INTRODUCTION
The discipline of Clinical Metal Toxicology is evolving and the next 10 years are going to be very exciting. The impetus started with a group of advanced thinking doctors working with forward thinking laboratories and pharmacies, like Medaus Pharmacy in Birmingham, Alabama. Over a quarter century ago these physicians formed the American Board of Chelation Therapy. Today it is called the American Board of Clinical Metal Toxicology.

As the story goes, workers were painting warships with leaded paint and became toxic. They began receiving EDTA, a chelating agent, for lead toxicity and it was noted that those who had symptoms of heart disease were showing some improvement. This phenomenon was apparently ignored by conventional doctors but some progressive doctors started using EDTA chelation therapy to treat heart disease. Hence, the smear began! Doctors who did chelation therapy were quacks, charlatans, duping the public. However, not only was a majority of the patients’ cardiac symptoms improving but there were improvements in a myriad of other symptoms and disease processes.

So the line was drawn in the sand. Doctors continued to use chelation therapy to treat their patients, even though they were threatened with loss of their license to practice medicine. They were and still are targeted by medical boards and other establishment organizations.

However, the tide is changing. There presently is a 30 million dollar study, TACT (Trial to Assess Chelation Therapy), to assess the use of EDTA chelation therapy to treat heart disease. We certainly hope that neither politics nor personal prejudices will taint the results of this study.

What are we really looking at when we talk about heart disease or other diseases that respond favorably to chelation therapy? What we are not looking at is an example of acute intoxication with a toxic metal. What we are observing is some contribution to the disease process by an insidious chronic exposure to toxic metals. The slow, behind the scenes, destruction that toxic metals do to our bodies manifests itself in the form of some disease process. Are all diseases caused by toxic metals? Of course not! But toxic metals contribute, sometimes in a small way and many times in a big way to many pathological processes.

SEMANTICS
The current terminology used is heavy metals or toxic heavy metals. Heavy refers to the atomic weight of the element. For example, molybdenum is a heavy but essential metal, while beryllium is a light but very toxic metal. Additionally, essential metals like calcium can be toxic at supraphysiologic levels and chromium as the Cr\(^{+3}\) ion is an essential trace element important for maintaining correct blood sugar levels, but as the Cr\(^{+6}\) ion is a known human lung carcinogen. Also, arsenic which is considered a toxic metal is really a metalloid, not a metal. At this point I am using toxic metals to describe metals with no known biological function that may disrupt essential physiological processes. Examples of this are cadmium, lead, mercury and arsenic.
**TOXIC METALS**

Here is a list of toxic metals: Aluminum, Antimony, Arsenic, Barium, Beryllium, Bismuth, Cadmium, Chromium, Cobalt, Gadolinium, Gallium, Lead, Manganese, Mercury, Nickel, Palladium, Platinum, Polonium, Silver, Thallium, Tin, Thorium, Tungsten, Uranium and Vanadium. I recently added Gadolinium because of the suspected problems with MRI dyes.

**WHAT ARE METALS?**

Chemically, metals including toxic metals are distinguished from non-metals by their capacity to lose electrons, forming positively charged ions, in a chemical process called an oxidation-reduction or redox reaction. When an atom of a metal loses electrons it is being oxidized. The most common example of a redox reaction is the formation of rust. In moist air, iron tends to lose three electrons in a redox reaction with oxygen. When that happens, the iron (Fe) loses electrons (becoming the Fe$^{+3}$ ion) and oxygen picks them up. Arsenic, the metalloid, possesses this property, also.

**WHERE ARE METALS FOUND?**

Metals account for a quarter of the Earth’s mass, but a lower percentage of its crust. Sea water contains trace amounts of metals, as do all living organisms and even dust particles in the air. Volcanoes and natural weathering can release metals into the environment, but human activities now play the major role in dispersing metals on the earth’s surface.

