IMMUNOTOXIC METALS: DIAGNOSIS AND TREATMENT WITH SPECIAL EMPHASIS ON AUTOIMMUNITY

Lyn Patrick ND

DISCLOSURES

- Disclosure of Financial Relationships:
  - None
- Off-Label Usage
  - None

LEARNING OBJECTIVES

At the conclusion of this activity, the participant will be able to:

1. Identify conditions found in patients that have allergic/sensitization reactions to metals
2. Identify routes of exposure/avoidance/remediation strategies for toxicants that carry a risk of autoimmune effects.
3. Discuss direct immunotoxicant effects of metals.

WHAT DO THESE GREAT ARTISTS HAVE IN COMMON?

- Rheumatoid arthritis or
- Scleroderma
- Rubens, Renoir, Dufy, and Klee used significantly more bright and clear colors based on toxic heavy metals and fewer earth colors containing harmless iron and carbon compounds. These four painters may have been heavily exposed to mercury sulfide, cadmium sulfide, arsenic sulfide, lead, antimony, tin, cobalt, manganese, and chromium
- Route of exposure?
- Mechanism of action?

Pedersen LM, Permin H. Rheumatic disease, heavy-metal pigments, and the Great Masters. *Lancet*. 1988;1(8597):1267–1269.

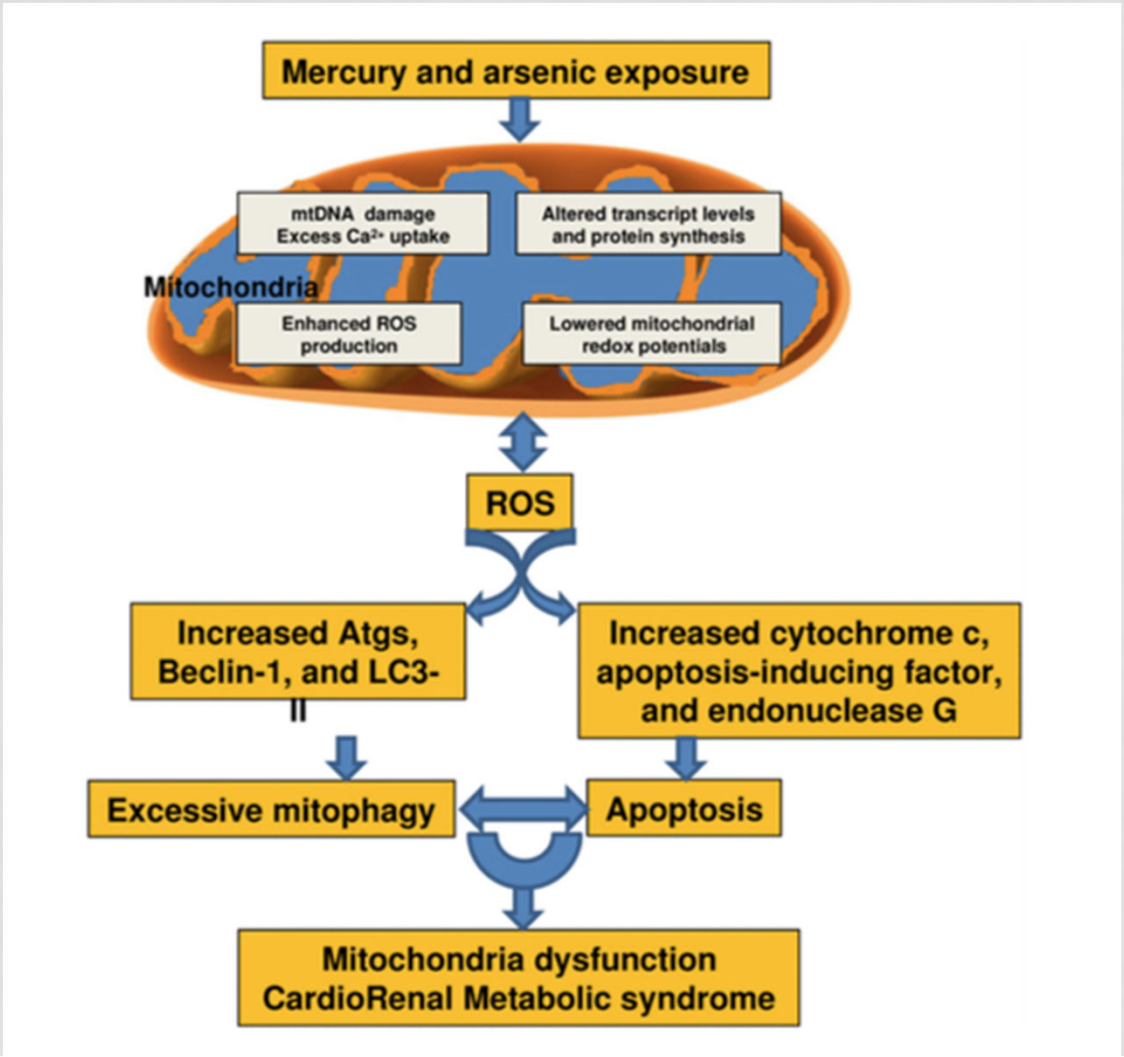
THE BIONIC HUMAN

- 200 various types synthetic (metal and nonmetal) implants used in U.S. today
- Includes dental fillings, metal implants, abdominal mesh, vascular grafts, heart valves, false teeth and eyes, lens implants, artificial joints and repair material for trauma and arthritic conditions.
- The average American has three dental fillings, while 25 percent of the population has 11 or more fillings.
- About 3 million people in the U.S. have dental implants, and another 500,000 implants are placed each year. The majority are titanium alloy.

Ecotoxicology and Environmental Safety, 2016; 134: 213
Br Dent J 218:556 (2015) doi:10.1038/sj.bdj.2015.394

MERCURY AND ARSENIC: MITOCHONDRIAL TOXINS

Arch Toxicol. 2015;89(2): 147-153.



MITOCHONDRIAL DAMAGE

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Arch Toxicol. Author manuscript; available in PMC 2016 February 01.

