen one patient who experienced a severe vasculitis after treatment with edetic acid. That resulted in near death to the patient and even the use of pericardiocentesis for pericardial tamponade. My associate has also seen another patient who experience what he believed was a hemolytic anemia while the patient was receiving edetic acid therapy and who subsequently suffered a myocardial infarction. I believe that there is a correlation between the use of edetic acid and these two autoimmune episodes. I suspect that the reason that more

adverse side effects have not been reported is not because of the lack of these but the lack of reporting."

1983 -- EDTA

*ADVERSE*
The American Medical Association offered this assessment ("Diagnostic and therapeutic technology assessment (DATTA): chelation therapy," J Am Med Assoc 250:652, 1983:

"The Department of Health and Human Services released a report entitled EDTA Chelation Therapy for Atherosclerosis in 1981 (HRST Assessment Report Series, Vol. 1, No. 18). It noted that chelation for this indication is controversial, that there is no accepted rationale for its effectiveness, and that its safety is questioned. The Medical Letter reviewed the experience over 20 years and concluded that there is no acceptable evidence that chelation therapy with EDTA is effective in the treatment of atherosclerosis and the adverse effects of the drug can be lethal. The American Heart Association has also reviewed the data and found no scientific evidence to support the claims of benefit in patients with atherosclerosis. This opinion is shared by the American College of Physicians, The American Academy of Family Physicians, The American Society for Clinical Pharmacology and Therapeutics, the American College of Cardiology, and the American Osteopathic Association. In summary, there is general agreement that chelation therapy has not been established as an acceptable treatment for coronary or other arterial atherosclerosis."

*ADVERSE*
David Shaw (Senior Medical Student, National Heart Foundation Summer Studentship, Christchurch) offered a critical "Letter to the editor on the benefits of EDTA chelation therapy," N Z Med J 96:144-145, 1983. He referred to Sir Dove-Myer Robinson's letter (N Z Med J 95:750, 1982, noted above) in faulting the performance and conclusions of the studies presented from the Soviet bloc.

1983 -- BAL

T. D. Hoover and H. Vasken Aposhian noted that "BAL increases the arsenic-74 content of rabbit brain," Toxicol & Appl Pharmacol 70(1):160-162, Aug 1983. "The use of BAL as the drug of choice for treatment of arsenic intoxication should be viewed with caution and reexamined."

1983 -- DMPS/DMSA

H. Vasken Aposhian published extensively on "DMSA and DMPS -- Water soluble antidotes for heavy metal poisoning," Ann Rev Pharmacol Toxicol 23:193-215, 1983. "DMSA and DMPS are water soluble analogs of British Anti-Lewisite. They are effective when given by mouth, sc, im, and ip as antidotes for intoxication by heavy metals. DMPS has been studies extensively in the Soviet Union since 1954, where it is an official drug called Unithiol. Since 1956 in the People's Republic of China and the Soviet Union, DMSA has been investigated. ... These two dimercapto compounds are effective in treating poisoning by compounds of arsenic, lead, organic and inorganic mercury, and other heavy metals. ..... When used in therapeutic ... doses, neither DMSA or DMPS appears to have any marked effect on the trace metals in the body except that urinary excretion of Cu and Zn increase."

H. Vasken Aposhian reviewed "DMSA and DMPS -- water soluble antidotes for heavy metal intoxication," Annual Rev Pharmacol Toxicol 23:193-215, 1983.

1983 -- CHEMISTRY/PHYSIOLOGY

A series of papers were published acknowledging the growing awareness of physiologic and toxicologic metal activities in human health and illness: Biological Aspects of Metals and Metal-Related Diseases, edited by Bibudhendra Sarkar, published by Raven Press, New York, New York.

S. A. Levine and J. H. Reinhardt presented data on "Biochemical pathology initiated by free radicals, oxidant chemicals, and therapeutic drugs in the etiology of chemical hypersensitivity diseases," J Orthomol Psychiatr 12:166-183, 1983.

Alan R. Gaby, M. D., reviewed the role of nutritional factors in the pathophysiology of cardiovascular disease. J Holist Med 5:20-XXX, 1983.

G. M. Vincent, et alia described the role of coronary artery spasm as a primary etiology of coronary thromboses and acute myocardial infarction. N Eng J Med 309:220-239, 1983.

Results of one of the most extensive reviews of bypass surgery were published by CASS Principal Investigators and the Associates: "Coronary artery surgery study (CASS): a randomized trial of coronary artery bypass surgery: Survival data,"

Circulation 68:989-950, 1983. This comprehensive review showed that coronary artery bypass surgery has an average mortality of 4 to 10 per cent.

A. P. Freeman, R. W. Giles, V. A. Berdoukas, W. R. Walsh, D. Choy, and P. C. Murray published observations on "Early left ventricular dysfunction and chelation therapy in thalassemia major," Ann Intern Med 99(4):450-454, Oct 1983.

Albrecht Fleckenstein, M. D., professor of physiology and the University of Freiburg, Federal Republic of Germany, published Calcium Antagonism in Heart and Smooth Muscle: Experimental Facts and Therapeutic Prospects, New York: John Wiley & Sons, 1983.

V. Batuman, E. Landy, J. K. Maesaka, and R. P. Wedeen described the "Contribution of lead to hypertension with renal impairment," N Engl J Med 309(1):17-XX, 1983.

1983 -- ORGANIZATION

The American Board of Chelation Therapy (ABCT) was founded in May 1983 to provide, develop, and promulgate standards for training and clinical practice; Charles H. Farr, M. D., Ph. D., was selected as first chairman.

1983 -- ORGANIZATION

The Great Lakes Association of Clinical Medicine (GLACM) was founded by a number of physicians interested in having a mutually supportive "study group" close enough for frequent meetings. Co-founders included Josephine Arenica, M. D., John Baron, D. O., Adam Frens, D. O., D. B. Hill, D. O., Philip J. Hoekstra, Jr., Ph. D., Sheldon Katanics, D. O., Howard T. Lewis, M. D., Derrick Lonsdale, M. D., Leo Modzinski, D. O., James M. Nutt, D. O., Paul A. Parente, D. O., E. Duane Powers, D. O., Al J. Scarchilli, D. O., William C. Schmeltzer, M. D., Jack Slingluff, D. O., Richard E. Tapert, D. O., Harold J. Wilson, M. D., with the assistance of Warren DeLano and Gregory D. Seeley, Esq. Jack Slingluff, D. O., was chosen as first president.

1983 -- ORGANIZATION

The International Society of Chelation Technicians (ISCT) was founded to provide

standards for training, testing, and certifying para-professional medical personnel in the administration of EDTA chelation therapy. Robert L. White, P. A.-C., Ph. D., was selected as first executive director.

1983 -- EDUCATIONAL

Jonathan Collin, M. D., began to publish the Townsend Newsletter, an informal newsletter for Doctors Communicating to Doctors. This offered a forum for discussing EDTA chelation therapy for cardiovascular disease, nutritional medicine approaches, and other controversial issues relating to health care. This is now titled the Townsend Letter for Doctors & Patients, and presents 100+ pages each month on a variety of "medical alternatives" topics. To subscribe, call AC 360/385-6021, fax 360-385-0699, or write 911 Tyler Street, Port Townsend, Washington 98368 USA.

Chelation expert Edward W. McDonagh, D. O., published the first edition of his lay book, Chelation Can Cure (1983).

Richard A. Passwater, Ph. D., and Elmer M. Cranton, M. D., published a comprehensive review, Trace Elements, Hair Analysis and Nutrition, New Canaan, Connecticut: Keats Publishing, Inc., 1983.

Durk Pearson and Sandy Shaw popularized the concepts of nutrition in their very popular lay book, Life Extension: A Practical Scientific Approach (1983). They further educated the public (and some physicians) in their later volume, Life Extension Companion (1985).

1984 -- EDTA

Elmer M. Cranton and James P. Frackelton published in the Journal of Holistic Medicine (6(1):6-37, 1984) a definitive review of "Free radical pathology in age-associated diseases: treatment with EDTA chelation, nutrition, and antioxidants," drawing heavily as a foundation on the proposal in 1955 by Denham Harman, M. D. that free-radical chemistry could explain aging and disease.

"Recent discoveries in the field of free radical pathology provide a coherent, unifying scientific basis to explain many of the diverse benefits reported with EDTA chelation therapy. The free radical concept provides a scientific basis for the treatment and prevention of the major causes of disability and death; including

atherosclerosis, dementia, cancer, arthritis and numerous other diseases."

Keith W. Sehnert, A. F. Clague, and E. Cheraskin documented "The improvement in renal function following EDTA chelation and multivitamin-trace mineral therapy: a study in creatinine clearance," Medical Hypothesis 15:301-304, 1984.

Noting that one of the most commonly alleged contraindications to the use of EDTA is possible renal damage, the authors study 13 patients with chronic degenerative disorders and with renal damage. After 20 infusions, creatinine clearance significantly improved. "Within the limits of this study, creatinine clearance approaches the optimal (100 ml/min/1.74 cm2) following chelation therapy under the conditions outlined in this report."

ADVERSE

Kaye l. Rathmann, B. S. Pharm., and Larry K. Golightly, Pharm. D., (Rocky Mountain Drug Consultation Center, Denver General Hospital, Denver, Colorado) offered "An Opinion: Chelation therapy of atherosclerosis," Drug Intell Clin Pharm 18:1000-1003, Dec 1984. In what takes on the appearance of a scholarly review of literature critical of chelation, the authors conclude that "One common reference (AMA Drug Evaluations) suggests that the nephrotoxic potential of this agent limits its usefulness to dire emergencies when death from hypercalcemic crisis is judged to be imminent. ..... There is consensus that chelation therapy has not been established as an acceptable therapy for coronary or other arterial atherosclerosis and has serious toxicities." How pleasantly surprising that the opponents of chelation therapy are so assured that their assessment represents a consensus that actually ..... matters.

ADVERSE

Larry D. Oliver, M. D., Rai Mehta, M. B., and Harry E. Sarles, M. D., reported "Acute renal failure following the administration of ethylenediamine-tetraacetic acid (EDTA)," Texas Med 80:40-XX, 1984. "... [A] 73-year-old man with a 12-year history of hypertension, a one-year history of mild renal insufficiency, and a serum creatinine level of 2.1 mg/dL began EDTA chelation therapy for treatment of atherosclerosis and hypertension. During the next four weeks, the patient received one treatment with EDTA per day (except weekends) for a total of 19 treatments. ... We assume that he received 50 mg/kg/day of EDTA (not exceeding 3 gm) ... The need to hospitalize the patient became apparent near the end of the treatment period, when he reported malaise, anorexia, nausea, vomiting, and oliguria. ..... Laboratory evaluation showed ... blood urea nitrogen, 106 mg/dL; creatinine 13.8 mg/dL ... A 24 hour urine collection showed creatinine clearance of 3 mL/min and protein excretion of 1.04 gm. ..... [After hospital dialysis and renal biopsy] the

patient was discharged to a local maintenance dialysis facility ... By [one month later], the patient's serum creatinine level had fallen to 4.3 mg/dL with a creatinine clearance of 17 mL/min. Hemodialysis was therefore discontinued. Two months [later], the patient had a creatinine clearance of 35 mL/min and a serum creatinine level of 2.4 mg/dL."

*ADVERSE*
Paul Pentel, M. D., Charles Jorgensen, M. D., and James Somerville, M. D., authored a scholarly-appearing but opinionated review of selected issues, "Chelation therapy for the treatment of atherosclerosis," Minn Med 67:101-103, Feb 1984. They concluded: "The use of Na2EDTA to treat atherosclerosis is not supported by the available data. All studies claiming therapeutic benefit are flawed in one or more aspects of experimental design, the most important of which is the lack of suitable control groups. The clinical use of Na2EDTA to treat any form of atherosclerosis has no scientific basis and is not an acceptable therapy for this disease. ..... EDTA chelation therapy should be regarded as investigational because of a lack of objective evidence of its efficacy and questions regarding its safety. ... It is inappropriate and misleading for medical practitioners to offer chelation to patients as 'experimental' therapy if the drug is being administered as a routine clinical treatment rather than as part of [a rigorously designed] study."

*ADVERSE*
A. Soffer repeated his criticisms in an editorial, "Chelation clinics -- an abuse of the physician's freedom of choice," Chest 2:157-158, Aug 1984, and Arch Int Med 144(9):1741-1742, Sep 1984.

1984 -- DMSA/DMPS

H. Vasken Aposhian, D. E. Carter, T. D. Hoover, C. A. Hsu, R. M. Maiorino, and E. Stine described "DMSA, DMPS, and DMPA -- as arsenic antidotes," Fund & Appl Toxicol 4(2 Pt 2):S58-70, Apr 1984. "... DMSA, ... DMPS, ... and N-(2,3-dimercaptopropyl)-phthalamidic acid (DMPA) are water soluble analogs of 2,3-dimercapto-1-propanol (BAL). The relative effectiveness or therapeutic index of these dimercapto compounds in protecting mice from the lethal effects of an LD99 of sodium arsenite is DMSA is greater than DMPS greater than DMPA greater than BAL in the magnitude of 42:14:4:1, respectively. DMPS, DMPA, or DMSA will mobilize tissue arsenic. BAL, however, increases the arsenic content of the brain of rabbits injected with sodium arsenite. ..... These dimercapto compounds are in a great many respects orphan drugs. At this stage of their development, it is very difficult for the clinician to obtain funds to study them clinically even though they appear to be useful for treatment of poisoning by any one of the heavy metals."

1984 -- CHEMISTRY/PHYSIOLOGY

W. L. Cashin, M. E. Sanmarco, S. A. Nessim, and D. H. Blankenhorn reported on "Accelerated progression of atherosclerosis in coronary vessels with minimal lesions that are bypassed," N Engl J Med 311:824-828, 1984. Coronary bypasses commonly re-stenose within 7 years.

U. Leuschner, H. Baumgartel, R. David, C. M. Kirchmaier, F. Hagenmuller, J. Sieratzki, and K. Hubner (Wolfgang Goethe University, Frankfurt/Main, West Germany) reported on attempts to use EDTA-bile salt complexes as irrigation solutions through a sterile indwelling nasobiliary tube endoscopically introduced in an attempt to dissolve bile duct calculi. A variety of minimal side effects were encountered. "We recommend that [irrigation therapy] be used only when endoscopic papillotomy and attempted extraction have not succeeded." "Biochemical and morphological investigations of the toxicity of a Capmul preparation and a bile salt-EDTA solution in patients with bile duct stones," Am J Gastroenterol 79(4):291-298, Apr 1984.