Mining and smelting of metal ores can create piles of waste, or tailings, which often still contain relatively high concentrations of metals that can be carried into watersheds or transported by the wind. Metals are also released into the atmosphere from fossil fuel power plants, trash incineration and combustion of leaded gasoline.

The problem with certain toxic metals is that they tend to form very stable and long-lasting complexes with sulfur in biological molecules, which can disrupt their biological function. In some cases this allows these metals to become concentrated at higher levels of the food chain.

**WHAT ROLE DO METALS PLAY IN LIVING THINGS?**

Many metals play critical roles in maintaining life. Some are important for the structure of biological materials, as calcium is for bone. Other metals stabilize proteins in unique and active conformations or structures. Zinc often performs this function. Magnesium in the form of Mg$^{+2}$ plays a role in balancing the negatively charged phosphates that serves as the backbone of DNA and RNA.

Metals also serve a chemically important role as essential components of many enzymes. These metalloenzymes are involved in the synthesis, repair and degradation of biological molecules, the release and recognition of certain biological signaling molecules, and the transfer of small molecules and electrons in crucial processes such as photosynthesis and respiration. For example, iron-containing hemoglobin transports oxygen in blood.
WHAT MAKES METALS TOXIC?

The toxic effects of most metals can be traced to their ability to disrupt the function of essential biological molecules, such as proteins, enzymes and DNA. Biological molecules have specific structures and certain components that are essential for their roles. If this structure is altered or a specific part of the protein becomes damaged, then it may no longer be able to carry out its necessary role. If a metal ion binds to the amino acids of a protein, the resulting metal-protein complex may lack the protein's original biological activity. Certain toxic metals have a high affinity for sulfur and will bind tightly to the essential cysteine, inhibiting the enzyme from functioning. One toxic metal may also substitute for another similar essential metal. For example, the toxic metals, mercury and cadmium, can substitute for the essential metals, zinc and selenium. Similarly, lead can substitute for calcium and iron.

In some cases the disruption of a few biological molecules has an amplified effect. One example is the transcription factor proteins that, in response to a signal, bind to DNA and initiate the synthesis of new proteins required for development, normal cellular metabolism or response to some stress. Another example is enzymes, the biological catalysts that are needed in only small amounts but which play essential roles in all biological processes. A third example is proteins that are involved in the repair of damage to biological molecules. While most damaged proteins are simply replaced, DNA must be repaired if the information in an organism's genome is to remain intact. Disruption of DNA repair leads to propagation of errors in an organism's blueprint. Living organisms have also developed mechanisms for dealing with certain toxic metals and toxic levels of essential metals.

METALLOTHIONEINS (MTs)

These are low molecular cysteine rich proteins. One of the primary roles of MTs is toxic metal detoxification. Also, MTs are involved in the homeostasis of copper and especially zinc ions. MTs are significant antioxidant and antiapoptotic proteins. They are also involved in the control of the redox status of cells and in energy metabolism. As a consequence of their high cysteine content, they serve as a toxic metal detoxification system for mercury, cadmium and silver. The affinity of the metal ions for the binding sites is: mercury$^{II}$$>$ silver$^{I}$$>$ copper$^{I}$$>$ cadmium$^{II}$$>$ zinc$^{II}$. The goal of the MTs is to do their work in the cytosol and keep the toxic metals away from the mitochondria and nucleus of the cell. With toxic exposure there is an up regulation in production of the MTs.

RESEARCH

There has been a lot of research done on the toxic metals, mostly in animals. It shows that they are endocrine toxic, developmental and reproductive toxic, immunotoxic, cardiovascular toxic, neurotoxic, genotoxic, carcinogenic, hepatotoxic and nephrotoxic. Also, we are seeing more papers in the peer reviewed journals based on live patients.