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Arch Toxicol. 2015 February ; 89(2): 147–153. doi:10.1007/s00204-014-1431-3.

Mitochondrial Functional Impairment in Response to Environmental Toxins in the Cardiorenal Metabolic Syndrome

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MITOCHONDRIAL DAMAGE

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"Mitochondrial dysfunction is recognized as playing a central role in the development of various abnormalities, including disturbed glucose homeostasis, insulin resistance (IR), abdominal fat accumulation, dyslipidemia, hypertension and associated cardiac and renal pathology, all of which characterize the CRS."

METAL HYPERSENSITIVITY/AUTOIMMUNITY: MECHANISMS

- Metal hypersensitivity affects: skin, oral cavity, heart, joints, brain and thyroid gland.
- Mechanism: binding to protein sulfhydryl groups and other protein groups in the mitochondria, enzymes and cell proteins.
- When metals lose the outermost electrons to form metal ions (corrosion, etc.) they become water-soluble haptens, which have strong affinity for the sulfhydryl protein keratin (skin, hair follicle).
- Fat-containing organs such as the brain or collagen-containing structures are especially rich in sulfhydryl proteins.
- Metals can also also bind to -OH, NH_2 and Cl groups in proteins, enzymes, co-enzymes and cell membranes.
- Transition metals can induce free radical formation, inactivate enzyme and mitochondrial activity, and act as triggers of inflammation, hypersensitivity and autoimmunity.

IMAJ 2014; 16: 753–758.

AUTOIMMUNITY: MECHANISMS

- Mast cells are also direct targets for autoimmunity-inducing metals both in vitro and in vivo and play a role in the development of metal-induced autoimmune disorders.
- Mast cells are also direct targets for autoimmunity-inducing metals both in vitro and in vivo and play a role in the development of metal-induced autoimmune disorders.
- Mercury, gold and silver have been shown to modulate mast cell function, including degranulation and secretion of arachidonic acid metabolites and cytokines: interleukin-4.