P. A. Edwards, S. F. Lan, and A. M. Fogelman noted that "High density lipoproteins and lecithin dispersions increase the activity of 3-hydroxy-3-methylglutaryl [HMG] coenzyme A reductase by increasing the rate of synthesis and decreasing the rate of degradation of the enzyme," J Biol Chem 259(13):8190-8194, Jul 10 1984.

1984 -- EDUCATIONAL

Chelation expert Elmer M. Cranton, M. D., and medical writer Arline Brecher published the first edition of their very popular lay book, Bypassing Bypass: The New Technique of Chelation Therapy, New York: Stein and Day, 1984.

Medical writer Morton Walker, D. P. M., published the third popular lay book, The Miracle Healing Power of Chelation Therapy: The Intravenous and Oral Treatment For Reversal and Prevention of Hardening Of the Arteries and Other Common Degenerative Diseases (1984).

Chelation expert James J. Julian, M. D., published his second lay book on chelation therapy: Chelation Companion (1984).

1984 -- POLITICAL/LEGAL

*ADVERSE*
Antonio Gotto, M. D., a professor of medicine at Baylor University and then-president of the American Heart Association, issued a negative report, "The status of EDTA chelation therapy in Texas," Texas Med 84:36-37, 1984.

1985 -- EDTA

A. Zechmeister (Czechoslovakia) presented data to the AAMP spring conference detailing his studies in minipigs. He demonstrated "microcalcification" patterns in peripheral arteries, "macrocalcification" patterns in cerebral arteries, and a mixture of the two patterns in coronary arteries. These data conform to and help explain observations that peripheral arterial occlusive disease responds more rapidly and to a greater extent than do coronary occlusive changes, while cerebral occlusive changes respond most slowly and least well.

Refer to his published works:

"Mineralization of elastic and muscular types of arteries" (Czech. text), dissertation, J. E. Purkyne University, Brno, 1977.

"A new selective ultrahistochemical method for the demonstration on calcium using N,N-Naphthaloylhydroxyl amine," Histochem 61:223-232, 1979.

"Effect of glucagon on lipid and calcium deposition in arterial wall," Folia morphol (Prague) 27:23-25, 1979.

"Subcellular metabolism of Ca2+ in smooth muscle and myocardium (an ultrahistochemical study)," Folia morphol (Prague) 29(4):333-335, 1981.

"The therapeutic effect of glucagon and Chelaton III on the arterial wall after experimental lipidosis and calcification," V. Malinovska, A. Zechmeister, L. Malinovsky, O. Brucknerova, E. Hadasova, and P. Matonoha, Scripta medica (Brno) 56(7):391-400, 1983. "Glucagon alone removed the lipid inclusions from the wall of the aorta, but did not significantly affect the calcium deposits in the subintimal layers of the media. The combined administration of glucagon and Chelaton III removed most of the calcium and the lipids, however, so that only negligible residues of these substances were found in the aortal wall in the electron

microscope [under experimental conditions in 11 rabbits with induced experimental calcification of the aorta]."

"The effect of glucagon on lipid and calcium deposition in the aortic wall," A. Zechmeister, V. Malinovska, L. Malinovsky, E. Hadasova, and K. Rysanek, Scripta medica (Brno) 58(6):345-352, 1985. "The administration of glucagon seems to be a highly effective was of prevention of lipid accumulation and to a lesser degree of calcium deposition in the arterial wall under experimental conditions." "Glucagon application increases the metabolic activity of cell organelles, above all mitochondria."

"The effect of clofibrate and Normalip on lipid deposition and lipid deposits in the aortic wall in two experimental models," V. Malinovska, A. Zechmeister, L. Malinovsky, and E. Hadasova, Scripta medica (Brno) 58(2):67-80, 1985. "The authors ... conclude that clofibrate use is indicated rather in cases where the vessel wall is not yet flooded with lipids, i. e. in the early stage of the disease ... [and] that the combination of nicotinic acid ester with clofibrate in Normalip can produce unfavourable mutual interaction [in rats and rabbits with experimentally induced atherosclerosis]."

"The role of calcium in the effect of stress hormones," (Czech.) Cas Lek Cesk 130(22-23):631-634, Nov 29 1991.

"Free oxygen radicals in patients with hypertension," (Czech.) Cas Lek Cesk 130(22-23):645-647, Nov 29 1991.

ADVERSE

Alex Silverglade, M. D., retired medical director of 3M/Riker Laboratories, Inc., offered his negative opinions in a letter to the editor, "Chelation Clinics," Chest 87(2):274-275, Feb 1985. "Not only is efficacy unproven, but there is a report of a study done more than 20 years ago indicating that this form of treatment does not work. [citing Kitchell's reappraisal article, 1963] This is the best evidence to date that chelation therapy with the disodium salt of EDTA is not a useful method of treatment of coronary heart disease."

ADVERSE

Schettler, et alia, performed the first double-blind placebo controlled study on the administration of EDTA, funded by Tiemann Pharmaceuticals, the manufacturer of FLUDILAT, a platelet inhibitor. Performed at the University of Heidelberg, West Germany, this study showed a 250 per cent increase in average walking distance for patients treated with EDTA, contrasting to a 64 per cent increase in patients receiving Fludilat. Of interest, four patients treated with EDTA were dropped from

the study -- they had walked 1000 meters more than on their pre-treatment exercise testing. As a result of this unusual manipulation of the data, they concluded that EDTA was no better than placebo -- which, in this case, was their (poorly) active drug, Fludilat. Another factor not reported was that EDTA treated patients continued to improve after 30 days of concluding treatment, while the Fludilat group gradually reverted to their pre-treatment status on cessation of treatment. Information presented here was obtained from material presented by Charles Farr, M. D., Ph. D., who reportedly obtained raw data of the study from an employee of the performing company -- since the study was never published. (See also the detailed account on pages 89-91 in Racketeering in Medicine: The Suppression of Alternatives, by James P. Carter, M. D. Dr. P. H., Norfolk, Virginia: Hampton Roads, 1992)

K. E. Perizzolo, S. Sullivan, and D. F. Waugh presented their data on "Effects of calcium binding and of EDTA and CaEDTA on the clotting of bovine fibrinogen by thrombin," Arch Biochem Biophys 237(2):520-534, 1985.

*ADVERSE*

Marcia B. Cardelli, M. D., Mary Russell,, R. N. Curtis A. Bagne, Ph. D., and Nunzio Pomara, M. D., published their concerns about "Chelation therapy: unproved modality in the treatment of Alzheimer-type dementia," J Am Geriat Soc 33(8):548-551, August 1985. They reported on two cases, females who had a four- and an eight-year history of intellectual deterioration, who had no documented history of hypertension, diabetes, stroke, heart disease, or cancer (the longer-ill patient had a history of "blackouts,' a questionable stroke, and a heart murmur). Twenty-seven and eighty-two EDTA chelation infusions were provided, respectively, with "no beneficial effects" noted by family members. The authors concluded that resorting to chelation "may reflect a genuine but desperate need on the part of families to try to do something in the way of treatment for these patients" where "evaluations had failed to turn up any treatable condition."

The authors criticized "the failure of the chelation clinics to do a proper dementia workup before initiation of chelation treatments"; asserted that "the chelation clinics exhibited a tendency to overdiagnose a vascular dementia as opposed to an Alzheimer-type dementia even thought the individuals did not meet current accepted criteria for vascular dementia"; and claimed that "there are no well-controlled studies to substantiate the claim that EDTA removes calcium in atherosclerotic plaques" and that "even if EDTA did remove some calcium from plaques, other constituents such as smooth muscle cells, fibrin, and cholesterol are still present to impeded flow."

Further, they noted that "the role of aluminum in AD [Alzheimer-type dementia] is

still a much disputed issue," and "only further research and carefully controlled studies will show if chelation removes aluminum from inside neurons, and whether or not such treatment results in significant improvement for AD patients." Finally, they assert "the fact that EDTA is not without side effects," reciting a litany of potential problems reported from past literature.

In summary, they stated: "Therefore, until the safety and efficacy of chelating agents are demonstrated by [rigorous double-blind clinical] studies, there is no scientific rationale for the use of chelating agents in the treatment of Alzheimer-type dementia."

T. J. Baily Gibson again wrote a "Letter to the editor -- Chelation therapy," N Z Med J, 98:653-654, Aug 14 1985, this time criticizing the Report No. 44 in the Technical Report Series of the National Heart Foundation entitled, Chelation for Degenerative Arterial Disease, written by Dr. David S. Cole. "The introduction is basically a political comment. ..... Dr. Cole [in his report] seems to suggest that the proposed mechanisms of action of EDTA are speculative. He sets up the paper tiger of plaque dissolution so that he can dismiss it. Few doctors using chelation would claim that this occurs in patients after as little as 10 -- 20 chelations, so it can hardly be the reason that the patients' symptoms improve. The point is, though, that improve they do."

1985 -- CHEMISTRY/PHYSIOLOGY

G. Link, A. Pinson, and C. Hershko published on "Heart cells in culture: a model of iron overload and chelation," J Lab Clin Med 106(2):147-153, Aug 1985.

1985 -- EDUCATIONAL

Stephen A. Levine, Ph. D., and Parris M. Kidd, Ph. D., published Antioxidant Adaptation: Its Role in Free Radical Pathology (1985). This monograph clearly summarizes the chemical, physiological, and pathological bases upon which are founded many of the clinical improvements seen in administering nutritional treatment programs and chelation therapy.

Robert W. Bradford, Henry W. Allen, and Michael L. Culbert published Oxidology: The Study of Reactive Oxygen Toxic Species (ROTS) and Their Metabolism in Health and Disease (1985). This monograph is an excellent supplement to Antioxidant Adaptation, noted above.

Chelation expert John Parks Trowbridge M. D. and medical writer Morton Walker, D. P. M., published The Healing Powers of Chelation Therapy (1985), a short and easily understandable explanation of the many benefits that patients can derive from having EDTA chelation treatments.

1986 -- EDTA

The American Institute of Medical Preventics (AIMP) and the International Chelation Research Foundation (ICRF) were granted IND [Investigational New Drug] #128.847 by the U. S. Food and Drug Adminstration, to study the use of "Disodium EDTA with Magnesium" in the treatment of claudicatory peripheral vascular disease. The studies were to be performed at Letterman Army Medical Center Hospital in San Francisco and at Walter Reed Army Medical Center Hospital in Bethesda, Maryland. FDA approval was obtained largely as a result of persistent efforts of Ross Gordon, M. D., leading a group of ACAM physicians who compiled the study protocol.

In approving the IND application for EDTA, the FDA did not require any further safety studies.

R. J. Levy, S. L. Howard, and L. J. Oshry published their results on "Carboxyglutamic acid (Gla) containing proteins of human calcified atherosclerotic plaque solubilized by EDTA ..." Atherosclerosis 59(2):155-160, Feb 1986. "Proteins containing the calcium binding amino acid, gamma-carboxyglutamic acid (Gla) are abundant in calcified human atherosclerotic plaque, but are detectable only at trace levels in the normal arterial wall and non-mineralized atherosclerotic lesions. These proteins have been incompletely characterized and their role in the pathophysiology of atherosclerosis is not known."

1986 -- DFO

P. S. Rahko, R. Salerni, and B. F. Uretsky described "Successful reversal by chelation therapy of congestive cardiomyopathy due to iron overload," J Amer Coll Cardiol 8:436-440, 1986. "Deferroxamine mesylate, a chelating agent, was administered daily for more than 2 years and produced significant improvement in ventricular function which was associated with a biopsy-proven decrease in myocardial iron stores. This is the first reported case in which a severe

cardiomyopathy due to iron overload was reversed by chelation therapy alone."

1986 -- DMSA

J. H. Graziano published "Role of 2,3-dimercaptosuccinic acid in the treatment of heavy metal poisoning," Med Toxicol 1986;1:155-62.

1986 -- CHEMISTRY/PHYSIOLOGY

J. Valles, V. Matinez-Sales, J. Aznar, and M. T. Santos reported "The effect of EDTA on the production of prostacyclin by rat aorta," Thromb Res 43(4):479-483, 1986.

1986 -- ORGANIZATION

The members of the American Academy of Medical Preventics (AAMP), recognizing that their training, experience, and clinical practice would form the basis for emergence of new medical paradigm, changed the name of their organization to the American College for Advancement in Medicine (ACAM).

1987 -- EDTA

D. A. Cory-Slechta, B. Weiss, and C. Cox published "Mobilization and redistribution of lead over the course of calcium disodium ethylenediamine tetraacetate therapy," J Pharmacol Exp Ther, 1987;243:804-13.

J. M. C. Gutteridge described "Ferrous-salt-promoted damage to deoxyribose and benzonate, the increased effectiveness of hydroxyl-radical scavengers in the presence of EDTA," Biochem J 243:709-714, 1987. "Hydroxyl radicals (OH:) in free solution react with scavengers at rates predictable from their known second-order rate constants. However, when OH: radicals are produced in biological systems by metal-ion-dependent Fenton-type reactions scavengers do not always appear to conform to these established rate constants. ... In the presence of EDTA the rate constant for the reaction of scavengers with OH: was generally higher than in the absence of EDTA. This radiomimetic effect of EDTA can be explained by the removal of iron from the detector molecule [deoxyribose and benzoate], where it

brings about a site-specific reaction, by EDTA, allowing more OH: radicals to escape into free solution to react with added scavengers."

1987 -- DMSA

Y. Bentur, J. G. Brook, R. Behar and coworkers published "Meso-2,3-dimercaptosuccininc acid (DMSA) in the diagnosis and treatment of lead poisoning," Clin Toxicol 1987;25:39-51.

1987 -- CHEMISTRY/PHYSIOLOGY

T. B. Graboys, B. Biegelson, S. Lampert, C. M. Blatt, and B. Lown published their "Results of a second-opinion program for coronary artery bypass grafting surgery." They noted the costs for coronary bypass surgery commonly amount to $30,000 to $50,000. J Am Med Assoc 258:611-614, 1987.

