Until recently there has been great interest in the potential role of infection, more specifically with Chlamydia pneumoniae (CP), as a potential cause of ischemic heart disease, atherosclerosis, and stroke. There is much evidence to support that theory, which includes serological data, histopathology, and extensive epidemiology. A literature search reveals several infectious agents (viruses, bacteria, and parasites) to be associated with risk of vascular disease. The association for some organisms, like Helicobacter pylori, Chlamydia pneumonia, and Cytomegalovirus, is very strong indeed. Evidence for Chlamydia can be found in diseased arteries and plaque microscopically, serologically, and with PCR DNA studies. Negative results from clinical trials using conventional antibiotics caused a loss of interest in this theory, notwithstanding the very large amount of scientific and epidemiologic data to support continued research. [1-4] The mechanism of action for EDTA theorized below can also be applied to other species of pathogenic organisms. Atherosclerosis may be a generic response to infection with a number of different types of infection.

Chlamydia pneumoniae is the principal suspect as an infectious cause of vascular disease, although a number of other microorganisms have also been mentioned. Clinical trials with antibiotic therapy were based on the mistaken assumption that once established, infection with CP persists in a metabolically active state that remains susceptible to conventional antibiotic treatment. We now know that CP reverts periodically to a cryptic, intracellular, metabolically inert, and arrested state, that cannot be cultured, is immunologically muted, and is immune to antibiotics. [4] Treatment with antibiotics may actually cause CP to temporarily convert into its inert state. That cryptic state cyclically reactivates to become an active infection. Failure of antibiotic treatment was therefore to be expected and can be explained by the multiphasic growth cycle of this complex organism. Continued investigation of CP as a likely 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 is of marked benefit in treatment of atherosclerotic heart disease. That suggests a new approach to CP research, based on the antibiotic and antiseptic properties of infused EDTA. [5,6,8] The mechanism of action by which EDTA chelation produces benefit as a treatment for atherosclerosis is unknown, despite a number of hypotheses. It is theorized here that benefit from EDTA in ischemic heart disease results from its antimicrobial action against CP—even against metabolically inert CP that becomes resistant to conventional antibiotics.
Unlike other antibiotics, the antimicrobial activity of EDTA does not require metabolic activity of a viable organism. EDTA acts like an antiseptic. EDTA strips essential trace elements from microorganisms, including zinc, iron, manganese, and others, without which growth and replication are not possible. Metalloenzymes are inactivated, without which a microorganism cannot grow or replicate.

That is how EDTA functions as a food preservative. It is self-sterilizing in solution. When infused, EDTA circulates in its highest concentration in plasma, where it penetrates plaque and sterilizes the endothelium.

CP as a cause of atherosclerosis can be explained, at least partially, by activity of metallo-proteins created or upregulated in blood vessel walls by CP. The principal action of EDTA is binding of cationic metals. It is estimated that from one third to half of the proteins in the body contain a metal co-factor for enzymatic activity. EDTA can disassociate metals from proteins and inactivate enzyme activity. Similar evidence stems from anecdotal reports of intravenous EDTA to treat rattlesnake and spider bites. Toxicity of those venoms is mediated by metallo-enzymes.

A $30 million, NIH-funded, controlled and blinded trial of intravenous EDTA chelation therapy showed striking success in treatment of atherosclerotic cardiovascular disease. [5,6] In the "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 3-hour infusions of either disodium EDTA or placebo, with a median follow-up of almost 5 years. Chelation with intravenous EDTA reduced overall 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 reduction in all-cause mortality (5-year NNT = 12).

**Doubtful That Toxic Heavy Metals Are the Mechanism of Action**

EDTA has one principal action in the body—it binds and removes (or displaces) polyvalent metal cations. A currently favored explanation for benefit in atherosclerosis is the removal of xenobiotic metallic toxins (e.g., toxic heavy metals). However, the link between xenobiotic metals and atherosclerosis is very weak. The excretion of toxic metals following chelation is no greater in healthy control subjects, when compared to patients with atherosclerotic cardiovascular disease. [8] EDTA binds to essential, nutritional metals, i.e.
zinc, iron, manganese, with a much stronger affinity—greater by an order of magnitude or more, when compared to binding and excretion of toxic metals.