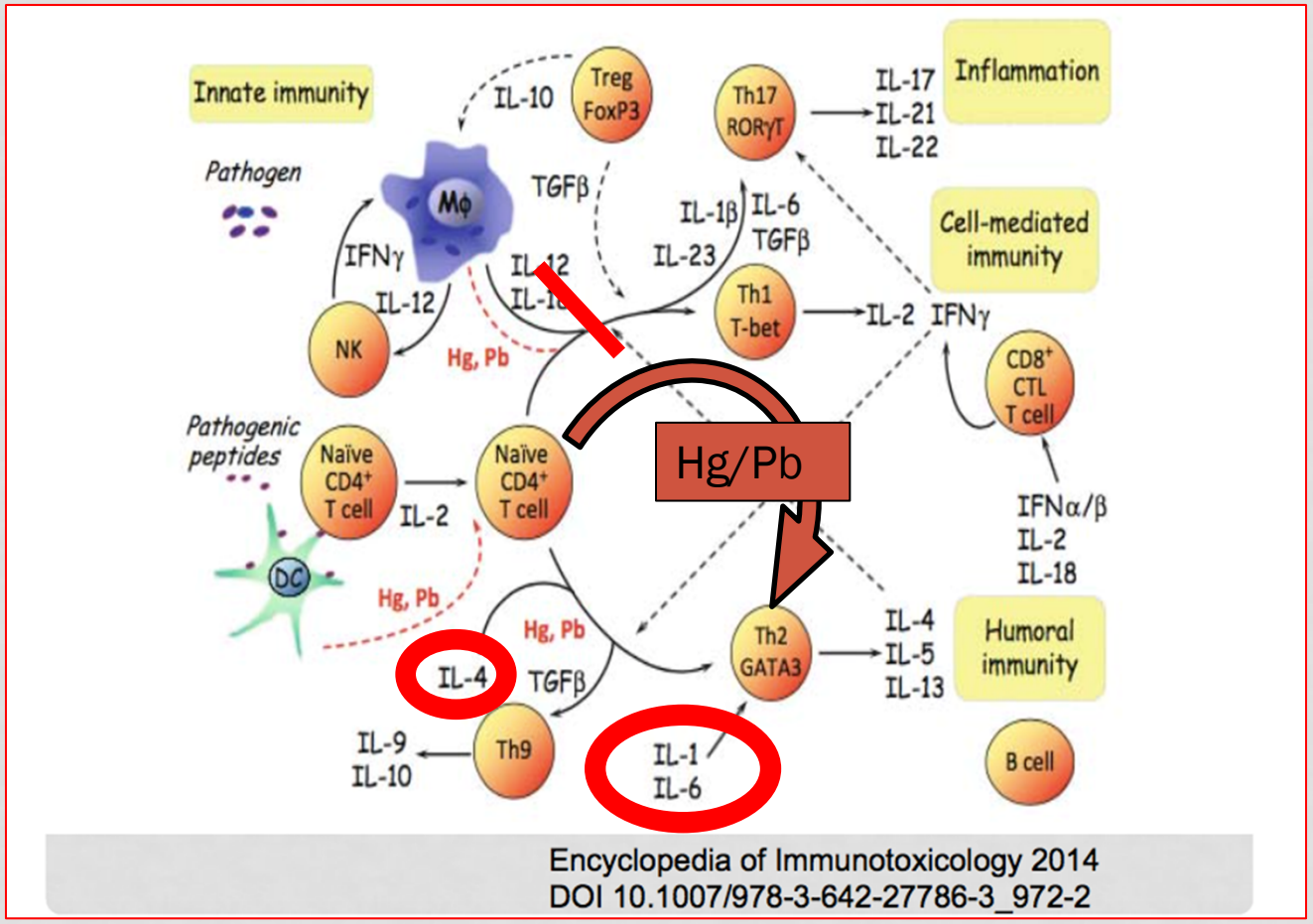
Curr Pharm Des. 2011;17(34):3805–3814

CYTOKINE IMBALANCE LEADS TO AUTOIMMUNITY

- Metals modify cytokine production. The resulting imbalance between Th1 and Th2 activation (via increased IL-4 production) can result in impaired cell-mediated immunity and/or aberrant humoral immunity.
- Lead and mercury have been shown to increase IL-4 production by a Th2 clone (and inhibited Th1 proliferation) *in vitro* and *in vivo*. This suggests that these metals may induce an autoimmune response by dysregulating the balance between Th1 and Th2, which can enhance the production of antibodies to self-antigens Metals can enhance antigen-specific IgE responses from gold salts, mercury, platinum and aluminum.

Int Arch Allergy Appl Immunol 1986; 80:405–11.
Ann Allergy 1978; 40:272–5. Lupus 1994;3(6): 449-453.

METALS INCREASE TH2



PMID 28339013

AUTOIMMUNITY

- Autoimmune diseases are the third leading cause of morbidity and mortality in the industrialized world, surpassed only by cancer and heart disease.
- According to Fred Miller, director of the Environmental Autoimmunity Group at the National Institute of Environmental Health Sciences, “autoimmune diseases are now recognized as among the leading causes of death for young and middle-aged women in the United States” .
- What’s more, prevalence rates for some of these illnesses are rising for what Miller says must largely be “environmental exposure reasons”

Environmental Health Perspectives 2011;112(6):A249.

MERCURY 101

**Organic mercury: methylmercury (fish), ethylmercury (thimerosal in vaccines), phenylmercury (exterior and oil based paints, caulks, eye area cosmetics, and toiletries.)

- Elemental mercury: coal-fired power plants(air), amalgam fillings,

**Inorganic mercury: Hg+2, skin-lightening creams, the form of mercury that dental amalgam mercury becomes in the body very quickly after absorption in the lungs.

Mercury is stored in the liver, kidneys, and CNS as inorganic mercury.

