A Theoretical Mechanism of Action for EDTA Chelation Therapy Using Anti-Chlamydia Activity

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Until recently there was great interest in the potential role of *Chlamydia pneumoniae* **(CP)** as a cause of atherosclerosis, ischemic heart disease and stroke. Negative results from clinical trials using antibiotic therapy led to subsequent loss of interest in this theory, notwithstanding a very large amount of excellent scientific and epidemiologic data that supports continued research. [1-4]

Chlamydia pneumoniae is the principal suspect for infectious causation of cardiovascular disease. Clinical trials with antibiotic therapy were based on the mistaken assumption that an active infection with CP was needed. We now know that CP can persist intracellularly in a cryptic and arrested state, that cannot be cultured, is immunologically muted, and becomes resistant to antibiotics.[4] Moreover, treatment with antibiotics can cause CP to convert into this inert, resistant, and hidden state. Failure of antibiotic treatment is therefore expected and can easily be explained by the complex and multiphasic growth cycle of CP. Consideration of CP as a cause of atherosclerosis remains an important avenue for research.

Atherosclerosis Successfully Treated with EDTA Chelation Therapy

In a different, but related field, intravenous EDTA chelation therapy was recently shown to be of marked benefit in atherosclerotic heart disease, which suggests a new approach to CP research. The mechanism of action by EDTA chelation as a treatment for . atherosclerosis remains unknown, despite a number of theories. It is theorized in this paper that benefit from EDTA results from an action against CP.

CP as a cause of atherosclerosis can at least partially be explained by metallo-proteins that are created or upregulated by CP. The principal effect of the EDTA is binding of metals. It is estimated that from one third to half of all proteins in the body require a metal co-factor for biological function. EDTA can disassociate metals from those proteins. Possible evidence that this occurs comes from early (although anecdotal) reports of success using intravenous EDTA to treat rattlesnake and spider bites. Those toxic venoms contain a variety of metallo-proteins that mediate their toxicity.

A $30 million, NIH funded clinical trial of intravenous EDTA chelation therapy has shown success in treatment of atherosclerotic cardiovascular disease. [5,6] In that "Trial to Assess Chelation Therapy (TACT)," the composite primary endpoint was death, reinfarction, stroke, coronary revascularization, or hospitalization for angina. A total of 1,708 post-myocardial infarction patients who were 50 years or older received 55,222 infusions of either disodium EDTA or placebo, with a median follow-up of 55 months. Overall, EDTA chelation therapy reduced cardiovascular events by 18%, with a 5-year

number needed to treat (NNT) of 18. A subgroup of 550 patients with diabetes mellitus experienced a 41% reduction in the primary endpoint (5-year NNT = 6.5), and a 43% 5-year relative risk reduction in all-cause mortality (5-year NNT = 12).

Doubtful that Removal of Xenobiotic Metals Is the Mechanism of Action

EDTA has one principal action in the body—it binds (chelates) polyvalent cationic metals. The currently favored explanation for benefit in atherosclerosis is by removal of xenobiotic metallic toxins (toxic heavy metals). However, the link between xenobiotic metals and atherosclerosis is weak. Consider also that provoked excretion of toxic metals following chelation is no greater in healthy control subjects, compared with patients suffering atherosclerotic cardiovascular disease. [author's unpublished data] EDTA binds to essential, nutritional metals with a much stronger affinity, greater by an order of magnitude compared with known toxins.

It is a common misconception that toxins remain toxic in a linear fashion down to low levels— the "linear-no-threshold model." This is rarely true. Threshold levels for safe tolerance exist for virtually all toxins, below which they are safely tolerated. Conversely, excessive levels of essential nutritional metals all cause toxicity. Provoked urinary increase of a range of metals occurs following infusion of EDTA. Increases of essential nutritional metals greatly exceed excretion of known toxins.

All metals are potentially toxic, even essential nutrients**.** That applies to all metals, without exception, not just known toxins. Essential nutritional metals also become toxic when maldistributed within the body (i.e., intracellular calcium or sodium). There commonly exists a narrow margin between optimal and toxic levels for metals. A two or three fold increase can be toxic.