A study on Marked Elevation of Myocardial Trace Elements (TE) in Idiopathic Dilated Cardiomyopathy Compared with Secondary Cardiac Dysfunction in the journal of the American College of Cardiology in 1999 found that a large, significant increase of
myocardial (endomyocardial biopsy) TE several times normal (mercury at 22,900x, antimony at 12,800x, arsenic at 250x) was present in IDCM but not in secondary cardiac dysfunction and the increased concentration of TE in patients with IDCM may adversely affect mitochondrial activity and myocardial metabolism and worsen cellular function.

**MERCURY**

Some major sources of contamination are fossil fuel burning factories, breast feeding and dental amalgams.

Some of the general symptoms of toxicity are chronic fatigue, not improved with rest, depression, increased irritability, nervous excitability, moodiness, inability to concentrate, loss of memory, insomnia or drowsiness, vertigo, tinnitus, headache, twitching, lack of coordination, gait disturbances, muscle pain and body aches, mild nasal congestion, stuffy nose, hair loss, swollen lymph nodes around the TMJ area with tenderness, dark pigmentation of the gums, tremors, hyporeflexia of the lower extremities, bruxism, and metallic taste in the mouth.

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A study on Methylmercury in the New England Journal of Medicine in 2003 found that the fetal brain is more susceptible than the adult brain to mercury-induced damage and mercury inhibits the division and migration of neuronal cells and disrupts the cytoarchitecture of the developing brain.

A study on Methylmercury & Inorganic Mercury in Pregnant Women & in Cord Blood: From Fish in Environmental Health Perspectives in 2003 found that both hair total mercury and cord blood methylmercury increased with increasing consumption of seafood and that inorganic mercury in cord blood increased significantly with increasing number of maternal dental amalgam fillings.

A study on Mercury’s Link to Heart Disease Begins in Blood Vessel Walls in the International Journal of Toxicology in 2007 found that mercury’s link to heart disease can be traced to activation of an enzyme, phospholipase D (PLD), which triggers a process leading to plaque buildup in blood vessel walls. Types of mercury compounds studied were methylmercury chloride, (environmental), thimerosal (pharmaceutical) and mercuric chloride (inorganic). Chelation & antioxidants helped and this is a model for other toxic metals also.

A study on Apolipoprotein-E Genotyping as a Potential Biomarker for Mercury Neurotoxicity in the Journal of Alzheimers Disease in 2003 found that apolipoprotein-E genotyping has been investigated as an indicator of susceptibility to heavy metal (i.e., lead) neurotoxicity, a statistically relevant shift toward the at-risk apo-E4 groups was found in the patients (p<0.001). The patients possessed a mean of 13.7 dental amalgam fillings and 31.5 amalgam surfaces and confirmation of an elevated body burden of mercury was made by measuring urinary mercury, after provocation with DMPS and this was measured in 150 patients.

A study on Mercury from Fish, Lipid Peroxidation & the Risk of Myocardial Infarction & Cardiovascular Disease & Death in the journal of Circulation in 1995 found that a high intake of mercury from non-fatty freshwater fish and the consequent accumulation of mercury in the body are associated with an excess risk of acute MI as well as death from coronary heart disease, CVD, and any cause in Eastern Finnish men and this increased risk may be due to the promotion of lipid peroxidation by mercury.

A study on Mercury, Fish Oils & the Risk of Myocardial Infarction in the International Journal of Toxicology in 2003 found that the toenail mercury level was directly associated with the risk of MI, the adipose-tissue DHA level was inversely associated with the risk and high mercury content may diminish the cardio-protective effect of fish intake.

A study on Reduced Levels of Mercury in First Baby Haircuts of Autistic Children in the International Journal of Toxicology in 2003 found that, the reduced levels of mercury in the first baby haircut of autistic infants raises clear questions about the detoxification capacity of this subset of infants and despite hair levels suggesting low exposure, these
infants had measured exposures at least equal to a control population, suggesting that control infants were able to eliminate mercury more effectively.