- **these separate form of mercury DO NOT cross-react so have to be tested separately with LLT/MELISA test
- Hg2+ is a stronger autoantibody inducer than methyl Hg

MERCURY IS KNOWN INDUCER OF AUTOIMMUNITY

- Skin-whitening creams, fluorescent tube recycling factory worker-exposure: can induce membranous nephropathy or autoimmune nephritis
- Mercury induces antinuclear antibodies, scleroderma-like disease, lichen planus, or membranous nephropathy in some individuals.
- Mercury can also induce delayed-type T cell hypersensitivity detected by lymphocyte transformation test (LTT-MELISA).

- T-cell hypersensitivity to mercury has been seen in other AI conditions: autoimmune thyroiditis, MS, SLE, psoriasis, atopic eczema

Environ Health Perspect 107(suppl 5):753-765 (1999)./Neuro Endocrinol Lett 2010;31(3):283.

MERCURY AND THYROGLOBULIN AUTOANTIBODY

Relative to women (n = 2047 between the ages of with the lowest blood mercury levels (≤ 0.40 µg/L), women with mercury > 1.81 µg/L (upper quintile) showed 2.24 (95% CI = 1.22, 4.12) greater odds for thyroglobulin autoantibody positivity. No association was observed with TPO antibody positivity.

According to the EPA, safe levels of whole blood mercury are 5.8 µg/L and below. In pregnant women this level drops to 3.5 µg/L and below due to bioconcentration of mercury in the placenta and fetal circulation during pregnancy.

Environ Int. 2012;40:39–43.

MERCURY, GOLD, SILVER

- Hg, Au, and Ag enhance autoantibody levels to a number of autoantigens including fibrillarin, a protein localized exclusively in the fibrillar region of the nucleolus.
- Fibrillarin is the target of autoantibodies in some systemic sclerosis patients.
- With exposure to relatively low doses of Hg2+, the deposition of autoantibody/antigen complexes in organs such as the kidney and brain has been reported to be responsible for the pathology.

J Autoimmun 2012; 39:285–293. NIEHS WORKSHOP ON METALS AND AUTOIMMUNITY

MERCURY, SLE AND RA

Environmental Health

BioMed Central

Research

Open Access

Cluster of systemic lupus erythematosus (SLE) associated with an oil field waste site: a cross sectional study

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* Corresponding author

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Environmental Health 2007, **6**:8 doi:10.1186/1476-069X-6-8

This article is available from: http://www.ehjournal.net/content/6/1/8

Received: 11 May 2006

Accepted: 22 February 2007

MERCURY AND SLE: ODDS RATION OF 19.3
IF YOU LIVE IN THIS SUPERFUND SITE NEIGHBORHOOD

Abstract

Background: This is a community comparison study that examines persons living in a subdivision exposed to petroleum products and mercury.

Methods: We compared their health status and questionnaire responses to those living in another community with no known exposures of this type.

Results: Pristane house dust among the exposed homes was higher than in the comparison communities. The exposed subdivision has higher ambient air mercury levels compared to the control community. The prevalence of rheumatic diseases (OR = 10.78; CI = 4.14, 28.12) and lupus (OR = 19.33; CI = 1.96, 190.72) was greater in the exposed population compared to the unexposed. A higher prevalence of neurological symptoms, respiratory symptoms and several cardiovascular problems including stroke (OR = 15.41; CI = 0.78, 304.68) and angina (OR = 5.72; CI = 1.68, 19.43) was seen.

Conclusion: There were statistically significant differences in B cells, Natural Killer Cells, gamma glutamyl transferase, globulin and serum calcium levels between control and exposed subjects.

LABS IN HOBBS EXPOSED SUBDIVISION VS UNEXPOSED CONTROL

Table 6: Ordinary least squares regression analysis comparing blood results between exposed and unexposed, controlling for age.

Adults	Exposed		Unexposed		Comparison Estimates	
	Number	Mean (SD)	Number	Mean (SD)	Parameter Estimate	P-value
% CD 19 (B-cell)	43	18.07(6.11)	47	14.02(4.68)	3.98	0.0006
% Natural Killer Cells[1]	43	10.77(5.65)	47	14.26(7.33)	-3.41	0.01
Total bilirubin	87	0.61(0.23)	37	0.54(0.16)	0.07	0.12
gamma-Glutamyl transferase (IU/L)	87	40.07(50.25)	37	19.30(11.53)	21.60	0.01
Globulin (mg%)	87	3.02(0.50)	37	2.86(0.34)	0.15	0.09
Serum CALCIUM (mg%)	87	9.71(0.38)	37	9.23(0.36)	0.48	<0.0001
Creatinine Phosphokinase (IU/L)	87	127.44(90.63)	37	110.43(54.02)	16.02	0.32