Margaret E. Haberland, Ph. D., and Alan M. Fogelman, M. D., reviewed "The role of altered lipoproteins in the pathogenesis of atherosclerosis," Am Heart J 113(2 Pt 2):573-577, Feb 1987. "These in vitro studies have implicated altered lipoproteins in a number of important events associated with the initiation or propagation of the atherosclerotic reaction. Macrophages, identified as progenitors of many of the lipid-laden foam cells of the early lesions of atherosclerosis, internalize altered cholesterol-rich lipoproteins by receptor mechanisms, which could account for the massive deposition of cholesteryl ester droplets in macrophage-derived foam cells. Altered lipoproteins may trigger other cellular responses contributing to the pathogenesis of atherosclerosis, including monocyte chemotaxis, macrophage secretory events, regulation of metabolic functions in endothelial cells and differentiating monocytes, and cytotoxicity. The potential role of altered lipoproteins in the pathogenesis of atherosclerosis awaits identification of in vivo physiologically altered LDL or those processes demonstrated to operate in vivo that produce physiologically altered LDL."

1987 -- EDUCATIONAL

Medical professor Melvyn R. Werbach, M. D., at the UCLA School of Medicine, published Nutritional Influences on Illness: A Sourcebook of Clinical Research (1987). This text serves as an excellent compendium of peer-reviewed medical literature relating nutritional deficiencies to the onset and/or progression of disease.

1987 -- ORGANIZATION

The International Bio-Oxidation Medicine Foundation (IBOM) was founded on June 10, 1987, to encourage development and dissemination of the technologies of oxidation therapies (such as hydrogen peroxide). Charles H. Farr, M. D., Ph. D., was chosen as first chair.

1987 -- LEGAL/POLITICAL

*ADVERSE*
The Council of the College of Physicians and Surgeons of Ontario, Canada, passed regulations prohibiting the administration of EDTA chelation therapy for the treatment of atherosclerotic disease or any other disease or condition other than poisoning by heavy metals (June 10, 1987). In response, members of the public formed The EDTA Chelation Lobby of B. C. to overcome the governmental suppression of this therapy. Headed by the late Ted Dixon, the lobby did an excellent job of education layment and politicians in Canada.

1988 -- EDTA

Efrain Olszewer and James P. Carter published results of a 28-month retrospective analysis of 2,870 patients with documented atherosclerosis and other degenerative, age-associated diseases treated with intravenous disodium magnesium EDTA, showing marked improvement in 76.9% and good improvement in 17% of treated patients with ischemic coronary artery disease; marked improvement in 91% and good improvement in 8% of treated patients with peripheral vascular disease and intermittent claudication; and marked improvement in 24% and good improvement in 30% of treated patients with cerebrovascular and other degenerative cerebral diseases. Overall, almost 90% of the patients showed good to excellent improvement as measured by walking distance, ECG, and Doppler changes. ("EDTA chelation therapy: a retrospective study of 2,870 patients," Medical Hypoth 27:41-49, 1988)

1988 -- EDTA

D. P. Deucher published his observations on "EDTA chelation therapy; an antioxidant strategy," J Adv Med 1(4):182-190, 1988. "A new understanding of

many degenerative disease of aging is proposed, based on recent findings in the areas of molecular biology and oxygen free radical reactions. EDTA chelation therapy causes an increased excretion of polyvalent metals from the body, both toxic heavy metals and transition metals which catalyze free radical pathology. Antioxidant effects are proposed as a cause of the observed clinical benefits following intravenous EDTA chelation therapy. ..... Patients with free radical-related diseases other than atherosclerosis were also treated, with good to excellent results in 91 per cent of patients."

ADVERSE

Mark J. McGillem, B. S., and G. B. John Mancini, M. D., offered their opinion regarding "Inefficacy of EDTA chelation therapy for coronary atherosclerosis," N Eng J Med 318(24):1618-1619, Jun 16 1988. "Unfortunately, chelation therapy remains attractive to patients seeking an alternative to surgical intervention for occlusive vascular disorders, and it continues to receive support in the popular press and certain segments of the medical community. ..... A 55-year-old man was referred to the cardiac-catheterization laboratory for evaluation of chest pain. Severe multivessel coronary disease was documented, including disease of the left main coronary artery. The patient refused surgery ... and [later] informed us that he had taken a 30-week course of chelation therapy that cost $4,000 and consisted of one or two infusions of EDTA per week. The usual dose for such therapy is approximately 3 g per infusion, but the patient said that because of renal failure, he had received half the usual dose. ..... Shortly after completing the chelation treatments, the patient had a myocardial infarction and ... again underwent ... catheterization. ..... [Cross-sectional area of occlusion had worsened, diameter of stenosis had worsened, lesion length had increased, and minimum diameter had decreased.] ..... This report offers quantitative in vivo support of other work describing the ineffectiveness of EDTA chelation therapy for decalcification and regression of atherosclerosis. We believe that this costly and potentially dangerous treatment is unacceptable for coronary disease." The "other work" they cite is the 1963 Kitchell et alia study, already reviewed here, and the 1984 Rathmann and Golightly "opinion" article, also reviewed, which introduced no new data.

ADVERSE

D. R. Hay of the National Heart Foundation of New Zealand presented his criticism in a "Letter to the editor -- chelation therapy," N Z Med J 101:21, 1988, noting that a province in Canada had recently enacted regulations that banned the use of chelation therapy in the treatment of atherosclerosis, except where advisable in the public interest for competent investigators to conduct properly controlled trials of the therapy.

M. E. Godfrey, R. Agnihotri, and A. Strauss offered their positive comments in a

"Letter to the editor -- Chelation and arteriosclerosis," N Z Med J 101:122, Mar 9 1988. "Sir, -- 'The Physician has but a single task: to cure; and if he succeeds, it matters not a whit by what means he has succeeded.' Hippocrates 400 BC. ..... Diabetics are justifiably angry when they realise that they may not have had to lose a foot or leg after chelation has reversed the ischaemic changes in the remaining limb. Clinical observation has always preceded published scientific proof and medicine is still hopefully an art rather than being part of a protectionist industry. ..... In this respect a quote from Benjamin Rush MD, a cosignatory of the Declaration of Independence, may still be appropriate. 'The Constitution of this Republic should make special provisions for medical freedom as well as religious freedom. To restrict the art of healing to one class of men and deny equal privileges to others will constitute the Bastille of medical science. All such laws are un-American and despotic.'"

T. J. Baily Gibson offered an interesting counter to the earlier letter by Dr. Hay (N Z Med J 110:21, 1988) in his "Letter to the editor -- Chelation therapy," N Z Med J 101:149-150, Mar 23 1988. "I am suspicious of motive when a treatment is singled out [making EDTA chelation unacceptable apart from in the treatment of poisoning by heavy metals], bearing in mind that the standard treatments for the sequelae of atherosclerosis are effectively controlled by this august body [National Heart Foundation]. ..... Funds are donated by the people of New Zealand, presumably in the fond hope that the foundation will look dispassionately at the options available fro the treatment of heart disease."

ADVERSE

John Scott again offered a critical opinion article, "Chelation therapy -- evolution or devolution of a nostrum?" in N Z Med J 9:109-110, 1988.

This brief note was again answered by T. Baily Gibson in an eloquent "Letter to the editor -- chelation therapy," N Z Med J 9:182, 1988. "The big kids are throwing their weight around in the playground again. ... I wonder why it is that chelation receives so much attention, whilst other controversial treatments are left alone. Perhaps it is because chelation gives the patient a choice of treatments, and perhaps a way out of the two year waiting list for CABG surgery. ..... Scott uses the hyperbole and emotive language that he accuses us of. He uses terms like 'nostrum,' 'panacea,' 'con,' 'neo-magical,' 'pseudo-scientific,' 'fraud,' and 'dishonest propagation of magical ideas.' He likens chelation therapy to laetrile. In his last paper on the subject, he compared it with iridology. He is simply expressing his opinion in a clearly biased and bigoted manner. When such bias is exposed, it is difficult to give any credence to what he has to say. ..... It remains a fact, and I think this is where Scott has real difficulty, that the patient is better -- and that the doctor's role remains that of a healer. If the majority of my patients did not

improve with chelation therapy, word would rapidly spread in the community and people would no longer request treatment."

Charles H. Farr, M. D., Ph. D., proposed that a principal mechanism of action of EDTA is the chelation of ferrous iron and the consequent reduction of free radical production. Plzen Lek Sborn Supp 56:171-173, 1988.

1988 -- DMSA

L. Fournier, G. Thomas, A. Garnier and coworkers published their experience with DMSA: "2,3-dimercaptosuccinic acid treatment of heavy metal poisoning in humans," Med Toxicol 1988;3:499-504.

1988 -- CHEMISTRY/PHYSIOLOGY

L. H. Edmunds, L. W. Stephenson, R. N. Edie, and M. B. Ratcliffe reported on "Open-heart surgery in octogenarians," where survival data showed one-half of the patients alive at one year postoperatively -- far less than would be expected without surgical intervention. Coronary artery bypass surgery has an average mortality of 4 to 10 per cent, with mortality highest among older patients. N Engl J Med 319:131-136, 1988.

K. V. Arom, D. E. Cohen, and F. T. Strobl reported on the "Effect of intraoperative intervention on neurological outcome based on electroencephalographic monitoring during cardiopulmonary bypass," showing that some patients -- particularly older people -- experience significant cerebral dysfunction after coronary bypass operations. Ann Thorac Surg 48:476-483, 1988.

J. Zylke noted the difficulties encountered with tissue hypoxia and reperfusion injury in "Studying oxygen's life-and-death roles if taken form or reintroduced into tissue," J Amer Med Assoc 259:964-965, 1988.

1988 -- EDUCATIONAL

In the spring of 1988, the first issue of the Journal of Advancement in Medicine (J Adv Med) was published. Elmer Cranton, M. D., served as first editor, replaced by Derrick Lonsdale, M. D., in the fall of 1989.

ACAM compiled and made available from the world literature a collection of 3,539 abstracts on EDTA and EDTA chelation therapy.

Nutritional medicine expert Ward Dean, M. D., published Biological Aging Measurement: Clinical Applications (1988), which serves as a physician's manual to document pathophysiological changes associated with free radical damage, collagen cross-linkage, and the other aging processes.

1989 -- EDTA

The Journal of Advancement in Medicine (J Adv Med) published a special issue edited by Elmer M. Cranton, M. D.: A Textbook on EDTA Chelation Therapy. The volume is a collection of key papers published over the previous 10 years, with the ACAM protocol for safe and effective administration of EDTA appended. J Adv Med 2(1,2), 1989, 460 pages. When given according to the published protocol, EDTA is safe, with a mortality rate the approaches zero and minimal morbidity.

Elmer M. Cranton and James P. Frackelton published a review on "Current status of EDTA chelation therapy in occlusive arterial disease," J Adv Med 2:107-119, 1989. "Benefits of intravenous chelation therapy are unknown to most physicians. A series of circumstances led to the cessation of investigations and the lack of acceptance of an effective non-invasive therapy, which is less expensive and safer than bypass surgery. ... This review supports the use of EDTA in treatment of occlusive arterial disease and is a companion reference to reports of a series of highly significant controlled studies showing the safety and effectiveness of this therapy."

C. J. Rudolph, E. W. McDonagh, and R. K. Barber reported on pulmonary function improvements in chronic lung disorders in 38 patients studied before and after 30 EDTA infusions. Overall, 30 of 38 subjects (90.5%) improved in PFTs; significant improvements occurred in FVC (forced vital capacity) and FEV1 (forced expiratory volume first second). Patients with more abnormal tests had higher percentage improvements. "Effect of EDTA Chelation and Supportive Multivitamin/Trace Mineral Supplementation on Chronic Lung Disorders: A Study of FVC and FEV1," J Adv Med 2(4):553-561, 1989.

George Kindness and James P. Frackelton reported that EDTA significantly inhibits aggregation of human platelets in vitro -- as well as extends the partial thromboplastin time. "Effect of ethylene diamine tetraacetic acid (EDTA) on platelet aggregation in human blood," J Adv Med 2(4):519-530, 1989.

Peter J. van der Schaar reported significant improvements in exercise tolerance in 111 patients studied before and after 25 EDTA infusions. Double- and triple-product measurements on treadmill testing improved in patients with coronary artery disease, peripheral vascular disease, and cerebrovascular disease. "Brief communication: Exercise tolerance tests in chelation therapy," J Adv Med 2(4):563-566, 1989.

Ed W. McDonagh, Charles J. Rudolph, and E. Cheraskin published their findings on "The effect of EDTA chelation therapy plus multivitamin/trace mineral supplementation upon vascular dynamics: ankle/brachial Doppler systolic blood pressure ratio," in J Adv Med 2(1,2):XXX-XXX, 1989. They studied 117 lower extremities in 77 elderly patients with documented occlusive peripheral vascular stenosis, pre- and post-treatment with approximately 26 EDTA infusions over 60 days. The ankle/brachial blood pressure ratios improved, indicating significant arterial blood flow improvement ($p < 0.001$).

Walter Blumer and Elmer M. Cranton published the 18-year follow-up report on the possible role of EDTA chelation therapy in preventing cancer. Blumer studied 59 patients who lived next to a heavily-traveled highway and who were given calcium-EDTA infusions because of lead exposure in automobile exhaust gases. Controls were 172 people living in the same neighborhood. Only 1 of 59 treated patients (1.7%) died of cancer while 30 of 172 nontreated control subjects (17.6%) died over the 18 year study period. "Ninety Percent Reduction in Cancer Mortality After Chelation Therapy with EDTA," J Adv Med 2(1,2):183-188, 1989.

J. Bjorksten published on "Possibilities and limitations of chelation as a means for life extension," J Adv Med 2(1-2):77-78, 1989. "An overview is presented of functions and limitations of chelation for removing undesired metals, including but not limited to acute poisons, chronic environmental poisons, bone-seeking radioisotopes, and cumulative poisons active in senile dementias and scleroses. The chelating techniques are applicable to all metals. Present trends include the development of injectable or oral chelation. Among promising developments are mentioned cholyl hydroxamic acid, which discharges metal through the liver and digestive tract as well as by the diney route, and other orally administrable chelators which on the basis of animal tests appear to have advantages over those now in use."