**LEAD**

Some major sources are leaded gasoline, lead-containing paint, cigarettes, water (lead pipes and lead solder), food and air. The half-life of lead in the body is 25 days in blood, 40 days in soft tissue and 20+ years in bone.
Adapted from ASTDR Toxicology Profile for Lead 1989
A study on Blood Lead and Hypertension in Peri-menopausal & Post-menopausal Women in the Journal of American Medical Association in 2003 found that at levels well below the current US occupational exposure limit guidelines (40 μg/dL), blood lead level is positively associated with both systolic and diastolic blood pressure and risks of both systolic and diastolic hypertension among women aged 40 to 59 years, the relationship between blood lead level and systolic and diastolic hypertension is most pronounced in postmenopausal women and these results provide support for continued efforts to reduce lead levels in the general population, especially women.

A study on Blood Lead Below 0.48 μmol/L (10 μg/dl) and Mortality Among US Adults in the journal of Circulation in 2006 found that the association between blood lead levels and increased all-cause and cardiovascular mortality was observed at substantially lower blood lead levels than previously reported and despite the marked decrease in blood lead levels over the past 3 decades, environmental lead exposures remain a significant determinant of cardiovascular mortality in the general population, constituting a major public health problem.

A study on Intellectual Impairment in Children with Blood Lead Concentrations below 10 μg/dl in the New England Journal of Medicine in 2003 found that blood lead concentrations, even those below 10 μg per deciliter, are inversely associated with children's IQ scores at three and five years of age, and associated declines in IQ are greater at these concentrations than at higher concentrations and these findings.
suggest that more U.S. children may be adversely affected by environmental lead more than previously estimated.

A study on Low Level Environmental Lead Exposure and Children's Intellectual Function: an International Pooled Analysis in Environmental Health Perspectives in 2005 found that for a given increase in blood lead, the lead-associated intellectual decrement for children with a maximal blood lead level < 7.5 μg/dL was significantly greater than that observed for those with a maximal blood lead level ≥ 7.5 μg/dL (p = 0.015) and we conclude that environmental lead exposure in children who have maximal blood lead levels < 7.5 μg/dL is associated with intellectual deficits.

**Arsenic**

The use of arsenic is dropping off because of its toxicity. Some major sources are 90% used as wood preservative (although this too is being phased out), silicon based computer chips, feed additive (poultry and swine), cotton fields, chemotherapeutic and some in food and water.

Some of the general symptoms of toxicity are headache, drowsiness, fatigue, chronic fatigue syndrome, confusion, brittle nails, follicular dermatitis, hoarse voice, pigmented spots on trunk, Raynaud's syndrome (poor circulation to extremities), weakness and muscular atrophy and palmar and plantar keratoses, atypical (pre-cancerous) keratoses on hands, feet, and trunk.

One route of elimination of inorganic arsenic which is more toxic than the organic form is \( \text{As}^{5+} \) (Arsenate) to \( \text{As}^{3+} \) (Arsenite) to Methylarsenite (in liver) to Dimethylarsenite which is readily eliminated – urine.

A study on Folic Acid Supplementation Lowers Blood Arsenic in the American Journal of Clinical Nutrition in 2007 found that folic acid supplementation to participants with low plasma concentrations of folate lowered blood arsenic concentrations, primarily by decreasing blood monomethylarsonic (MMAs) and increasing urinary dimethylarsinic (DMAs) acids and therapeutic strategies to facilitate arsenic methylation, particularly in populations with folate deficiency or hyperhomocysteinemia or both, may lower blood arsenic concentrations and thereby contribute to the prevention of arsenic-induced illnesses.