1. Natural Killer Cells = CD16 + 56+/CD45+
SD = Standard Deviation

MERCURY AND SYSTEMIC CONTACT DERMATITIS

- Source: Hg-containing creams and contact lens solutions, inhalation of Hg vapor and broken thermometers
- Symptoms: nausea, vomiting, headache, malaise, arthralgia, and diarrhea can be related to systemic contact dermatitis
- Mercury is also found in piercings, tattoos, PVC shoes and boots,

Inflamm Allergy Drug Targets 2008; 7 (3): 145-62.

GOLD

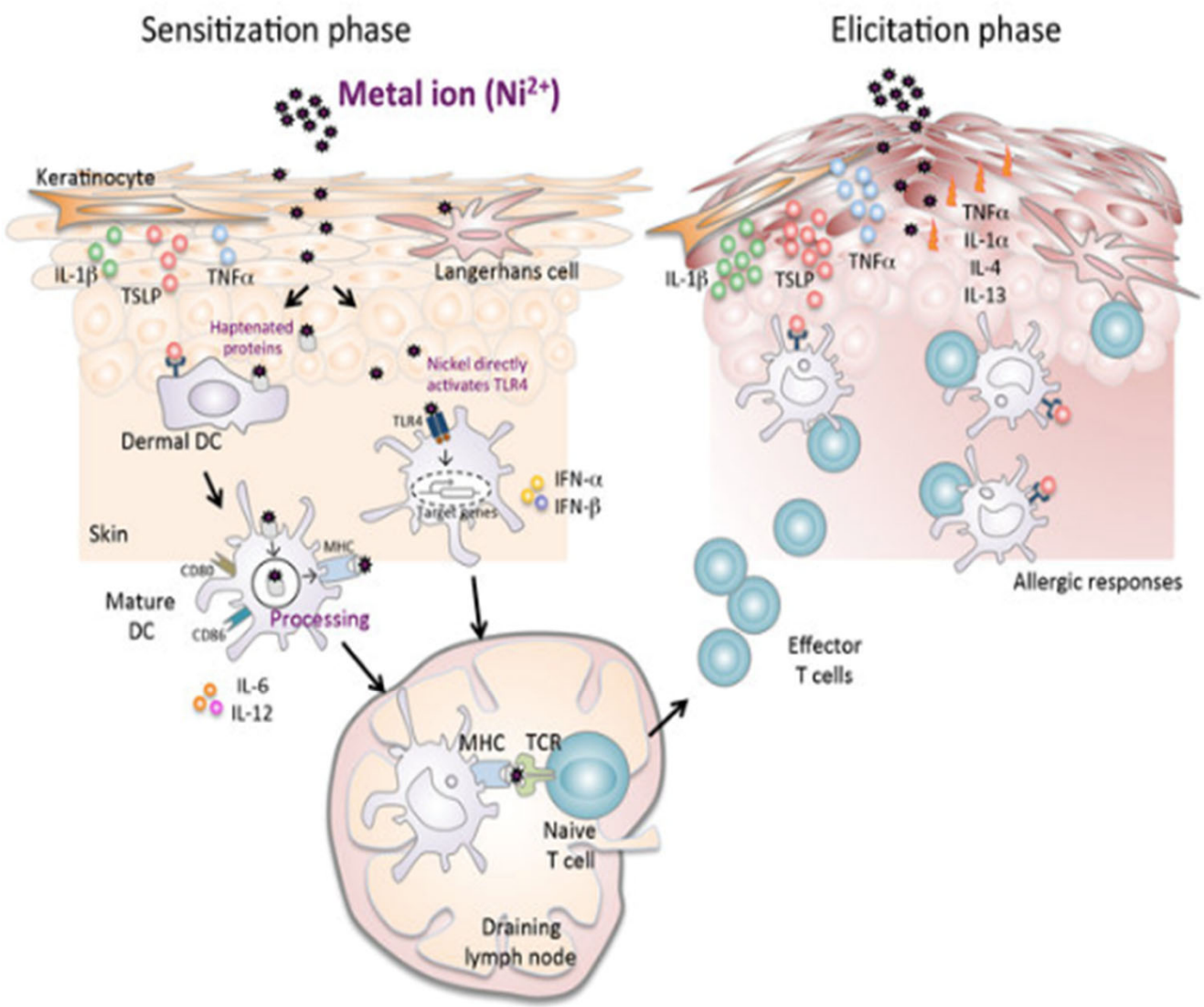
- Gold injections used to treat RA have caused neuropathology, autoimmune thrombocytopenia, and created autoantibodies against the glycoprotein (GP)IIb–IIIa or GPIb–IX and occasionally against GPIa–IIa or GPV of platelets.
- Gold is used in crowns and dentures, bridges, implants and has been shown to oxidize when in contact with amalgam filling (gold crown over amalgam filling).