It is a common misconception that toxins remain toxic in a linear fashion, down to very low levels—this is the so-called "linear-no-threshold model." This is rarely true. Threshold levels for safe tolerance exist for virtually all toxins, below which they are safely tolerated. Modern laboratory instruments are extremely sensitive, able to measure down to vanishingly low levels.

Urinary increase of a wide range of metals occurs following infusion of EDTA, but excretion of essential nutritional metals greatly exceeds the excretion of heavy metal toxins—higher by an order of magnitude or more.

The Table below shows that EDTA chelation has a much greater impact on essential nutritional metals, compared with excretion of known toxins. Chelation of essential nutritional elements is thus likely to be more important for benefit from EDTA than removal of toxic and xenobiotic metals.

This author personally chelated thousands of patients with intravenous disodium EDTA between 1972 and 2003. Using state-of-the-art, inductively coupled, argon plasma photo-emission spectrometry and atomic absorption spectrophotometry, he measured urinary increases of a range of excreted metals. Urine samples were collected immediately before and after the first EDTA infusion on 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 waited idly for several hours while a family member received treatment. Other patients were healthy individuals, convinced that chelation therapy would delay or prevent atherosclerosis in later life. The healthy patients did not excrete any more toxic metals after chelation than heart disease patients.

**EDTA Not Indicated for Chronic, Long-Term Environmental Lead Exposure**

Little-known is the fact is that EDTA is not effective for chelation of chronic, long-term, environmental lead exposure. Ninety percent of lead in adults is sequestered tightly in cortical bone and teeth. Lead in bone has an elimination half-life of approximately 30 years and is only released from bone into blood and soft tissues during bone reabsorption. [7] Bones therefore act to protect vital, soft-tissue organs against lead toxicity.

EDTA does not penetrate bone to chelate lead. EDTA remains extra cellular after infusion, circulating only briefly in plasma and interstitial fluids, before renal excretion, with a half-life in the body of approximately 45 minutes. EDTA is restricted
to plasma and interstitial fluids, which compose less than 20% of the body mass. It does not penetrate living cells. Circulating lead must also compete for binding sites on EDTA with many other cations, which are in much higher concentrations than lead, greatly reducing lead chelation.

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

<table>
<thead>
<tr>
<th>Nutritional Elements</th>
<th>Toxic Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manganese 132 times baseline excretion</td>
<td>Lead 8 times baseline excretion</td>
</tr>
<tr>
<td>Zinc 62 times baseline</td>
<td>Cadmium 5 times baseline</td>
</tr>
<tr>
<td>Iron 56 times baseline</td>
<td>Nickel 5 times baseline</td>
</tr>
<tr>
<td>Cobalt 12 times baseline</td>
<td>Aluminum 3 times baseline</td>
</tr>
<tr>
<td>Calcium 10 times baseline</td>
<td>Arsenic 2 times baseline</td>
</tr>
<tr>
<td>Mercury 2 times baseline</td>
<td></td>
</tr>
</tbody>
</table>

The above data were published in the TEXTBOOK OF EDTA CHELATION THERAPY, chapters 36 and 37. [8]

Chelation treatment is not indicated for patients with blood lead levels of less than 25 µg/dL. [7] EDTA is approved for treatment of recent, high-level exposure to lead causing toxicity in brain and other organs. Such recent and high-level toxicity is not seen in patients being treated for atherosclerotic cardiovascular disease. [8]

Low-level environmental exposures of toxic metals cause small amounts to accumulate in everyone, usually at levels below the threshold for toxicity. There is no solid evidence to support the theory that benefit from EDTA
chelation in cardiovascular disease results from removal of xenobiotic metals—although this is a preferred theory of most chelationists at this time. In fact, EDTA chelation does not significantly remove chronic lead deposits from the body.

During acute lead toxicity following a high-level, recent exposure, EDTA can rapidly lower lead levels in body fluids surrounding soft tissue organs. Over the long-term, however, low levels of lead are tightly sequestered in bones and teeth where lead cannot be chelated by EDTA. Infused EDTA remains in extracellular fluids. EDTA does not enter cells and bones significantly.