A conclusion in the CA Cancer Journal for Clinicians in 2001 stated that there is strong epidemiological evidence that arsenic is a human carcinogen. Inhaling arsenic increases the risk of lung cancer and ingesting arsenic increases the risk of skin, urinary tract, and lung cancer. Based on this evidence, expert agencies have classified arsenic as a human carcinogen. Because of the cancer risk and other health hazards associated with arsenic, exposures to arsenic should be minimized.
**Cadmium**

It is toxic to every body system and accumulates in body tissue. There is concern about the increase in environmental cadmium that has occurred as a result of its increasing industrial use. Inhaled is better absorbed than ingested. Elimination rate is generally very slow and the toxicity is significantly influenced by dietary intake of other elements such as zinc, copper, and selenium.

Some of the general symptoms of toxicity are fatigue, chronic fatigue syndrome, hypertension (possibly related to increased concentration of cadmium in renal parenchyma), iron deficiency anemia, osteomalacia in parous women over 40 years of age with dietary deficiencies, anosmia (loss of sense of smell), yellowing of teeth, reduced birth weight in newborns, renal colic (with passage of calculi), nephrocalcinosis, hypercalcuria, emphysema and liver damage.

Some of the major sources are drinking water, soft water, causing uptake of cadmium from galvanized pipes, soft drinks from vending machines with cadmium piping, refined wheat flour (increased cadmium:zinc ratio), batteries (Ni-Cd), evaporated milk, many processed foods, oysters, kidney, liver, rice (irrigated by Cd contaminated water), cigarettes and tobacco, super-phosphate fertilizers, cadmium alloys (e.g. dental prosthetics), ceramics, paint pigments (yellow tint) and electroplating.

A study by the National Swedish Institute of Environmental Medicine and Department of Environmental Hygiene concluded that smokers have higher concentration of cadmium in their blood than non-smokers.

**Metal Binding Agents**

They have been developed over the last 50 years. An ideal MBA would mobilize the toxic metal and increase its excretion through the kidneys as a water soluble complex. There have been tens of thousands of metal binders created but only a dozen in use. They are underutilized.

The major natural pathway for excretion of toxic metals is via the liver, gall bladder and into the stool. With an acute toxic overload you can detect metals in the urine.
This is a schematic diagram of how EDTA which has 6 potential negative sites engulfs a metal ion and carries it out of the body via the kidneys.

**EDTA**

In disodium EDTA the sodium was added to make the molecule more water soluble. It is used for treatment of ventricular arrhythmias and hypercalcemia.

Calcium disodium EDTA is used primarily for lead poisoning and does not interfere with serum ionized Ca. It is safe to use in little children. However, all available product is contaminated with aluminum.

EDTA is used intravenously and will bind chromium, iron$^{3+}$, mercury, copper, lead, nickel, zinc, cadmium, cobalt, aluminum, arsenic, iron$^{2+}$, calcium, magnesium and molybdenum.
DMSA

It is used orally and will bind with mercury, methylmercury, copper, lead, nickel, zinc, cadmium, silver, and arsenic. It is 50 times less toxic than BAL and 5 times less toxic than EDTA. It does not affect essential minerals except zinc but less than EDTA. It works extracellular but does cross the blood brain barrier.

DMPS

It is used orally and intravenously and will bind with mercury, methylmercury, copper, lead, nickel, zinc, cadmium, silver, and arsenic. It is less toxic than BAL. It does not affect essential minerals except zinc but less than EDTA. It works extracellular but does not cross the blood brain barrier. It is excreted by the kidneys.

GLUTATHIONE (L-glutamylcysteinylglycine)

Glutathione is found almost exclusively in its reduced form, since the enzyme which reverts it from its oxidized form (GSSG), glutathione reductase, is constitutively active and inducible upon oxidative stress.