Blood 2002;100:344–346.
Semin Arthritis Rheum 1985;14:238–246.

DELAYED HYPERSENSITIVITY

- immune response can be mediated by humoral antibodies or by sensitized lymphocytes and can be classified in four types.
- type I is mediated by the release of IgE from the mast cells
- type II is mediated by the production of IgG or IgM after cytotoxic reactions
- type III is mediated by the deposition of the complex antibody- antigen in tissues
- type IV is due to T-cell mediated delayed hypersensitivity reaction

Handbook on the Toxicology of Metals; 2007, pp. 197-211.



International Journal of Molecular Sciences 2016;17(2):202

METAL HYPERSENSITIVITY

REVIEWS

Hypersensitivity Reactions to Implanted Metal Devices: Facts and Fictions

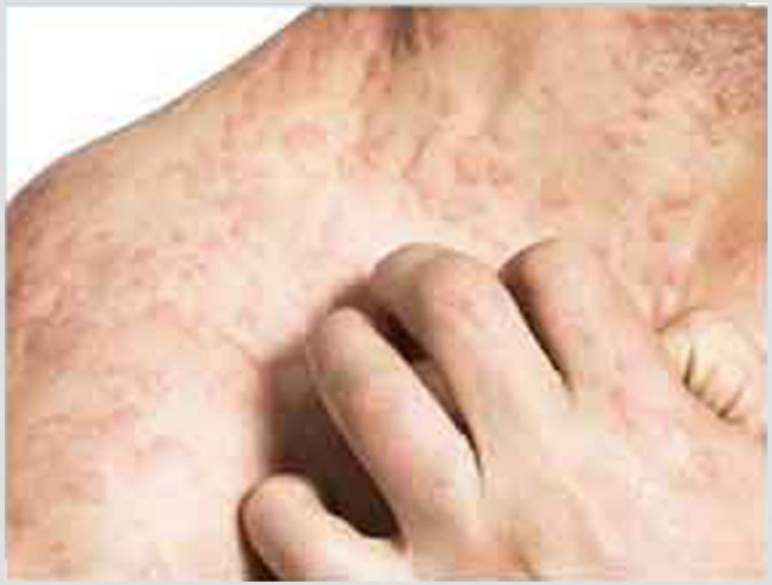
Teo ZWW, Schalock PC

Department of Dermatology, Massachusetts General Hospital, Harvard School of Medicine, Boston, Massachusetts, USA

J Investig Allergol Clin Immunol 2016; Vol. 26(5): 279-294
doi: 10.18176/jiaci.0095

"Dermal hypersensitivity to metal is common and can affect up to 15% of the population"

METAL HYPERSENSITIVITY EXPOSURE SOURCES



Allergic Contact Dermatitis from Nickel Allergy

- Chronic exposure to metals: release of metal ions from corroding dental restorations, orthopedic implants, IUDs, jewelry, vaccines, coated medical pills, foods, cigarette smoke, (cigarette smoke contains: nickel, cadmium, manganese, mercury, lead and arsenic)
- Cosmetic products contain metal pigments, including titanium dioxide, iron oxide, cadmium and lead.
- Contact lens solution, eyeglass frames, sunscreen, toothpaste

IMAJ 2014; 16: 753–758.

AUTOIMMUNE DISEASES LINKED TO METAL EXPOSURE/HYPERSENSITIVITY

- Sjogren's syndrome
- SLE
- Rheumatoid Arthritis
- Hashimoto's thyroiditis
- Oral lichen planus
- Autoimmunity-related chronic fatigue and fibromyalgia
- Membranous nephropathy
- Systemic sclerosis
- Scleroderma-like disease (Hg induces anti-nucleolar antibodies (ANoA), targeted against fibrillarin)
- Autoimmune thrombocytopenia
- ALS
- Immune-complex-mediated glomerulonephritis
- Multiple Sclerosis

Neuroendocrinol Lett 2013;34(6):559–565. Environ Health Perspect 1999;107(suppl5):753-765. Bigazzi P. Autoimmunity induced by Metals. In: Chang L, editor. Toxicology of metals. 1996. p. 835–52 J Neurol Neurosurg Psychiatry 1996; 60:698. Int J Risk Safety Med 1994; 4:229–36. *Neuroendocrinol Lett 1999; 20:351–364* . *Neuro Endocrinol Lett.* 2006 Dec;27(Suppl 1):7-16.