1989 -- CHEMISTRY/PHYSIOLOGY

P. Menasche and A. Pinwica reported on "Free radicals and myocardial protection: a surgical viewpoint," Ann Thorac Surg 47(6):939-945, June 1989.

E. Marban, Y. Koretsune, M. Corratti, V. P. Chacko, and H. Kusaka published findings on "Calcium and its role in myocardial cell injury during ischemia and reperfusion," Circulation 80(6 Supp)IV:17-22, Dec 1989.

L. Busch, J. Tessler, and P. M. Bazerque reported on "Effects of calcium and EDTA on rat skin capillary permeability and on its response to histamine, serotonin, and bradykinin," Acta Physiol Pharmacol Latinoam (Argentina) 39(3):227-234, 1989.

D. Steinberg, T. E. Carew, C. Fielding, A. M. Fogelman, R. W. Mahley, A. D. Sniderman, and D. B. Zilversmit reviewed "Lipoproteins and the pathogenesis of atherosclerosis," Circ 80(3):719-723, Sep 1989.

1989 -- ORGANIZATION

The Great Lakes Association of Clinical Medicine (GLACM) founded an Institutional Review Board (IRB) to provide an avenue for studies of alternatives in medical care to be reviewed for safety -- and to be critiqued for scientific merit. The IRB was organized and operates according to standards promulgated by the National Institutes of Health (NIH) and the U. S. Food and Drug Administration (FDA). University and hospital IRB's operate under these same guidelines. L. Terry Chappell, M. D., served as first chair.

Others constituting the IRB included James Carter, M. D., Ph. D., George Kindness, M. D., William Faber, D. O., Barbara Faber (attorney at-law), Nan Kienow, R. N., M. S., Tammy Guerkink, D. O., Jack Schubert, Ph. D. (non-GLACM member), Kirk D. Morgan, M. D. (non-GLACM member), and Conrad Maulfair, D. O.

1989 -- ORGANIZATION

ACAM received provisional status as a medical organization to issue Category I Continuing Medical Education Credits (CME) to attendee of its conferences. ACAM executive director Ed Shaw and program chair John Parks Trowbridge M. D. spearheaded the effort for approval.

1989 -- LEGAL/POLITICAL

Warren M. Levin, M. D., of New York City, was brought before a hearing committee of the State Board for Professional Medical Conduct, with charges based on conduct of patient care from 1975 through August 1988. The State offered

Victor Herbert, M. D., as its sole witness. The Administrative Law Judge discharged Dr. Herbert as a witness because he refused to answer questions to determine whether he had secretly reported Dr. Levin to the Board. The hearing committee issued a report dated November 30, 1989, recommended that the charges be dismissed in that the State had presented no proof relative to the charges and further recommended that the Commissioner of Health review the ruling and remand the matter for further proceedings if appropriate.

On February 7, 1990, the Commissioner of Health (a physician, not a lawyer) ordered that the Administrative Law Judge's ruling be reversed and that Dr. Herbert's testimony be admitted in a new hearing, in which the question whether Dr. Herbert had been the complainant (and thus would be a biased witness) could not be allowed! The hearing resumed on May 14, 1990, with a total of 28 additional hearing sessions, during which other State witnesses (originally not planned to be called) were presented. Dr. Herbert frequently called Dr. Levin and his practices a "fraud" and characterized him and his practices as "gross incompetence." The hearing committee chose to consider that defense testimony offered by such experts as Nobel Laureate Linus Pauling was "not germane to the issues in the case." The hearing committee found Dr. Levin guilty of several counts of professional misconduct and recommended that his license be revoked.

The Commissioner of Health recommended that the Board of Regents accept the findings, conclusions, and recommendation of the hearing committee. The Administrative Officer had notified Dr. Levin's attorney that several of his defense exhibits would not be forwarded to the Regents for their review. On June 29, 1993, Dr. Levin appeared before the Regents for oral arguments.
The Regents agreed -- after exhaustive review of the 5,000 page transcript -- that Dr. Herbert's pervasive conduct "tainted" the proceedings and deprived respondent of a fair hearing on the merits of the charges. The Regents further held that "inappropriate conduct by the [State's] counsel compounds the unfairness resulting from Dr. V. H.'s testimony and 'destroys confidence in the fairness' of the hearing procedure and decision."

In a detailed (69 page) report issued on September 2, 1994, the Regents Review Committee dismissed all major charges outright and recommended that some of the minor charges should be remanded to a new hearing committee," consisting of different members for a hearing de novo." The State has chosen, as of November 1994, to drop all charges.

ADVERSE
The FDA Consumer newsletter, in its October 1989 edition (volume 23, number 8) listed EDTA chelation therapy as one of the top 10 health frauds. Several wire

services picked up the listing, spreading the mis-information far and wide. Ross Gordon, M. D., wrote a letter pointing out that the FDA had issued an IND for study of EDTA chelation therapy in peripheral vascular disease ... so the FDA Consumer issued an apology in its February 1989 issue (volume 24, number 1).

1990 -- EDTA

Efrain Olszewer, F. C. Sabbag, and James P. Carter authored the first double-blind placebo-controlled study published in a peer-reviewed medical journal, detailing the effectiveness of EDTA chelation for peripheral vascular disease. "A Pilot Double-Blind Study of Sodium-Magnesium EDTA in Peripheral Vascular Disease", J Nat Med Assoc 82(3):173-177, 1990.

Olszewer, Sabbag and Carter originally planned a series of 20 chelation infusions OR magnesium-B Complex - Vit C - Ringers lactate solution, given in double blind fashion to 10 male patients with peripheral vascular disease. These 41 to 53 y/o men had diabetes or atherosclerosis, aggravated by prior smoking, with intermittent claudication. The 5 treatment group patients received 1.5 grams (10 ml) of EDTA added to the base solution; the 5 control patients received distilled water added to the base solution. After 10 treatments, half the patients were showing significant improvement in both walking distance and ankle/brachial indices, so investigators chose to break the blind -- all improving patients were in the treatment group. So the study was concluded in single-blind fashion, with the control group receiving EDTA solution as their last 10 treatments as crossover and the original treatment group completing a total of 20 EDTA infusions. The crossover patients, originally showing no improvement with 10 placebo treatments, showed the same level of measured improvements in their 10 final infusions (with EDTA) as they had seen in the original treated group in their first 10 treatments and they improved even more as they, too, later completed 20 EDTA treatments.

Charles J. Rudolph and Ed W. McDonagh provided new insights in "Effect of EDTA chelation and supportive multivitamin/trace mineral supplementation on carotid circulation: case report," J Adv Med 3(1):5-11, Spring 1990. This single patient had severe carotid artery occlusive disease and visibly evident shear motion in her right carotid artery. Using duplex scanning, the authors showed that 98 per cent occlusion was reduced to 33 per cent after 30 chelation therapy treatments. The shear motion observed initially resolved to normal. See their subsequent reports on this issue in 1991.

R. L. Kaman, Charles J. Rudolph, Ed W. McDonagh, and F. M. Walker showed that rabbits, whether on a standard laboratory diet or a high cholesterol-containing

atherogenic diet, when infused with EDTA had significantly less calcium in their aortas. Controls included similarly fed untreated animals and those infused with saline. "Effect of EDTA Chelation Therapy on Aortic Calcium in Rabbits on Atherogenic Diets: Quantitative and Histochemical Studies," J Adv Med 3(1):13-21, 1990.

Charles J. Rudolph, Ed W. McDonagh, and R. K. Barber noted beneficial results in "An observation of the effect of EDTA chelation and supportive multivitamin/trace mineral supplementation on blood platelet volume: a brief communication," J Adv Med 3:179-184, 1990. They showed that mean platelet volume was significantly increased in a group of 85 patients receiving 30 or more EDTA chelation infusions over a period of 13 months ($p < 0.001$). Overall, 72 patients (85 per cent) had increased mean platelet volumes, where a low platelet volume is associated with an increased risk of an adverse cardiovascular event.

S. J. Flora and S. K. Tandon presented data on the "Beneficial effects of zinc supplementation during chelation treatment of lead intoxication in rats," J Toxicol 64(2):129-139, Nov 1990.

M. E. Godfrey wrote briefly on "EDTA chelation as treatment of arteriosclerosis," N Z Med J 103(887):162-163, 1990.

1990 -- DMSA

H. Vasken Aposhian and M. M. Aposhian reviewed "meso-2,3-Dimercaptosuccinic acid: chemical, pharmacological and toxicological properties of an orally effective metal chelating agent," Ann Rev Pharmacol & Toxicol 30:279-306, 1990.

J. Montalvan, P. Okose, and S. Marcus published "Outpatient chelation therapy of 24 patients with lead intoxication by dimercaptosuccinic acid," Vet Hum Toxicol 1990;4:364 (abstract).

M. E. Mortensen and P. M. Valenzuela published "2,3-dimercapto-succinic acid (DMSA) chelation in mercury (Hg) vapor poisoning," Vet Hum Toxicol 1990;4:362 (abstract).

1990 -- CHEMISTRY/PHYSIOLOGY

J. May, W. Loesche, and S. Heptinstall noted that "Glucose increases spontaneous

platelet aggregation in whole blood," Thrombosis Research 59(3):489-495, 1990.

D. G. Berger, D. I. Gregg, and P. A. Succop described the use of unstimulated urinary lead excretion to assess the need for chelation in the treatment of lead poisoning. J Pediatrics 116(1):46-51, Jan 1990.

T. B. Rajavashisth, A. Andalibi, M. C. Territo, J. A. Berliner, M. Navab, A. M. Fogelman, and A. J. Lusis published data showing "Induction of endothelial cell expression of granulocyte and macrophage colony-stimulating factors by modified low-density lipoproteins," Nature 344(6263):254-257, Mar 15 1990.

J. A. Berliner, M. C. Territo, A. Sevanian, S. Ramin, J. A. Kim, B. Bamsahd, M. Esterson, and A. M. Fogelman reported that "Minimally modified low density lipoprotein stimulates monocyte endothelial interactions," J Clin Invest 85(4):1260-1206, Apr 1990.

Carpenter, Rejuvenation, 1980: "In approximately 90 per cent of the cases, death due to arteriosclerosis-produced vascular insufficiency is now avoidable. Furthermore, clinical evidence reveals that the arteriosclerotic deposits can be, and are being, removed by appropriate treatment." (CITATION NEEDED 1990)

1990 -- ORGANIZATION

The American College for Advancement in Medicine received final approval to grant CME credits to conference attendees from the ACCME. During its provisional accrediting period, ACAM programs were of such caliber that ACCME granted a four year approval instead of the anticipated two year period. The Chicago meeting with ACCME was attended by Michael Schachter, M. D. (president), John Parks Trowbridge M. D. (past program chair and president-elect), Ralph Miranda M. D. (program chair and vice-president), and Ed Shaw, Ph. D. (executive director).

The American College for Advancement in Medicine founded its Fellows program, to identify and honor those physicians who had made exemplary scientific contributions to the field of preventive medicine and whose leadership efforts had advanced the organization as well. During the first year, the following members were designated as Fellows of the Academy (FACAM): H. Richard Casdorph, M. D., Ph. D.; L. Terry Chappell, M. D.; Elmer M. Cranton, M. D.; Stephen K. Elsasser, D. O.; James P. Frackelton, M. D.; Derrick Lonsdale, M. D.; Conrad G.

Maulfair, Jr., D. O.; Ed W. McDonagh, D. O.; Charles J. Rudolph, D. O., Ph. D.; John Parks Trowbridge M. D.; and Harvey Walker, Jr., M. D., Ph. D.

1990 -- EDUCATIONAL

Chelation expert Robert C. Atkins, M. D., published Dr. Atkins' Health Revolution: How Complementary Medicine Can Extend Your Life (1990), in which he carefully and clearly reviewed for the lay public (and the uninformed physician) many of the diagnostic and treatment concepts involved in "complementary" medicine.

Houston (Texas) cardiologist Dean Ornish, M. D., published a book for the lay public, Dr. Dean Ornish's Program for Reversing Heart Disease, providing clear scientific documentation that dietary reversal of heart disease and atherosclerotic lesions is possible. His book has no listing for "chelation therapy" in the index, even though more published articles demonstrating that this treatment reverses heart disease than are available for any other modality.

Ornish had already published (and subsequently continued to report) a number of articles on risk factor modification affecting atherosclerotic pathology:

"Effects of stress management training and dietary changes in treating ischemic heart disease," J Am Med Assoc 249(1):54-59, Jan 7 1983.

"Plasma lipoprotein levels in vegetarians. The effect of ingestion of fats from dairy products," J Am Med Assoc 254(10):1337-1341, Sep 14, 1985.

"Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial," Lancet 336(8708):129-133, Jul 21 1990.

"Reversing heart disease through diet, exercise, and stress management: an interview with Dean Ornish," J Am Diet Assoc, 91(2):162-165, Feb 1991.

"Improved stenosis geometry by quantitative coronary arteriography after vigorous risk factor modification," Am J Cardiol, 69(9):845-853, Apr 1 1992.

"Can lifestyle changes reverse coronary heart disease?" World Rev Nutr Diet, 72:38-48, 1993.

"Dietary treatment of hyperlipidemia," J Cardiovas Risk 1(4):283-286, Dec 1994.

"Changes in myocardial perfusion abnormalities by positron emission tomography after long-term, intense risk factor modification," J Am Med Assoc 274(11):894-901, Sep 20 1995.

The People's Medical Society issued a Special Report on Chelation Therapy which was objective and generally favorable.

1990 -- LEGAL/POLITICAL

Robert J. Rowen, M. D., persuaded Alaska State Legislature to pass a "freedom of choice in health care" law: physicians practicing alternative medicine could no longer be brought up on administrative, civil, or criminal charges simply because they were practicing differently than the accepted standard.

During 1990 -- 1991, the Canadian-based EDTA Chelation Lobby Association of B. C. (British Columbia) accelerated its educational and political activity, informing the public in Canada AND in the United States as to the benefits of chelation therapy for cardiovascular disease. When the College of Physicians and Surgeons of British Columbia attempted to investigate two chelating physicians in what appeared to be an unusual and unfair manner, a massive public relations campaign and a counter-suit at law seemed to put an end to the investigation.

1990 – EDUCATION

Morton Walker, D. P. M., published The Chelation Way, updating his earlier works on this topic (Avery Publishing Group).