Correlation, By Itself, Is Not Good Evidence For Causation

In March, 2018, Dr. Lanphear and associates in Vancouver, Canada, published a frightening study suggesting that 400,000 deaths per year in the USA are caused by low-level lead toxicity. The news media immediately picked up on this issuing sensationalistic headlines. Careful review of that study data, however, reveals a number of flaws. The conclusions are not well supported by the data. [9]

Blood lead samples were obtained 30 years prior to publication, at a time when residual contamination from leaded gasoline, leaded paint, lead in plumbing fixtures, etc., was much higher. Lead levels were correlated with deaths only 20 years later.

More importantly, Table 1 shows that blood lead increased consistently with age (p<.0001). Study subjects ranged in age up to 90 years old. We know that cardiovascular deaths increase with age and also that the most common cause of age-related death is cardiovascular disease.

Therefore, what this study actually shows is that all-cause mortality and cardiovascular deaths increase with age, which will surprise no one. Because age correlated with blood lead, deaths also correlated with lead.

The authors themselves, in their conclusion, state that these findings only "suggested" that low-level lead was a risk factor. They openly acknowledge that correlation, by itself, is not good evidence for causation.

Low-level lead toxicity is sometimes attributed to lowering of enzyme activity, with no other evidence for an accompanying disease and no symptoms of illness. Whether that represents true toxicity is moot. For example, decreasing activity of alkaline phosphatase, a zinc containing enzyme, correlates with very low levels of blood lead, but with an absence of any other evidence of illness.

Lead competes for zinc in metalloenzymes, blocking enzyme activity. Zinc deficiency can therefore be confused with lead toxicity. Similar conditions relate to calcium, iron, and copper nutriture.

Chlamydia as a Cause of Cardiovascular Disease
Many published studies have linked CP to atherosclerosis. [1-4] A literature search brings up a very large number of references. The data are inconsistent and not all studies confirm an association. Contradictions become understandable with newer discoveries concerning the complex growth stages of CP.

Ninety percent or more of the population eventually becomes infected with CP, usually in childhood, which persists throughout life. The incidence of infection increases with age and correlates well with atherosclerosis. CP remains in the body for decades, probably for life, in a low-grade, inflammatory state, periodically becoming dormant, then cyclically reactivating.

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 somewhat susceptible to antibiotics—although not during the dormant stages of its life cycle.

The initial, acute phase of a CP infection commonly lasts for only a week or two, and is usually respiratory. It can be relatively mild or even unsuspected, following which the organism migrates throughout the body via monocytes (macrophages). It hibernates as inert, cryptic, and immunologically attenuated intracellular inclusion bodies. These inclusions are persistent and periodically reactivate as infections. They can hide away for decades, possibly a lifetime, causing chronic, low-grade, lingering symptoms. Traditional risk factors for atherosclerosis may trigger reactivation of CP in a variety of ways. Atherosclerosis develops slowly, and it is proposed that this may be a host responses to injury caused by a sustained, low-grade CP infection.

This is only a theory. The study of CP is complex and only partially understood at this time. Because virtually every adult harbors CP, with or without atherosclerosis, research into the presence or absence of CP has been frustrating and thus far has not proven causation.

The slow, chronic, long-term, multiphasic, and variable nature of intravascular CP prevents use of Koch's postulates, despite the infectious nature of this agent. Traits of CP that may cause atherosclerosis require the presence of metalloprotein co-factors, that can be 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. [9,10,11]

It is counter-intuitive, but factual, that the inside diameter of a sclerotic blood vessel need only be increased by approximately 10% to double the flow of blood. Poiseuille's Law of hemodynamics (a fourth power equation) shows that with perfect laminar blood flow, a mere 19 percent increase in the diameter of an artery doubles the rate of flow, all other factors remaining constant. In a disease vessel with turbulent flow around plaque, doubling of flow can result from less than a 10% increase in vessel diameter. With compromised circulation, an increase in blood flow of less than that could bring functional improvement and some relief of symptoms. Changes in diameter of such small magnitude cannot be detected on arteriograms or other forms of imaging. Elimination of CP might mediate such benefit and reduce risk of acute events. Merely smoothing over the rough surface of a plaque, converting turbulent flow to laminar flow could have important benefit. It is theorized that the anti-chlamydia properties of EDTA can reduce plaque size and turbulence, stabilizing against disruption.