OTHER CONDITIONS RELATED TO METAL SENSITIVITY- ADD REFERENCE

- Fibromyalgia
- Crohn's Disease
- DM type I
- Macrophagic myofascitis
- primary ovarian insufficiency
- depression
- autism
- pancreatitis
- antiphospholipid syndrome
- transverse myelitis
- lymphoma
- POTS (postural orthostatic tachycardia syndrome)
- antiphospholipid antibody syndrome.
- Gulf War Syndrome

Expert Rev Clin Immunol 2013 Apr;9(4):361-73.
Int. Arch. Allergy Immunol. 1996, 109, 11.
.J Autoimmune 2011: 36:4-8

SYMPTOMS WITHOUT OTHER DIAGNOSES

- chronic fatigue,
- cognitive dysfunction
- eczema
- dermatitis
- fibromyalgia
- chronic infections
- chemical sensitivity
- headaches
- severe pain
- autonomic nervous system dysfunction.

IMAJ 2014:16. 753-758.

STEJSKAL, SHOENFELD PIONEERS IN METAL HYPERSENSITIVITY AND ASIA

IMAJ • VOL 16 • DECEMBER 2014

Metals as a Common Trigger of Inflammation Resulting in Non-Specific Symptoms: Diagnosis and Treatment

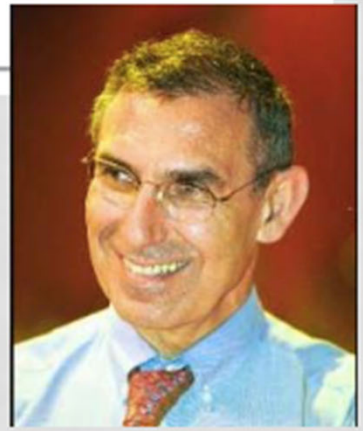
Vera Stejskal PhD

Wenner-Gren Institute for Experimental Biology, University of Stockholm, Stockholm, Sweden

Vera Stejskal PhD
IMAJ 2014; 16: 753–758.

Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) 2013: Unveiling the pathogenic, clinical and diagnostic aspects.

Recently, a new syndrome was introduced, autoimmune/inflammatory syndrome induced by adjuvants (ASIA), that includes postvaccination phenomena, macrophagic myofasciitis, Gulf War syndrome and siliconosis. This syndrome is characterized by nonspecific and specific manifestations of autoimmune disease.



Yehuda Shoenfeld MD

J Autoimmun 2011;36: 4–8.

ASIA: AUTOIMMUNE (AUTOINFLAMMATORY) SYNDROME INDUCED BY ADJUVANTS (J AUTOIMMUN 2011;36: 4–8.)

Table 2 Suggested criteria for ASIA diagnosis

Major criteria	Minor criteria
Exposure to an external stimulus (infection, vaccine, silicone, adjuvant) *prior* to clinical manifestations.	Appearance of autoantibodies or antibodies directed at the suspected adjuvant.
Appearance of one of the clinical manifestations listed below: myalgia, myositis, or muscular weakness. Arthralgia and/or arthritis. Chronic fatigue, non-restful sleeps, or sleep disturbances. Neurological manifestations (especially those associated with demyelination), cognitive impairment, memory loss. Pyrexia. Dry mouth.	Other clinical manifestations (i.e., irritable bowel syndrome).
Removal of inciting agent induces improvement.	Specific HLA (i.e., HLA DRB1, HLA DQB1)
Typical biopsy of involved organs.	Evolvement of an autoimmune disease (i.e., multiple sclerosis, systemic sclerosis).

There must be the presence of at least two major or one major and two minor criteria.

Silicone, aluminum, mercury, infection

METAL SENSITIZATION CAVEATS

- Sensitization to metal can develop years after an implant or device has been placed and that adverse effects can occur *with or without* the sign of a rash or eruption on the skin or in the mouth. PMID: 21957996
- Sensitization appears most frequently after the amalgam has been present in the mouth for more than 5 years PMID: 5262217
- Hypersensitivity reactions can be misdiagnosed as infection PMID: 21957996

SENSITIZING METALS

- Nickel*, aluminum, beryllium, cadmium, chromium*, cobalt*, copper, gold, iridium, inorganic mercury, ethylmercury (thimerosal), palladium, platinum, rhodium and titanium
- Incidence of contact dermatitis in U.S. :14% for Ni, 4 % for Cr and 9% for Co
- *potent skin sensitizers
- Frequent sensitizers (in red)
- In 1998–2000, gold ranked as the sixth most frequent cause of positive patch test reactions.
- The prevalence of titanium sensitivity is increasing due to increased us of titanium alloys as dental implants and other prosthetic devices.