1991 -- EDTA

*ADVERSE*
J. Sloth-Nielsen, Bernadette Guldager, Christian Mouritzen, Elisabeth B. Lund, Marianne Egeblad, O. Norregaard, Svend Juul Jorgensen, and Rolf Jeines published results of their study of EDTA chelation in a purported double-blind, placebo-controlled study. "Arteriographic findings in EDTA chelation therapy on peripheral arteriosclerosis," Am J Surg 162:122-125, Aug 1991. (Data were presented in more detail by Guldager in 1992.) The authors focused on 30 of the 153 patients enrolled in the so-called double-blind, placebo controlled study -- and claimed to find no benefits in the treatment group -- the FIRST published paper

involving the clinical use of EDTA that showed NO benefit from the treatment. Even though 50 -- 60 per cent of treated patients improved, they concluded that data did not support the effectiveness of chelation treatment because of very high response rates in the placebo group.

ACAM experts questioned the quality and veracity of the study for a number of reasons. The study failed to use magnesium in the solution, as required by the ACAM protocol they claimed to be following. Of obvious disparity is that they reported no difference in burning at the infusion site, even though allegedly 3 grams of EDTA in 1000 ml of saline were infused. Patients so treated -- especially without local anesthetic or magnesium -- should have complained more than controls.

Some patients complained that their infusions hurt very badly on some days -- but not at all on others; this suggests that treatment and placebo groups were either erroneously mixed up or that an unreported crossover occurred. When interviewed, patients stated that they were sent home with iv needles in their veins "for convenience sake," and sometimes they had to start their own iv's. Reportedly they would simply take an iv bottle from the shelf and "hook themselves up" without close supervision.

Further, patients were given a mineral supplement containing iron during their treatment period, regardless of serum ferritin levels.

On page 264 of their article, the authors document an increase in maximal walking distance but no significant differences between placebo and EDTA treatment groups. If paients were crossed over during the study (perhaps repeatedly?), as patient interviews would support, the results as published might occur.

The study did not follow the ACAM protocol for EDTA treatment, although the investigators claimed to do so. The study has been reviewed by the Danish Committee for Investigation into Scientific Dishonesty and has been criticized in at least 4 journals ("EDTA chelation: a rebuttal," J Adv Med 5:3-5, 1994, editorial; E. M. Cranton and J. P. Frackelton, "Negative Danish study of EDTA chelation biased," Townsend Lett Doctors July 1992:604-605; C. Hancke and K. Flytlie, "Manipulation with EDTA," Ugeskar Laegar 154(2):213-215, 1992; and Derrick Lonsdale, "EDTA chelation therapy," Am J Surg 166:316, 1993, letter)

Charles J. Rudolph, Ed W. McDonagh, and R. K. Barber demonstrated a reduction in iron as an "Effect of EDTA chelation on serum iron." Reduced iron load is one of the potential mechanisms of the anti-inflammatory (antioxidant) effects of EDTA. J Adv Med 4:39-45, 1991. "One hundred twenty-two patients suffering from various chronic degenerative disorders were evaluated objectively for fasting serum iron values before and after EDTA chelation plus multivitamin mineral (excluding iron)

supplementation. After 30 intravenous 3 gram treatments of EDTA, average serum iron levels dropped 17.5% ($p<0.001$). Abnormally high initial iron decreased 43.1% ($p<0.001$), while low initial iron increased 41% ($p<0.01$)."

1991 -- EDTA

Charles J. Rudolph, Ed W. McDonagh, and R. K. Barber reported on the striking and highly significant reversal of atherosclerotic stenosis of both internal carotid arteries at the bifurcation in 30 patients treated with 30 EDTA infusions over a 10 month period. Ultrasound imaging showed overall intraarterial obstruction was decreased 20.9% (+/-2.3%) ($p < 0.001$), with patients showing more severe stenosis having even greater reduction. This study showed clear evidence of reversal of atherosclerotic cardiovascular disease. "A nonsurgical approach to obstructive carotid stenosis using EDTA chelation," J Adv Med 4(3):157-168, 1991.

1990 - 1992 -- EDTA

The FDA approved (IND) study on EDTA in claudicatory peripheral vascular disease slowed and came to a halt as overseeing medical personnel were transferred from Walter Reed Army Medical Center Hospital and Letterman Army Medical Center Hospital to the Persian Gulf for Operation Desert Storm.

Wyeth-Ayerst Pharmaceutical Company, which had helped to support earlier portions of the study, agreed to finance the remainder with an investment of $6,000,000. Following the hiring of a new medical director, a former director at the National Heart and Lung Institute and long an opponent of chelation therapy, Wyeth reneged on funding and on completing the study.

Some thirty-plus patients had completed treatment and testing in the study. IND holders started to review options with regard to the still-blinded data in the now-defunct study.

1991 -- EDTA

K. Kostial, B. Kargacin, R. Arezina, M. Landeka, and I. Simonovic reported on the many "Factors influencing the efficiency of chelation therapy," J Hyg Epidem Microbiol Immunol 35(4):337-350, 1991.

J. F. Rosen, M. E. Markowitz, P. E. Bijur, S. T. Janks, L. Wielopolski, J. A. Kalef-Ezra, and D. N. Slatkin presented their observations on the "Importance of sequential measurements of bone lead content by L x-ray fluorescence in CaNa2EDTA treated lead toxic children," J Environ Health Perspect 93:271-277, Jun 1991.

1991 -- CHEMISTRY/PHYSIOLOGY

L. E. Mallette, B. W. Hollis, K. Dunn, M. Stinson, J. K. Dunn, E. Wittels, and A. M. Gotto published their observations that "Ten weeks of intermittent hypocalcemic stimulation does not produce functional parathyroid hyperplasia," Amer J Med Sci 302(3):138-141, 1991. "Lowering ionized serum calcium to values below the normal range [by an average of 0.20 mmol/L at 2 hours by administration of EDTA 50 mg/kg infused over 3 hours] three times a week for 10 weeks is not a sufficient stimulus to cause a detectable increase in basal or stimulated parathyroid function."

The participation of Baylor cardiology chief, Antonio Gotto, M. D., in this study with Kim Dunn, originally a medical student at the University of Texas/Houston, is certainly provocative. Gotto, head of the American Heart Association in 1985, had at that time the opportunity to meet with (and see the positive chelation data of) Zechmeister from Czhekoslovakia. Also in that year, the AHA produced the "snake oil" pamphlet that dramatically reduced patient entries into chelation therapy clinics in some areas of the country. Dunn had approached Ross Gordon, M. D., for guidance in conducting clinical studies into the effectiveness of chelation therapy, while she was still a medical student. This report shows that both Dunn and Gotto clearly had a chance to see patients progress through a chelation regimen -- yet no positive results were ever reported.

L. Badimon, J. J. Badimon, R. Lassila, M. Heras, et alia published their observations on "Thrombin regulation of platelet interaction with damaged vessel wall and isolated collagen type-I of arterial flow conditions in a porcine model -- effects of hirudins, heparin, and calcium chelation," Blood 78(2):423-434, Jul 15, 1991.

W. Zheng, D. F. Perry, D. L. Nelson, and H. Vasken Aposhian described their rat and rabbit studies showing that "Choroid plexus protects cerebrospinal fluid against toxic metals," FASEB J 5(8):2188-2193, May 1991. "The lateral choroid plexus sequesters Pb, Cd, As, and Hg. It appears to be one of the important mechanisms that protects the CSF and the brain from the fluxes of toxic heavy metals in the blood."

1991 -- EDUCATIONAL

Medical expert and renowned writer Julian Whitaker, M. D., began to publish the monthly Health & Healing newsletter, to educate the lay public on diverse health-related topics, especially effective nutritional, pharmacological, and other strategies to help improve their wellbeing.

1991 -- LEGAL/POLITICAL

In July 1991, the Arizona Board of Osteopathic Medicine passed a resolution which declared the administration of EDTA chelation therapy for cardiovascular diseases to be an act of unprofessional conduct, subject to license revocation. Considerable pressure from patients in the form of letters to the governor and the legislators -- as well as a threatened lawsuit -- induced the Attorney General to persuade the Board to rescind their resolution. Michael Schachter, M. D., then-president of ACAM, and Julian Whitaker, M. D., helped encouraged Governor Fife Symington to understand the political realities in this issue.

During 1991, the West Virginia State Board of Medicine passed a resolution declaring illegal the use of EDTA chelation therapy for conditions other than heavy metal toxicity. This action was supported by the State legislature as well, with an enactment in law. ACAM member Steven Zekan, M. D., was instrumental in setting up a hearing before the Board, at which physicians and patients testified. As a result, the Board reversed its position in January 1992 and requested that the Secretary of State repeal the law on an emergency basis.

1992 -- EDTA

B. Guldager, R. Jelsnes, S. J. Jorgensen, J. S. Nielsen, A. Kaerke, K. Mogensen, K. E. Larsen, E. Reimers, J. Holm, and A. S. Ottesen published the complete Danish double-blind placebo-controlled study involving 153 intermittent claudication patients using 20 disodium EDTA infusions without magnesium. (The first portion of the study was published in 1991, American Journal of Surgery, reported above.) The authors reported no clear differences between treatment and placebo groups in measure pain-free and maximal walking distances on a treadmill. During the 3-month (n=149) and 6-month (n=123) follow-up periods, the authors reported that no long-term therapeutic effects of EDTA could be demonstrated. They further claimed that ankle-brachial indices remained unchanged throughout the study. These findings are in marked contrast to findings reported in other studies over the previous 30 years. "EDTA Treatment of Intermittent Claudication -- a

Double-Blind, Placebo-Controlled Study," J Intern Med 231:261-267, 1992.

The conclusion by the Danish vascular surgeons was that chelation treatment provided no difference when compared to controls. This led to a major outcry in scientific circles, including a complaint to the Danish Committee for Investigation into Scientific Dishonesty. The Committee reported improper randomization and double-blinding and premature breaking of the blinded coding. The Committee on Scientific Dishonesty (UVVU), "Conclusion concerning complaints in connection with trial of EDTA versus placebo in the treatment of arteriosclerosis," Danish Research Councils.

Technical faults of the study published by the Danish vascular surgeons have been reviewed in several articles. "EDTA chelation: a rebuttal," J Adv Med 5:3-5, 1992; Elmer M. Cranton and James P. Frackelton, "Negative Danish study of EDTA chelation biased," Townsend Letter for Doctors, 1992:604-605, July; C. Hancke and K. Flytlie, "Manipulation with EDTA," Ugeskar Laeger 154:2213-2215, 1992; K. Flytlie and C. Hancke, "EDTA manipulated," J Adv Med 6:53-55, 1993.

Kurt Christensen, M. D., and Dorthe Theilade, M. D., in Denmark, in 1996 advanced a number of concerns about the performance of the Guldager studies (personal communication, submitted for publication 1996).

W. J. Adams and C. T. McGee identified lasting positive benefits in "Chelation therapy: a survey of treatment outcomes and selected socio-economic factors," J Adv Med 5(3):189-197, 1992. They reported on a follow-up survey of 54 patients who completed a course of chelation therapy treatments. Only 36 per cent of the 50 patients who had improved were asymptomatic, but a total of 92.6 per cent of all patients reported improvement. The distinction appeared to be that the asymptomatic group had started chelation with a year of onset of symptoms and ALL had continued with the necessary lifestyle changes, including daily nutritional supplementation.

D. J. Lamb and D. S. Leake described improved lipid patterns as "The effect of EDTA on the oxidation of low-density lipoprotein," Atherosclerosis 94:35-42, 1992. "Low density lipoprotein (LDL) is routinely isolated and stored in buffers containing ... (EDTA) to inhibit its autoxidation."

H. S. Uhl, R. C. Dysko, and R. W. St. Clair noted that "EDTA reduces liver cholesterol content in cholesterol-fed rabbits," Atherosclerosis 96(2-3):181-188, Oct 1992.

V. C. Simon and R. A. Cohen described how "EDTA influences reactivity of isolated

aorta from hypercholesterolemic rabbits," Am J Physiol Heart Circ 262(5):31-35, 1992.

1992 -- DFO

S. Katoh, J. Toyama, I. Kodama, T. Akita, and T. Abe described how "Desferroxamine, an iron chelator, reduces myocardial injury and free radical generation in isolated neonatal rabbit hearts subjected to a global ischaemia-reperfusion," J Mol Cell Cardiol 24(1):267-275, 1992.

T. Harada and M. R. Mayberg noted "Inhibition of delayed arterial narrowing by the iron-chelating agent deferoxamine," J Neurosurg 77:763-767, 1992.

P. O. Hagen, M. G. Davies, R. W. Schuman, and J. J. Murray reported on "Reduction of vein graft intimal hyperplasia by ex vivo treatment with Deferoxamine Manganese," J Vasc Res 29:405-409, 1992.

1992 -- DMPS/DMSA

H. Vasken Aposhian, D. C. Bruce, W. Alter, R. C. Dart, K. M. Hurlbut, and M. M. Aposhian reported on "Urine mercury after administration of 2,3-mercaptopropane-1-sulfonic acid: correlation with dental amalgam score," FASEB J 6(7):2472-2476, Apr 1992. "Linear regression analysis indicated a highly significant positive correlation between the mercury excreted in the urine 2 h after DMPS administration and the dental amalgam scores."

H. Vasken Aposhian, R. M. Maiorino, M. Rivera, D. C. Bruce, R. C. Dart, K. M. Hurlbut, D. J. Levine, W. Zheng, Q. Fernando, D. Carter, et alia described "Human studies with the chelating agents, DMPS and DMSA," J Toxicol - Clin Toxicol 30(4):505-528, 1992.

1992 -- CHEMISTRY/PHYSIOLOGY

Jukka T. Salonen, K. Nyyssonen, H. Korpela, J. Tuomilehto, R. Seppanen, and R. Salonen, devised a clinical study to follow on the fact that iron can induce lipid peroxidation in vitro and in vivo in humans and has promoted ischemic myocardial injury in experimental animals. They reported a 3-year prospective epidemiologic study (concluded in 1989) of acute myocardial infarctions in 1,931 asymptomatic

men aged 42, 48, 54, or 60 years at the onset. During the study, 51 participants had a heart attack and 9 of them died.