Each molecule of a toxic metal takes out 2 molecules of glutathione.
Functions
- Intracellular antioxidant.
- Essential donor of sulfhydryl groups necessary for the detoxification of the liver
- Enables conversion of Phase I Detox products to water-soluble forms
- Facilitates cell carbohydrate metabolism, calcium metabolism, blood platelet and membrane functions.
- Involved in amino acid transport across cell
- Part of the peptidoleukotrienes.
- Cofactor for enzymatic reactions
- Aids rearrangement of protein disulfide bonds
- DNA synthesis and repair
- Prostaglandin synthesis
- Metabolism of toxins & carcinogens
- Immune system enhancement
- Essential for thyroid hormone synthesis of T4 to T3
- Essential for hair growth

ProVocative Urine
Also called a urine challenge, it consists of giving the patient a dose of a metal binding agent (chelating agent) and collecting a urine sample for a set period of time. The urine is then sent to the lab to determine the metals that have been pulled out of the body by the MBA.

This has been recognized as a valid test by the CDC and independent researchers to evaluate the patient’s metal load when one is not concerned about acute toxicity. When used to evaluate smokers we always find high levels of lead and cadmium.

IN CONCLUSION
The bottom line is that we have to get more patients checked for metal toxicity. As discussed we are concerned about chronic toxicity. The science available does correlate with the clinical findings in the office once you start paying attention to metal toxicity. The process of challenging for metals and subsequently treating the patient to remove the metals is a very safe procedure when done properly. Removing this source of oxidative stress and inflammation is certainly a good beginning to ridding your patients of degenerative disease processes. I would encourage any physician interested in learning more about diagnosing and treating metal toxicity to contact the American Board of Clinical Metal Toxicology (www.abcmt.org).

Protocols
Toxic Metal Challenge
- No fish or dairy for 3 days before challenge
- No minerals or SH containing supplements for 24 hours before challenge
Serum creatinine must be normal
Reinforce nutritional status
Collect a pre-challenge urine sample
DMSA 500 mgs. orally
100 cc NS, extract air, add DMPS 125 mgs. and run in over 20-30 minutes
100 cc NS, add Ca Disodium EDTA 3000 mgs. (1 hr.)
Empty bladder prior to IV then collect 6 hour urine sample and ship to lab

DMSA - DETOXIFICATION - 14 DAY CYCLE
No minerals 24 hrs prior to or during taking of DMSA
Avoid fish for 3 days
Oral DMSA at 10 mg/kg tid for 3 days (500 mgs. Max)
Off for 11 days
Average is 5-10 cycles
Take minerals and SH-containing supplements 24 hrs after last dose
Perform provocative test about every 5th cycle

DMPS - DETOXIFICATION - 14 DAY CYCLE
Stop mineral and SH-containing supplements for 24 hours prior to dosing
Avoid fish for 3 days
Oral DMPS at 100-200 mgs tid or 10 mg/kg in 3 divided doses
Take for 3 days followed by 11 days off
Take minerals and SH-containing supplements 24 hrs after last dose
Average is 5-10 cycles
Perform provocative test about every 5th cycle

EDTA (DISODIUM) – TYPICAL IV BAG
500 cc of sterile water
Use 250 cc bag if fluid is a problem
Vitamin C 500 mg/cc, to adjust osmolarity above 290, usually 14 cc – 20 cc (500 cc bag)
Sodium bicarbonate at ½ the EDTA dose in milliliters
MgSO₄ – 4 cc or MgCl₂ – 10 cc
Lidocaine 2% - 2 cc
Heparin 5000 u/cc – 0.5 cc
Calculated dose of EDTA based on height, weight and serum creatinine
B-Complex – 1cc
B1-100 mgs, B2-2 mgs, B3-50 mgs, B5-2 mgs, B6-50 mgs, B12-1 mg, FA-1 mg
GLUTATHIONE INTRAVENOUS

IV Push
♦ Do a 5 cc IV flush of NS or Sterile water
♦ Administer 100 – 1000 mgs slow IV push at end of Challenge IV, EDTA IV or V/M IV to aid in detoxification
♦ Flush line with another 3-5 cc of NS or Sterile water

IV Bag
♦ Use a 100 cc bag of NS
♦ Add 1000 – 2000 mgs. Of GSH
♦ Run in over 30 – 45 minutes

REFERENCES
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