The Table below is taken from data published in the TEXTBOOK ON EDTA CHELATION THERAPY, [7] showing that EDTA chelation has a much greater impact on a number of essential nutritional metals, compared with known toxins.. These data suggest that chelation of essential nutritional elements might be more important for benefit from EDTA than action on toxic, xenobiotic metals.

This author personally chelated many hundreds of patients with EDTA between 1972 and 2003. Utilizing state-of-the-art inductively coupled argon plasma photo-emission spectrometry and atomic absorption spectrophotometry, provoked urinary increases of a range of metals were measured before and after infusion of EDTA in a large series of sequential patients.

Approximately one-third of tested chelation patients were healthy, with no known evidence of atherosclerosis. They elected chelation for purely preventive reasons . They were often spouses, who would otherwise have needed to wait idly for several hours while a family member received treatment. Others were healthy individuals, convinced that chelation therapy would delay or prevent atherosclerosis in later life.

Increase in urinary excretion of metals following I.V. disodium EDTA

Nutritional Elements

Manganese	132 times baseline excretion
Zinc	62 times baseline
Iron	56 times baseline
Cobalt	12 times baseline
Calcium	10 times baseline

Toxic Elements

Lead	8 times baseline excretion
Cadmium	5 times baseline
Nickel	5 times baseline
Aluminum	3 times baseline
Arsenic	2 times baseline
Mercury	2 times baseline

Results of those tests are published in the TEXTBOOK OF EDTA CHELATION THERAPY, chapters 37 and 37.[7] and are partially summarized in the table above. In particular, excretion of toxic elements was essentially the same for healthy individuals and compared with patients diagnosed with atherosclerosis. No association was found to indicate a causative relationship between toxic metals and atherosclerosis. [unpublished data, no longer available]

Life in the 20th century causes toxic metals to accumulate in all individuals, but usually at levels below a threshold for toxicity. These facts argue against the theory that benefit from EDTA chelation in cardiovascular disease results from removal of xenobiotic metals.

Chlamydia As A Cause Of Cardiovascular Disease
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Many published studies have linked CP to atherosclerosis.[1-4] A literature search brings up a very large number of such studies. The data are inconsistent and some studies fail to confirm the association. The contradictions become understandable with newer discoveries concerning   growth stages of CP.

90% or more of the adult population eventually become infected with CP. The incidence of infection Increases with age, parallel to the age-related incidence of atherosclerosis. Evidence exists that CP remains in the body for decades, perhaps throughout life, in a low-grade inflammatory but partially dormant state, much like Varicella virus.

Although classified as a bacterium, CP has many characteristics of a virus. It is an obligate, aerobic, intracellular, gram negative organism with a unique growth cycle of multiple stages. Like a virus, CP hijacks the energy metabolism of host cells for survival and replication. Unlike a virus, CP is partially susceptible to treatment with antibiotics—but not during some stages of its growth cycle.

The initial, acute phase of CP infection commonly lasts only a week or two, and is mainly respiratory. It can be relatively mild or even unsuspected, following which the organism migrates throughout the body in monocytes (macrophages). It then hibernates as inert, cryptic, and immunologically attenuated intracellular inclusions. These inclusions are persistent and remain potentially infective if reactivated. They can hide away for decades, possibly a lifetime, causing chronic, low-grade, lingering infections. Traditional risk factors for atherosclerosis can trigger reactivation. Atherosclerosis develops slowly, perhaps as a host responses to sustained low-grade infection.

The assertions here are simplified and speculative at times. The study of CP is complex and only partially understood.. Because virtually everyone can harbor CP, with or without atherosclerosis, research into the presence or absence of CP has been of little help to prove causation.

 EDTA Chelation Has Anti-Chlamydia Properties

The slow, chronic, long-term, multiphasic, and variable nature of intravascular CP prevents use of Koch's postulates, despite the infectious nature of this disease. Traits of CP leading to atherosclerosis require the presence of metal co-factors, that can be bound and inactivated by EDTA.