Men with serum ferritin over 200 mcg/l had a 2.2-fold risk factor-adjusted risk of acute myocardial infarction compared with men with a lower serum ferritin. For each 1 per cent increase in the amount of ferritin in the blood, they found more than a 4 per cent increased risk for heart attack. The association was stronger in men with serum LDL over 5.0 mmol/l (193 mg/dl) than in others. Also, dietary iron intake had a significant association with the disease risk. Ferritin was the second strongest risk factor for heart attacks, behind a combination of the number of cigarettes smoked and the number of years the participant had smoked. "High stored iron levels are associated with excess risk of myocardial infarction in Eastern Finnish men," Circulation 86:803-811, Sep 1992.
This study was widely reported, including coverage by the New York Times (front page, September 8, 1992) and the Wall Street Journal (same date). Clearly, the removal of excess iron by chelation therapy offers a logical treatment option to reduce excessive risk.

Denham Harman, M. D., published an excellent summary, "Free radical theory of aging: History," in Free Radicals and Aging, edited by I. Emerit and B. Chance, Basil: Birkhauser, 1992, pages 1-10. An extensive bibliography refers the reader to most of the key articles published in the past 40 years on free radicals, illness, and aging.

J. E. Enstrom, L. E. Kanim, and M. A. Klein reported an "Inverse relationship between the intake of vitamin C and mortality from all causes," Epidemiol 3:194-202, 1992. Their work at UCLA provided a ten year observation period of 11,348 adults. Several mainstream "medical newsletters" (from Harvard, Johns Hopkins, and the Diet-Health Letter) published favorable reviews of their conclusions.

A. F. Parisi, E. D. Folland, and P. A. Hartigan published a "Comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease." Their data suggest that angioplasty is not typically indicated for multivessel disease and restenosis rates remain as high as 30 per cent with 6 months. N Engl J Med 326:10-16, 1992.

T. B. Graboys, B. Biegelson, S. Lampert, C. M. Blatt, and B. Lown published their "Results of a second-opinion trial among patients recommended for coronary angiography," noting that cardiovascular mortality rates have declined for the past 20 years. J Am Med Assoc 258(2):537-540, 1992.

F. Lanza, A. Stierie, C. Gachet, and J. P. Cazenave published their observations on "Differential effects of extra- and intracellular calcium chelation on human platelet function and glycoprotein-IIB-IIIA complex stability," Nouvelle Revue Francaise D Hematologie V34 N1:123-131, Mar 1992.

S. Juneja, M. Wolf, and R. McLennan noted "Clumping of lymphoma cells in peripheral blood induced by EDTA," J Clin Pathol 45(6):538-540, Jun 1992.

J. J. Hwa, S. Zoliman, C. H. Warden, B. A. Taylor, P. A. Edwards, A. M. Fogelman, and A. J. Lusis reported "Genetic and dietary interactions in the regulation of HMG-CoA reductase gene expression," J Lipid Res 33(5):711-725, May 1992.

M. E. Haberland, G. M. Fless, A. M. Scanu, and A. M. Fogelman described that "Malondialdehyde modification of lipoprotein(a) produces avid uptake by human monocyte-macrophages," J Biol Chem 267(6):4143-4151, Feb 25 Feb 1992.

S. D. Cushing and A. M. Fogelman noted that "Monocytes may amplify their recruitment into inflammatory lesions by inducing monocyte chemotactic protein," Arterioscler & Thromb 12(1):78-82, Jan 1992.

1992 -- ORGANIZATION

With firm encouragement from Julian Whitaker, M. D., a few physicians and nutritional vendors joined forces to form the American Preventive Medical Association (APMA), to lobby for legislative reform and protection of alternative choices in health care. Dr. Whitaker was selected as first president. Alexander Schauss, Ph. D., executive director of Citizens for Health, was chosen to serve as first executive director.

Thanks to generous financial assistance from Dr. Whitaker, APMA funded an excellent video on alternative medicine in the United States, "Let Truth Be the Bias." Produced by Kevin Miller and narrated by James Earl Jones, this video clearly documents the bias against alterative and complementary methods of healing.

APMA also set up an increasingly effective fax network to help coordinate lobbying and public information activities. In 1994, Candace Campbell became the second executive director, later moving the national office to the Washington, D. C., area in order to enhance political effectiveness.

1992 -- EDUCATIONAL

Medical writers Arline and Harold Brecher published their immensely successful lay book, Forty-Something Forever: A Consumer's Guide to Chelation Therapy and other Heart-Savers (1992), HealthSavers Press, P. O. Box 683, Herndon, Virginia 22070.

Chelation expert Robert C. Atkins, M. D., published Dr. Atkins' New Diet Revolution (1992), in which he carefully and clearly reviews for the lay public (and the uninformed physician) the many faults involved in studies of cholesterol in the diet as it relates to hypercholesterolemia and atherogenesis.

Chelation expert and university professor James P. Carter, M. D., Dr. P. H., published Racketeering in Medicine: The Suppression of Alternatives (1992), exposing disturbing and thought-provoking evidence ..... that bona fide therapies are being disparaged as quackery, that alternative practitioners are being selectively persecuted, that government agencies participate in such harassment, that drug companies exert an undue influence in medical judgments, and that the "bottom line" all too often determines what medicine or treatment is researched, tested, and approved.

1992 -- LEGAL/POLITICAL

After a protracted hearings process, ACAM member William E. Doell, D. O., found his license to practice osteopathic medicine in Colorado was revoked -- because he was "unwilling to admit wrongdoing in the care of his patients." Dr. Doell's attorney stated that this refusal made sense, because the medical board failed to support its accusations. Evidence later uncovered by Dr. Doell suggested that the real reason for the board's attack on him was his immensely successful practice, using EDTA chelation therapy for cardiovascular diseases.

Governor Walter Hickel appointed Robert Rowen, M. D., to serve on the Alaska State Medical Board. In spite of severe and massive criticism by organized medicine, his appointment was confirmed by the State legislature in April, 1993. As Governor Hickel noted: "Dr. Rowen's perspective on preventive health care will be good for Alaskans and for the future of health care ... I am confident his experience will be valuable to the Medical Board ... and I believe he can increase awareness of alternative approaches to medicine."

FDA agents and armed local law enforcement officers invaded the office of Jonathan Wright, M. D., in Washington. The "raid" was carried out on the basis of a sealed affidavit, alleging illegal activities ..... but NO charges were ever filed against Dr. Wright or any members of his staff. The federal government confiscated his office equipment, medical supplies, and -- most unusually -- all of his patient records. Patients and staff alike were startled, alarmed, and incensed at the use of police force and the unreasonable actions of government agents.

Perhaps of interest is that Dr. Wright had earlier filed suit against the FDA for what he considered to be the unlawful limitation of importation of vitamin B12 without preservatives. Many observers saw this raid as the culmination of governmental harassment against nutritionally-oriented physicians. With assistance from the lay group, Citizens for Health, and from the professional group, American Preventive Medical Association, the public was mobilized against suppressive governmental intrusions. In 1995, the FDA finally agreed to return all seized property to Dr. Wright.

1993 -- EDTA

L. Terry Chappell, M. D., and John P. Stahl, Ph. D., published a sophisticated meta-analysis of nineteen published clinical research studies meeting strict criteria for inclusion, with a total of 22,765 patients. Eighty-seven percent of patients included in the meta-analysis showed clinical improvement by objective testing. The correlation coefficient of r=0.88 indicated a strong relationship between EDTA therapy and improved cardiovascular function. "The Correlation Between EDTA Chelation Therapy and Improvement in Cardiovascular Function: A Meta-Analysis," J Adv Med 6(3):139-160, Fall 1993.

1993 -- EDTA

C. Hancke, M. D., and K. Flytlie, M. D., published another Danish study that showed findings in marked contrast to those published earlier by Danish vascular surgeons (J. Sloth-Nielsen, Bernadette Guldager, and colleagues, described above). Improvements were noted in 80 to 91 percent of patients, depending on which of the measurements (mostly objective) was used.

They treated 65 patients with chelation therapy who were on the waiting list for bypass surgery for an average of 6 months. Eighty-nine percent (n=58) of these patients were able to cancel their surgery because of symptomatic improvement. Similarly, they treated 27 patients who were recommended for amputation, and 24

affected limbs were saved.

Of 92 patients referred for surgical intervention, only 10 required surgery after or during their treatment period with chelation therapy. The savings amounted to $3,000,000 in insurance benefits. The study spanned a period of six years, with no severe side effects or deaths arising from the treatment. The authors concluded that EDTA chelation therapy is safe, effective, and cost-saving. "Benefits of EDTA Chelation Therapy in Arteriosclerosis: A Retrospective Study of 470 Patients," J Adv Med 6(3):161-170, Fall 1993.

L. Terry Chappell, in a letter to the editor of the Journal of Advancement in Medicine, noted that if similar results were obtained in the United States of America, in 1992 alone, 363,000 of 407,000 coronary artery bypasses would have been avoided and 102,000 limbs would have been saved with treatment by chelation therapy. The direct cost savings, in 1992 alone, could have been as much as $8,000,000,000. ("Chelation therapy, smoking and health care costs," J Adv Med 7:107, 1994, letter to the editor)

The only plausible explanations for Hancke's positive data are that not all surgery is necessary or that the EDTA treatment is highly effective -- or both.

Ed W. McDonagh and Charles J. Rudolph published impressive results with "Noninvasive treatment for sequellae of failed coronary circulation: 100% occlusion of the left anterior descending coronary artery, 30% stenosis right coronary artery, and left ventricular contractility defect," J Neurol Orthop Med Surg 14:169-173, 1993. The patient had severe coronary heart disease revealed by angiogram and was advised to undergo bypass surgery. Instead, he chose EDTA chelation therapy; after 72 infusions, repeat coronary angiography showed improvement.

G. P. Monaco and S. Green published their critical opinions in "Recognizing deception in the promotion of untested and unproven medical treatments," N Y State J Med 2:88-91, 1993, prompting Michael B. Schachter issued a response, "Health fraud versus innovation -- a letter to the editor," J Adv Med 6:198-200, 1993.

1993 -- DFO

E. Patterson published on "Coronary vascular injury following transient coronary artery occlusion: prevention by pre-treatment with deferoxamine,

dimethylthiourea, and N-2-mercaptoproprionyl glycine," J Pharm Exp Ther 266(1):528-535, 1993.

1993 -- CHEMISTRY/PHYSIOLOGY

F. W. Sellke, T. Shafique, D. L. Edy, and R. M. Weintraub published data showing "Coronary endothelial injury after cardiopulmonary bypass and ischemic cardioplegia is mediated by oxygen-derived free radicals," Circulation 88:395-400, 1993.

J. A. Berliner, D. S. Schwartz, M. C. Territo, A. Andalibi, L. Almada, A. J. Lusis, D. Quismorio, Z. P. Fang, and A. M. Fogelman presented data on the "Induction of chemotactic cytokines by minimally oxidized LDL," Adv Exp Med Biol 351:13-18, 1993.

A. Andalibi, F. Liao, S. Imes, A. M. Fogelman, and A. J. Lusis noted that "Oxidized lipoproteins influence gene expression by causing oxidative stress and activating the transcription factor NF-kappa B," (Review) Bioc Soc Trans 21(Pt 3)(3):651-655, Aug 1993.

J. A. Berliner, F. Parhami, Z. T. Fang, A. M. Fogelman, and C. Territo described "Regulation of monocyte and neutrophil entry into the vessel wall," (Review) Behring Institute Mitteilungen (92):87-91, Aug 1993.

1993 -- ORGANIZATION

The Great Lakes Association of Clinical Medicine (GLACM) provided assistance to the American College for Advancement (ACAM) in Medicine in the founding of another Institutional Review Board (IRB) to provide yet another avenue for studies of alternatives in medical care to be reviewed for safety -- and to be critiqued for scientific merit. This IRB, founded in November 1993, also was organized and operates according to standards promulgated by the National Institutes of Health and the U. S. Food and Drug Administration. University and hospital IRB's operate under these same guidelines. Stephen K. Elsasser, D. O., for some time a member of the GLACM IRB, was selected as first chair of the ACAM IRB.

Other original members of ACAM IRB included Majid Ali, M. D., Jeffrey Bland, Ph. D., Kenneth Brock, M. D., Grant Born, D. O., H. Richard Casdorph, M. D., Ph. D., Rhonda Diehl, C. N. C., Derrick Lonsdale, M. D., Miriam O'Mahoney, Gregory

D. Seeley (attorney at-law), Melissa Taliaferro, M. D., and Aristo Vojdani, Ph. D.

1993 -- LEGAL/POLITICAL

The Governor of South Dakota signed a law prohibiting the medical board from bringing charges against physicians for doing chelation therapy.

1994 -- EDTA

*ADVERSE*
Andre M. van Rij, Clive Solomon, Stephen G. K. Packer, and William G. Hopkins published negative conclusions from their double-blind, randomized, placebo-controlled trial on the use of IV magnesium-EDTA chelation therapy for the treatment of intermittent claudicatory peripheral arterial occlusive disease. The study was performed at the University of Otago Medical School in Dunedin, New Zealand. Fifteen patients each received 20 infusions of vitamins in normal saline plus 3 grams of disodium EDTA and 0.76 grams of magnesium chloride with 0.84 grams of sodium bicarbonate neutralization. Seventeen control patients received the iv solution without EDTA, magnesium, and bicarbonate. Pre-, intermediate, and post-study end-point measurements included measured walking distance to (a) onset of pain and (b) stopping due to disabling claudication and ankle/brachial indices at rest and immediately after the treadmill exercise.

Of interest is that the authors concluded that "Chelation therapy has no significant beneficial effects over placebo in patients with intermittent claudication." ACAM experts have advanced a number of criticisms, including these:

1. The total number of subjects was only 32, making it difficult to detect small differences between the groups.

2. Severe multi-vessel disease patients were included, for whom only twenty infusions would be unlikely to produce desired therapeutic results.

3. Smoking status of patients and controls is unclear.

4. No true placebo group was present; both groups received intravenous vitamins and significant oral doses of vitamins and minerals. At the end of twenty infusions, about 60% of BOTH groups had improved their walking distances: this highly significant number shows that the placebo was not inert.

5. The EDTA group did show some statistically significant advantages, at three months after treatment, over the so-called control group with reported ankle/brachial indices and femoral pulsatility indices.