CP most usually 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. [11]

Tobacco smoke causes significant carbon monoxide to form carboxyhemoglobin, reducing oxygen tension. Bacteria grow better in a slightly reduced oxygen environment.

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

Atherosclerosis progresses more rapidly with diabetes. Elevated glucose levels promote bacterial growth.

CP needs iron for survival. Atherosclerosis is associated with increased iron levels. EDTA strongly chelates iron. The Chlamydia growth cycle has been disrupted by iron chelation, using deferoxamine, an iron chelator. [12] EDTA is also a strong iron chelator.

EDTA chelation therapy requires 30 to 40 slow, infusions, lasting for 3 or more hours. Full improvement does not occur for several months following infusion. Any proposed mechanism of action must take that delay into consideration. If harmful effects of CP are blocked, healing of infected tissues could require such time.

Although EDTA remains extracellular, a powerful extracellular-to-intracellular
diffusion gradient is created during the infusion. EDTA remains in its highest concentration in circulating plasma, in close contact with artery walls. Plaque is a diseased form of tissue, resembling scar, and does not possess a normal cell membrane. Infused intravascular EDTA can diffuse into plaque and attack sequestered microorganisms. [13] Disodium EDTA also removes calcification from plaque, which further increases permeability to EDTA. That does not occur with calcium EDTA. Calcium EDTA has never been shown effective in a clinical trial, although anecdotal reports do support benefit.

Although oral EDTA is slightly absorbed by mouth, it is rapidly excreted in urine and blood levels never become high enough to exert a significant chelating effect on plaque. Oral EDTA has never been shown effective in a clinical trial.

Atherosclerosis is considered by some authorities to be a non-specific response to injury of blood vessel walls from a variety of causes. In that context, CP is theorized to cause inflammatory injury and scarring of artery walls, which may become ulcerations, calcifications, fibrosis, and plaques. CP are known to induce macrophages which may become the foam cells associated with plaques. CP is lipophilic and may cause the lipid accumulations found in plaque. CP oxidizes LDL cholesterol which is associated with atherosclerosis. CP releases a variety of metallo-proteins that may potentially injure tissues. Active infection by CP may weaken vessel walls, leading to plaque rupture. CP releases inflammatory “shock proteins” in a cytokine cascade that can disrupt host tissues. CP is believed by some investigators to trigger a coagulation cascade, resulting in local hypercoagulability and thrombosis. CP growth cycles have been reported to be inhibited somewhat by statin drugs, unrelated to cholesterol. CP upregulates production of metallo-proteinases in atheromas, increasing risk of plaque rupture. CP is reported to disrupt apoptosis of smooth muscle cells in vascular walls. CP has been reported to cause thinning of fibrous caps on plaque, facilitating rupture. Microbiologists are encouraged to investigate this theory further, since cardiovascular specialists seem to have given up.

CP has been implicated in many other chronic diseases and autoimmune problems, which may help to explain why such a variety of symptoms have been reported to improve following EDTA chelation therapy. [8,16] Dr. Charles Stratton at Vanderbilt University Medical School, has reviewed extensively the complex and multiphasic CP growth cycle and its various clinical characteristics [14,15]. A final linked reference below describes the medical politics and complexities encountered in a clinical trial related to CP.[16]

The lowest rates of heart disease ever measured were recently reported in the remote Amazon rain forest of Bolivia among people of the Tsimiane Tribe. [17] This primitive tribe is totally isolated and has been in form of quarantine for centuries—with no exposure to infectious diseases common
elsewhere. No other reasons could be found for this finding. It will be interesting to follow these people. If atherosclerosis begins to occur, it will be more evidence of an infectious origin.

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