Significant correlations are known between metallic trace element levels in plasma, serum, and tissues, with the occurrence and treatment of a variety of infectious diseases. These data exist for metals that are bound tightly by EDTA, including copper, iron, zinc chromium, and manganese.[10]

It is counter-intuitive, but a fact, that the inside diameter of a sclerotic blood vessel need only be increased by 10% to double the flow of blood. Poiseuille's Law of hemodynamics (a fourth power equation) tells us that with perfect laminar blood flow, a mere 19 percent increase in the diameter of an artery

doubles the rate of flow. In a vessel with turbulent flow around a plaque, doubling of flow can result from less than 10% increase in vessel diameter. In an area with compromised circulation, an increase in blood flow of less than that could bring functional improvement and relief of symptoms. Changes in diameter of such small magnitude cannot be detected on arteriograms. CP might mediate such alterations in several ways, and reduce risk of acute events. Merely smoothing over the rough surface of a plaque, converting turbulent flow to laminar flow could have an important effect. Anti-Chlamydia properties of EDTA could reduce plaque turbulence and size, and stabilize plaque against disruption.

CP most often enters the body through the lungs. Smoking inhibits lung defenses increasing risk of CP. Perhaps that is a reason why smoking is a risk factor for atherosclerosis.

EDTA removes calcium from plaque, which might make CP inclusions more vulnerable to host defenses, in addition to increasing lumen diameter.

CP needs iron for survival. Atherosclerosis is associated with increased iron levels. EDTA strongly chelates iron. The Chlamydia growth cycle can be disrupted by iron chelation, using deferoxamine, an iron chelator.[9] EDTA is also a strong iron chelator.

Raulston JE. Response of Chlamydia trachomatis Serovar E to Iron Restriction In Vitro and Evidence for Iron-Regulated Chlamydial Proteins. *Infection and Immunity,* Nov. 1997, p. 4539–4547

EDTA chelation therapy requires many slow, infusions, lasting hours, with 30 or more infusions, requiring several months to achieve good benefit. Full improvement takes several more months following the last infusion. Any proposed mechanism of action must take this delay into consideration. If effects of CP are reduced, full healing of infected tissues could require such time.

Although EDTA remains mostly extracellular, a powerful extracellular-to-intracellular diffusion gradient is created during the infusion. The fibro-calcific-lipoid nature of plaque is unlike a viable cell and may be more permeable to the effect on of EDTA.

Bits and pieces to Think About

CP is speculated to initiate inflammatory scarring of artery walls, which could evolve into plaque. CP induces macrophages to become the type of foam cells associated with plaque formation. CP causes lipid accumulations as found in plaque. CP is lipophilic. CP oxidizes LDL cholesterol. CP releases a variety of metallo-proteins that can disrupt tissues. CP may facilitate plaque rupture. CP releases inflammatory "shock proteins" and a cytokine cascade that can disrupt host tissues. CP is believed by some investigators to trigger a coagulation cascade, causing local hypercoagulability and thrombosis. CP growth cycles have been reported to be inhibited by statin drugs, unrelated to cholesterol. CP upregulates production of metallo-proteinases in atheromas increasing risk of plaque rupture. CP disrupts apoptosis of smooth muscle cells in vascular walls. CP has been reported to cause thinning of fibrous caps on plaque facilitating rupture. CP can cause tissue

calcification and fibrosis as found in plaques. It is further speculated that Chlamydia-specific bacteriophage activity might genetically alter the host expression of this organism.

More Microbiological Research is Needed Using EDTA

It is hoped that microbiologists will find a way to investigate this theory further.

Miscellaneous Background Information

CP has been implicated in many other chronic or autoimmune diseases, which could explain why so many different conditions have been reported anecdotally to improve following EDTA chelation therapy. [11] A slide presentation by Dr. Charles Stratton at Vanderbilt University, is linked below. [12]. He reviews the complex, multiphasic CP growth cycle and various clinical characteristics. A final linked reference describes the complexities and medical politics encountered in a clinical trial related to CP. [13]

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