6. Inappropriate statistics were reported in drawing conclusions regarding

walking distances: raw data were log transformed, thereby muting the differences between individuals.

The patients in the van Rij EDTA chelation group improved significantly in five of the studied parameters (ankle/brachial indices in both better and worse legs, two different parameters of physical activity, and femoral pulsatility indices) compared to controls. Further, none of the EDTA patients worsened except one patient in one parameter (ankle/brachial indices in worse leg), although this was not true for the control subjects.

Raw data obtained for review reveal that 26% of the EDTA group achieved greater than 100% improvement in walking distance compared with only 12% of the controls. A decreased ankle/brachial index was seen in only 6% of the EDTA group compared with 35% of the controls. Among nonsmokers or those who had stopped smoking, 66% of the EDTA group improved with an average of an 86% increase in distance walked, but only 45% of the control subjects improved with an average of 56% increase in distance walked. Although his conclusion was negative, van Rij developed data that actually support the therapeutic effect of chelating solutions in patients with vascular disease.

In summary, the reported data and body of the study do not support the conclusions drawn by the authors. "Chelation Therapy for Intermittent Claudication: A Double-Blind, Randomized, Controlled Trial," Circulation 90(3):1194-1199, Sep 1994. The technical criticisms were published as letters to the editor by Michael B. Schachter, "Chelation Therapy," Circulation 91:2291, 1995; L. Terry Chappell, Ralph Miranda, Martin Rubin, et alia, "Chelation Therapy," Circulation 92:1350-1351, 1995; and M. E. Godfrey and L. Terry Chappell, "Chelation Therapy for intermittent claudication -- a reappraisal," N Z Med J 109:83, 1996.

1994 -- EDTA

For years, the removal of calcium from atheromatous and arteriosclerotic arteries has been demonstrated. Now, clinical evidence has been obtained showing the decrease of coronary calcification and improvement in the clinical status of two patients treated with Na2MgEDTA. (M. Rubin, T. Rozema, H. R. Casdorph, and A. Scarchilli, "Cardiac decalcification by Na2MgEDTA," presented at American Chemical Society, 208th meeting, Washington, D. C., August 25, 1994, documenting significant posttreatment decalcification of coronary arteries by ultrafast CT scan.)

L. Terry Chappell, J. P. Stahl, and R. Evans followed up the original meta-analysis (see 1993) with "EDTA chelation therapy for vascular disease: a meta-analysis

using unpublished data," J Adv Med 7:131-142, 1994. Their concern was that excluding unpublished data might lead to publication bias. This second study reviewed unpublished "file drawer" data on 1,241 patients from 32 clinicians. Eighty-eight per cent of the patients improved as measured by a variety of parameters (ECG, ankle/brachial index, walking distance, exercise activity, Doppler testing, and others). This study also showed a correlation coefficient of r=0.88, the same as in the earlier published meta-analysis study, again a very strong indication that EDTA is effective in treating vascular disease.

Charles J. Rudolph, R. T. Samuels, and Ed W. McDonagh documented "Visual field evidence of macular degeneration reversal using a combination of EDTA chelation and multiple vitamin and trace mineral therapy," J Adv Med 4(7):203-212, 1994. Their evidence included retinal photographs clearly showing improvement.

L. Terry Chappell published an extensive "Bibliography on mechanisms of action of EDTA," Townsend Lett Doctors 130:475-479, 1994.

L. Terry Chappell and S. Margolis argued fairly the pros and cons of treating vascular disease with EDTA in a "Point-Counterpoint on EDTA chelation therapy," published in Alternative Therapies 1:53-57, 1994.

1994 -- DFO

G. M. Brittenham, P. M. Griffith, A. W. Nienhuis, et alia described the "Efficacy of deferoxamine in preventing iron overload in patients with thalassemia major," N Engl J Med 331(9):567-573, 1994. The data showed that DFO prevented vascular complications in these patients. Iron is a free-radical initiator and EDTA is an iron chelator; this reaction might partly explain the beneficial results reported from EDTA chelation therapy.

1994 -- DMSA

R. C. Dart, K. M. Hurlbut, R. M. Maiorino, M. Mayersohn, H. Vasken Aposhian, and L. V. Hassen described "Pharmacokinetics of meso-2,3-dimercaptosuccinic acid in patients with lead poisoning and in healthy adults," J Pediatr 125(2):309-316, Aug 1994 [see comment in J Pediatr 125(2):233-234, Aug 1994]. "The DMSA appeared to enter the erythrocytes of patients with lead poisoning to a greater extent than in healthy adults. ... Elimination half-life of total DMSA ... was longer in children with lead poisoning (3.0 +/- 0.2 hours) than in adults with lead poisoning

(1.9 +/- 0.4 hours) and healthy adults (2.0 +/- 0.2 hours)."

1994 -- CHEMISTRY/PHYSIOLOGY

F. Liao, A. Andalibi, J. H. Qiao, H. Allayee, A. M. Fogelman, and A. J. Lusis described "Genetic evidence for a common pathway mediating oxidative stress, inflammatory gene induction, and aortic fatty streak formation in mice," J Clin Invest 94(2):877-884, Aug 1984. "In a previous survey of inbred mouse strains on an atherogenic diet, we observed that the susceptibility to aortic atherosclerotic lesion formation was associated with the accumulation of lipid peroxidation products, induction of inflammatory genes, and the activation of NF-kB-like transcription factors. We hypothesized that the inflammation-related processes were stimulated by oxidized lipids ... We now report that ... results provide strong evidence for the role of inflammatory mediators inducible by oxidative stress in atherogenesis. They also suggest that a major gene contributing to aortic lesion development in this mouse model ... may control either the accumulation of lipid peroxides in tissues or the cellular responses to such lipid peroxides." (See also F. Liao, A. Adalibi, F. C. deBeer, A. M. Fogelman, and A. J. Lusis, "Genetic control of inflammatory gene induction and JF-kappa B-like transcription factor activation in response to an atherogenic diet in mice," J Clin Invest 91(6):2572-2579, Jun 1993, and F. Liao, A. Andalibi, A. J. Lusis, and A. M. Fogelman, "Genetic control of the inflammatory response induced by oxidized lipids," (Review) Am J Cardiol 75(6):65B-66B, Feb 23 1995).

M. Navab, S. Y. Hama, T. B. Nguyen, and A. M. Fogelman noted aspects of "Monocyte adhesion and transmigration in atherosclerosis," (Review) Cor Art Dis 5(3):198-204, Mar 1994.

E. D. Grech, C. M. Bellamy, M. H. Jackson, R. A. Muirhead, E. B. Faragher, and D. R. Ramsdale described a marked increase in "Free-radical activity after primary coronary angioplasty in acute myocardial infarction," So Am Heart J 127(1):443-449, 1994.

Because chelating agents often control free-radical activity, they would appear to have a major role improving outcomes in patients with coronary artery disease, regardless of the primary treatments being employed. (See Patterson 1993, pre-treatment with DFO prevents coronary vascular injury after induced occlusion; and see Katoh 1992, DFO reduces myocardial injury and free radical generation in ischemia-reperfusion; and see Harada 1992, DFO inhibits delayed arterial narrowing.)

1994 -- CHEMISTRY/PHYSIOLOGY

Denham Harman, M. D., reviewed further scientific evidence based on the free radical theory in "Aging: Prospects for Further Increases in the Functional Life Span," Age 17:119-146, 1994.

" ... Aging is the accumulation of changes that increase the risk of death. ... Support for [the free radical theory of aging] is now extensive. There is growing consensus that the theory is correct and that in mammals, aging is the accumulation of deleterious changes produced by free radical reactions, most initiated by the mitochondria (at an increasing rate with age), while the life span is determined by the rate of such damage to the mitochondria. This consensus bodes well for future efforts to increase the functional life span, i. e., the period of healthy, productive life. ...

" ... [The] average life expectancy ... can be increased ... by: 1) keeping body weight down, at a level compatible with a sense of well-being, 2) ingesting diets adequate in essential nutrients and designed to minimize random damaging free radical reactions in the body, 3) supplementing the diet with one or more antioxidants, e. g., beta-carotene, and vitamins C and E, and 4) employing measures to minimize accumulation of metals in the body capable of initiating adverse free radical reaction and of those that can impair the activity of some enzymes."

Harman gives substantial information supporting the information presented in "Table 4. The "free radical" diseases. These include:

1. **Atherosclerosis.**
2. **Cancer.**
3. **Alzheimer's disease**
4. **Parkinson's disease**
5. **Essential hypertension**
6. **Cataracts.**
7. **Fanconi's anemia.**
8. **Bloom syndrome.**
9. **Amyloidosis.**
10. **Diabetes mellitus.**
11. **Laennec's cirrhosis.**
12. **Amyotrophic lateral sclerosis."**

An extensive bibliography provides persuasive scientific support of free radical theories for human illnesses and aging.

1994 -- LEGAL/POLITICAL

In July 1994, Governor Mario Cuomo of New York signed into law an act that gives to physicians who use alternative treatment modalities some protection against bias

by the medical board. The law now (1) recognizes that physicians can use non-conventional modalities if there is evidence for efficacy; and (2) requires that an investigator to get expert opinions concerning the alternative practice if the investigation involves that practice; (3) puts two physicians using alternative treatments on the Board of Professional Conduct; and (4) required that a panel report to the governor on the feasibility of having one of the three panel members hearing charges against a physician to be an expert in the specialty or modality of practice involved in the case. Efforts to pass this law were spearheaded by FAIM, the Foundation for Advancement in Medicine, in New York. The State became the fifth to pass legislation protective of alternative practitioners, following the lead of Alaska, Washington, North Carolina, and Oklahoma.

1994 – EDUCATION

Morton Walker, D. P. M., in consultation with Garry Gordon, M. D., published an updated edition of The Chelation Answer, which was the "original" book that popularized chelation therapy. (Published by Second Opinion Publishing Inc.)

1995 -- EDTA

G. A. Escobar, S. C. Escobar, I. Ordonez, and M. Gonzalez published "Chelation in peripheral arterial insufficiency," describing marked improvement in ankle/brachial indices in 76 of 80 patients treated with chelation therapy. Posterior tibial and dorsalis pedis arterial pulse oscillographic recordings also showed improvement. Twenty-eight of the diabetic patients had inoperable tibial artery lesions; 10 of these had already undergone amputation. Three of the patients had documented Leriche's syndrome. No patients suffered serious side effects from EDTA therapy. Kidney function was not impaired except for a temporary reduction in creatinine clearance in 6 patients -- ranging from 30 to 50% and returning to baseline normal within 30 days.

Their conclusion: "Because of the good results obtained, we consider that chelation with EDTA represents another alternative to treating arterial insufficiency due to atherosclerosis. This is especially effective in patients who are unable to be treated surgically, or also can be a complement to the surgical procedure." Cirugia y Cirujannos (Surgery and Surgeons) 61(2):58-62, 1995.

1995 -- DMPS/DMSA

H. Vasken Aposhian, R. M. Maiorino, D. Gonzalez-Ramierez, M. Zuniga-Charles, Z. Xu, K. M. Hurlbut, P. Junco-Munoz, R. C. Dart, and M. M. Aposhian reviewed "Mobilization of heavy metals by newer, therapeutically useful chelating agents," Toxicol 97(1-3):23-38, Mar 31 1995. "... CaNa2EDTA and ... BAL are becoming outmoded and can be expected to be replaced by ... DMSA ... for treatment of lead intoxication and by the sodium salt of ... DMPS for treating lead, mercury, or arsenic intoxication. ... The Dimaval[DMPS]-mercury challenge test holds great promise as a diagnostic test for mercury exposure, especially for low level mercurialism."

1995 -- CHEMISTRY/PHYSIOLOGY

J. A. Berliner, M. Navab, A. M. Fogelman, J. S. Frank, L. L. Demer, P. A. Edwards, A. D. Watson, and A. J. Lusis reported on "Atherosclerosis: basic mechanisms. Oxidation, inflammation, and genetics," Circulation 91(9):2488-2496, May 1, 1995. "The clinical events resulting from atherosclerosis are directly related to the oxidation of lipids in LDLs that become trapped in the extracellular matrix of the subendothelial cells. These oxidized lipids ... induce the expression of genes ... [and the] protein products of these genes initiates an inflammatory response that initially leads to the development of the fatty streak. The progression of the lesion is associated with the activation of genes that induce arterial calcification, which changes the mechanical characteristics of the artery wall and predisposes to plaque rupture at sites of monocytic infiltration. Plaque rupture exposes the flowing blood to tissue factor in the lesion, and this induces thrombosis, which is the proximate cause of the clinical event. There appear to be potent genetically determined systems for preventing lipid oxidation, inactivating biologically important oxidized lipids, and/or modulating the inflammatory response to oxidized lipids that may explain the differing susceptibility of individuals and populations to the development of atherosclerosis. Enzymes associated with HDL may play and important role in protecting against lipid oxidation in the artery wall and may account in part for the inverse relation between HDL and risk for atherosclerotic clinical events."

M. Navab, A. M. Fogelman, J. A. Berliner, M. C. Territo, L. L. Demer, J. S. Frank, A. D. Watson, P. A. Edwards, and A. J. Lusis described the "Pathogenesis of Atherosclerosis," in Am J Cardiol 76(9):18C-23C, Sep 28 1995 (special issue). "The earliest lesion in the development of an atherosclerotic plaque is the fatty streak. This chronic inflammatory reaction results from a sequence of events that begins with the trapping of low density lipoprotein (LDL) in the subendothelial space of the artery wall. The trapped LDL is seeded with oxidative species released by the

overlying endothelium, and lipid oxidation is initiated within the LDL particle. Some of the lipids that result lead to the activation of NFkB-like transcription factors that cause the expression of genes whose protein products mediate monocyte binding, monocyte chemotaxis into the subendothelial space, and conversion into macrophages. At least 1 major gene modulates the oxidation of LDL lipids and/or the biologic response to the lipids. The inverse relation between high density lipoprotein (HDL) and atherosclerotic events may in part be due to enzymes associated with HDL that destroy the biologically active lipids generated in LDL."

B. J. Vanienten, S. Y. Hama, F. C. Debeer, D. M. Stafforini, T. M. Mcintyre, S. M. Prescott, B. N. Ladu, A. M. Fogelman, and M. Navab demonstrated that during acute phase response in humans and rabbits, displacement and/or exchange of proteins associated with HDL (high density lipoprotein) results in a pro-inflammatory molecule. ("Anti-inflammatory HDL becomes pro-inflammatory during the acute phase response -- loss of protective effect of HDL against LDL oxidation in aortic wall cell cocultures," J Clin Invest 96(6):2758-2767, Dec 1995.)

They had previously reported that, under basal conditions, HDL protects against the oxidative modification of LDL (low density lipoprotein) induced by artery wall cells, causing those cells to produce pro-inflammatory molecules. They had also reported that enzyme systems associated with HDL were responsible for this anti-inflammatory property of HDL.

B. J. Van Lenten, J. Prieve, M. Navab, S. Hama, A. J. Lusis, and A. M. Fogelman reported on "Lipid-induced changes in intracellular iron homeostasis in vitro and in vivo," J Clin Invest 95(5):2104-2110, May 1995. "Iron promotes cellular damage via its capacity to catalyze hydroxyl radical formation and by peroxidation of unsaturated lipids. The major cellular iron storage depot, ferritin, acts as a critical antioxidant defense by sequestering unbound or "free" iron, limiting its participation in damaging oxidative reactions. In this study, we investigated the relationship between LDL modified by artery wall cells and the regulation of intracellular free iron levels [in mouse and human coculture models]. ... Iron loading of coculture cells resulted in elevations of cellular free iron and enhanced LDL-induced monocyte transmigration. Pretreatment of cells with apoferritin completely abolished iron-induced LDL modification. Addition of LDL to cocultures resulted in elevations in lipid peroxidation products, intracellular free iron, apoferritin mRNA expression, and apoferritin synthesis, suggesting a possible relationship between the oxidative modification of LDL and iron metabolism."

1995 -- EDUCATIONAL

Chelation expert Julian Whitaker, M. D., published Is Heart Surgery Necessary? What Your Doctor Won't Tell You (1995), in which he describes the use of chelation therapy to help patients with coronary artery disease.

For an interesting contrast, refer also to Heart Bypass: What Every Patient Must Know, by medical writer Gloria Hochman, New York: Ballantine Books, 1982.

Of further interest is that Dr. Whitaker had published his first major lay book, Reversing Heart Disease, in 1985 -- in which he had made no mention of chelation therapy (which he had not yet studied!).

1996 -- EDTA

PERSONAL COMMUNICATION -- PRESENTED WITH EXPRESS PERMISSION OF PHILIP P. HOEKSTRA, III, Ph. D. -- NOT FOR REPRODUCTION OR OTHER DISSEMINATION UNTIL AFTER FORMAL PUBLICATION -- Philip P. Hoekstra, III, Ph. D., John L. Gedye, M. B., Philip Hoekstra, Jr., Ph. D., Howard T. Lewis, M. D., Albert J. Scarchilli, D. O., Paul A. Parente, D. O., and John Baron, D. O., collaborated on the written presentation of a lengthy study on the effectiveness of serial infusions of magnesium disodium EDTA and in vivo perfusion in human extremities. As yet unpublished, their data lend considerable weight to the scientific evidence of clinical improvement with EDTA chelation therapy. For thirteen years, physicians within the United States referred patient studies to a single reference laboratory for tele-thermographic evaluations of peripheral vascular perfusion. Data were analyzed from 19,147 patients with middle-stage peripheral artery stenosis, before and after a series of MgNa2EDTA infusions. The authors derived rigorous quantitative criteria to classify the response of these patients and subjected the results to binomial analysis. Arterial perfusion of the upper and lower extremities demonstrated significant enhancement in 86 per cent of chelated patients, with a significant dose-response relationship evident. These results substantiated earlier clinical reports by Clarke, Lamar, and others, who noted symptomatic relief of atherosclerotic complications in as many as 87 per cent of patients treated with intravenous Na2EDTA or MgNa2EDTA. (See also the detailed account on pages 96-97 in Racketeering in Medicine: The Suppression of Alternatives, by James P. Carter, M. D., Dr. P. H., Norfolk, Virginia: Hampton Roads, 1992)

1996 -- EDUCATION

L. Terry Chappell and Michael Janson reported on the history and current status of

"EDTA Chelation Therapy in the Treatment of Vascular Disease," J Cardiovasc Nurs 10(3):78-86, April 1996. "EDTA chelation therapy does not preclude the use of surgery, and in spite of receiving chelation treatments, some patients will require surgical interventions. There is usually time for patients to try chelation therapy before surgery or amputation, as Graboys and associates found in 1987 and 1992. ... In addition, patients who are not surgical candidates and who are doing poorly often benefit from chelation therapy. ... This approach offers great potential benefit and is quite safe. It is also relatively inexpensive and does not interfere with other treatments."

1996 -- EDUCATION

Michael B. Schachter, M. D., published an "Overview, Historical Background, and Current Status of EDTA Chelation Therapy for Atherosclerosis," J Adv Med, 9(3):159-177, Fall 1996. Rich in historical detail, the article concludes with this hopeful note: "It is not unusual in the history of medicine for new and promising treatments to be rejected and ridiculed for years before they are finally accepted. The largely favorable clinical results that have been observed worldwide have recently led to the establishment of a number of ongoing clinical trials in several countries, including the United States. These clinical trials should finally answer the question as to efficacy of this treatment to the satisfaction of everyone."

1996 -- EDTA

Efrain Olszewer, M. D., Fuad Calil Sabbag, M. D., and James P. Carter, M. D., Dr. P. H., reported on "Side Effects Studies on Patients Treated with EDTA." In Brazil, more than 100,000 patients have undergone chelation, representing two million infusions in the last eleven years. This vast clinical experience prompted the authors to analyze prospectively a group of patients to investigate the most frequent side effects of EDTA chelation therapy, particularly those for which the drug has been criticized.

RENAL INSUFFICIENCY -- Data in 20 patients with normal pretreatment BUN and creatinine values showed no significant increases in mean values posttreatment. Data in 36 patients with varying renal insufficiency were analyzed retrospectively; posttreatment creatinine levels improved about 14 per cent in the 78 per cent of patients who were able to reach 75 per cent of the optimal dosage. In the 22 per cent of patients whose EDTA treatments were stopped because of worsening renal insufficiency, BUN levels had increased by 28 per cent and creatinine levels increased by 35 per cent.

THROMBOPHLEBITIS -- In 20,000 patients treated with EDTA with no heparin in the infusion, only 2 cases (0.001 per cent) developed thrombophlebitis. Of 200,000 total infusions (with and without heparin), only 16.5 per cent of patients mentioned burning sensation. Thrombophlebitis should be considered as a historical fact, rarely seen in practice.

OSTEOPOROSIS -- Bone densitometry studies for 78 patients were evaluated pre- and posttreatment. Bone density showed an improvement that was not statistically significant for Ward's triangle and the lumbar spine. No improvement was evident for measurements of the femoral head. The authors speculated that osteoporosis could occur in rare individual cases where parathyroid stimulation does no take place.

HYPOCALCEMIA -- No significant differences were found in calcium levels before and after EDTA chelation therapy in 63 patients with different heart problems. All patients were infused with 3.0 g EDTA over 150 to 210 minutes.

HEART FAILURE -- From various prospective observations in 11 patients, the authors concluded that patients with heart failure should be closely monitored while they are being treated with EDTA chelation. Many of them do improve with no significant side effects.

HYPOGLYCEMIA -- Only 2 patients of 12 with "typical symptoms" during therapy (sweating, peripheral coldness, tachycardia, faintness, hypotension, dizziness) actually had low levels of blood glucose -- only 0.005 per cent of the chelations done between 1991 and 1992. Both of these patients had symptoms after a very fast infusion (in less than 50 minutes) and one was being treated with oral hypoglycemic drugs. Therefore, hypoglycemia should be listed as a rare side effect.

Townsend Letter for Doctors & Patients, issue 157/58, August/September 1996, pages 92-94.

Thomas L. Hesselink, M. D., of Aurora, Illinois, offered a provocative theory that EDTA chelation achieves some of its beneficial effects by enhancing removal of an excessive hydrogen pool (personal communication, May). Development of these ideas in more detail for publication is underway.

1996 -- EDUCATION

In 1996, Martin Rubin, Ph. D., emeritus professor at Georgetown University,

authored a chapter entitled "Magnesium EDTA Chelation" in Messerli's Cardiovascular Drug Therapy textbook, 2nd edition. In this chapter, he included details of the coronary artery decalcification study (documented by ultrafast CAT scan) originally presented to the American Chemical Society meeting in 1994.

1996 -- DMPS

M. M. Aposhian, R. M. Maiorino, Z. F. Zu, and H. Vasken Aposhian demonstrated that "Sodium 2,3-dimercapto-1-propane-sulfonate (DMPS) treatment does not redistribute lead or mercury to the brain of rats," Toxicol 109(1):49-55, May 3 1966. Their object was to any concern about whether DMPS, as has been suggested for other chelating agents, when used therapeutically, might cause an initial redistribution of heavy metals to brain.

1996 -- ORGANIZATION

The members of the Great Lakes Association of Clinical Medicine (GLACM) voted to change the organization name to the Great Lakes College of Clinical Medicine (GLCCM).

1997 -- EDUCATION

L. Terry Chappell, M. D., authored a chapter on EDTA Chelation Therapy for Cardiovascular Diseases, scheduled to appear in an upcoming *textbook* on alternative therapies.

Hitrendra H. Shah, M. D., and Morton Walker, D. P. M., authored a book titled Everything You Should Know About Chelation Therapy, published by Keats.

1998 – EDUCATION

John Parks Trowbridge M. D. published a 3-hour audiocassette "book-on-tape," LIVING WELL PAST 50: Rejuvenate Your Heart and Arteries, featuring patient interviews, "plain English" explanations of chelation therapy, and an accompanying 28-page booklet. (Appleday Press, Houston)

Many of the seminal articles on chelation therapy can be found in A Textbook on

EDTA Chelation Therapy, edited by E. M. Cranton, published in the Journal of Advancement in Medicine, volume 2, numbers 1/2, Spring/Summer 1989.

Because of the difficulties in readily obtaining good translations of foreign medical publications, seminal articles of non-American research have not generally been included in this brief review.

ORGANIZATION: GLCCM

Presidents of the Great Lakes Association of Clinical Medicine have been Jack Slingluff, D. O. (1983-1985); Howard T. Lewis, M. D. (1985-1986); Al J. Scarchilli, D. O. (1986-1987); James M. Nutt, D. O. (1987-1988); L. Terry Chappell, M. D. (1988-1989); John Baron, D. O. (1989-1990); Arthur Koch, D. O. (1990-1991); Paul A. Parente, D. O. (1991-1992); Theodore C. Rozema, M. D. (1992-1993); James Ventresco, D. O. (1993-1994); John Parks Trowbridge M. D. (1994-1995); William J. Mauer, D. O. (1995-1996); John Wilson, M. D. (1996-1997); Leo Modzinski, D. O. (1997-1998).

ORGANIZATION: ACAM

Presidents of the American College for Advancement in Medicine have been Harold Harper, M. D. (1973-1976); Garry Gordon, M. D. (1976-1979); Bruce Halstead, M. D. (1979-1981); Murray Susser, M. D. (1981-1983); Ross Gordon, M. D. (1983-1985); James Frackelton, M. D. (1985-1987); H. Richard Casdorph, M. D., Ph. D. (1987-1989); Michael Schachter, M. D. (1989-1991); Elmer Cranton, M. D.(1991-1993); Ralph Miranda, M. D. (1993-1995); L. Terry Chappell, M. D. (1995-1997); Michael Janson, M. D. (1997-1999).

ORGANIZATION: ACAM

In 1989, the American College for Advancement in Medicine established the Annual Achievement Award in Preventive Medicine, to honor a clinician or scientist whose work had uniquely contributed to our understanding and treatment programs. The recipients of this award have been Jeremiah Stamler, M. D., Professor of Cardiology, Northwestern University Medical School (1989); Alfred Sommer, M. D., M. H. Sc., Professor and Director, Dana Center for Preventive Ophthalmology, The Johns Hopkins Schools of Medicine and Public Health (1990); Joseph Beasley, M. D., D. T. M. & H., M. P. H., Bard Fellow in Science and Medicine and Director, Institute of Health Policy, Bard College Center (1991); Linus Pauling, Ph. D., twice Nobel Laureate (1992); Karl Folkers, Ph. D., Director and Ashbel Smith Professor,

Institute for Biomedical Research, University of Texas/Austin (1994); Thomas B. Graboys, M. D., Director, Lown Cardiovascular Center, and Harvard Medical School (1995); and M. R. Malinow, M. D., Oregon Regional Primate Research Center, The Oregon Health Sciences University (1996); Ranjit K. Chandra, M. D., Janeway Child Health Centre, Newfoundland, Canada (1997).

ORGANIZATION: ACAM

The American College for Advancement in Medicine founded its Fellows program in 1990 (see above), to identify and honor those physicians who had made exemplary scientific contributions to the field of preventive medicine and whose leadership efforts had advanced the organization as well. As of January 1998, the following members were currently designated as Fellows of the Academy (FACAM): Norbert J. Becquet, M. D.; Kenneth A. Bock, M. D.; H. Richard Casdorph, M. D., Ph. D.; L. Terry Chappell, M. D.; Jonathan Collin, M. D.; Serafina Corsello, M. D.; Elmer M. Cranton, M. D.; Paul Cutler, M. D.; Charles H. Farr, M. D., Ph. D.; James P. Frackelton, M. D.; Michael E. Godfrey, M. B., B. S.; Ronald Hoffman, M. D.; H. Joseph Holliday, M. D.; Michael Janson, M. D.; Ralph Lev, M. D., M. S.; Derrick Lonsdale, M. D.; William J. Mauer, D. O.; Conrad G. Maulfair, Jr., D. O.; Edward W. McDonagh, D. O.; Ralph A. Miranda, M. D.; Kirk Morgan, M. D.; Theodore Rozema, M. D.; Charles J. Rudolph, D. O., Ph. D.; Michael B. Schachter, M. D.; John Parks Trowbridge M. D.; and Harvey Walker, Jr., M. D., Ph. D.

And there you have it, my friends. A brief set of selections of history -- people and ideas, places and events -- to get you started on sharing our exciting vision.

History, you see, is a happening thing.