Inflamm Allergy Drug Targets 2008; 7 (3): 145-62.
Neuroendocrinology Letters. 1999;20(5):289-98.
Vaccines and Autoimmunity. 2015 May 11:57.
The Israel Medical Association Journal: IMAJ. 2014 Dec;16(12):753-8.

Abridged List of Metals Used in Dentistry and Medicine
Compiled by the International Academy of Oral Medicine and Toxicology (IAOMT)
April 2018

Product	Metals
Dental Bridges, Crowns, Partial Dentures, and Implants	□ These items can contain aluminum, chromium, cobalt, copper, gallium, gold, indium, iridium, iron, manganese, nickel, palladium, platinum, silver, titanium, vanadium and more.[1] [2] [3] [4] □ Items made of cobalt-chromium-molybdenum steel contain those elements in addition to aluminum, nickel, titanium, and others.[5] □ Research has found that some of these dental materials can contain lead.[6]
Dental Fillings	□ Amalgam (silver) fillings contain about 50% mercury mixed with copper, silver, and tin, and they can also contain zinc[7] and other metals,[8] including lead and cadmium.[9] □ Some composite fillings, as well as dental cements and root-fillings, can contain titanium dioxide.[10] □ Dental gold alloys can also contain copper, gallium, indium, iridium, palladium, nickel, silver, tin, titanium, and zinc,[11] as well as beryllium.[12]
Gynecologic Devices	□ Some intrauterine devices (IUDs) contain copper,[13] and possible contaminants include manganese, nickel, and zinc.[14] □ Permanent contraceptive devices and clips (i.e. tubal ligation) can contain nickel and titanium.[15]
Intravascular Devices (i.e. coronary stents, perforated foramen occluders, pacemakers, and implantable defibrillators)	□ Cardiac/intravascular devices can be made of stainless steel[16] [17] (which can contain chromium, manganese, molybdenum, and nickel[18]). □ They can also be made of chromium, cobalt, molybdenum, and/or nitinol (which is 45% nickel and 55% titanium).[19] □ Stents can be coated in gold.[20] □ Pacemakers can contain aluminum, nickel, and titanium,[21] and can be coated in gold.[22]
Medication	□ Pills can contain titanium dioxide and other metal oxides.[23] □ Antacids can contain aluminum.[24]

Orthodontic Appliances (i.e. bands, braces, brackets, retainers, and wires)	• These can contain nickel[25 26 27 28] and titanium.[29 30] • They can also contain aluminum, chromium, cobalt, copper, iron, molybdenum, niobium, and vanadium,[31] as well as silicon and other elements.[32]
Orthopedic Implants (i.e. hip replacements, screws, nails, and clips)	• These often contain chromium, cobalt, nickel, and/or titanium.[33] • Items made with stainless steel[34] contain a large amount of nickel[35] with chromium, manganese, and molybdenum,[36] in addition to other elements.[37] • Items made with cobalt-chromium molybdenum steel contain those elements in addition to aluminum, iron, manganese, nickel, titanium, and tungsten.[38] • Items made with titanium can also contain aluminum, vanadium, trace amounts of nickel,[39] and other elements.[40] • Items made with nitinol contain nickel and titanium.[41] • Items made with Vitallium™ contain cobalt, chromium, manganese, molybdenum, iron, and other elements.[42]
Surgical Clips and Staples	• Items made with stainless steel can contain chromium, manganese, molybdenum, nickel, and other elements.[43] • Items made with titanium alloy contain aluminum, nickel, titanium, and vanadium.[44]
Vaccines/Flu Shots/Immunoglobulin Preparations	• These can contain aluminum[45 46] and/or mercury (as thimerosal).[47 48 49]

STENTS (Bare metal and drug-eluting)

Cobalt chromium alloy ASTM F75

Metal	%
Chromium	28.5
Molybdenum	6
Nickel	0.25
Manganese	0.5
Tungsten	<0.2
Cobalt	Balance

Stainless steel 316L

Metal	% average
Manganese	2
Chromium	17
Nickel	12
Molybdenum	2.5
Iron (not tested in MELISA)	Balance

Nitinol

Metal	% average
Nickel	50
Titanium (dioxide and sulphate)	50

Platinum chromium

Metal	% average
Platinum	33
Chromium	18
Molybdenum	3
Manganese	1
Iron (not tested in MELISA)	Balance

TESTING

- Patch testing- gold standard among allergist for metals, can't test titanium using patch testing
- LTT- lymphocyte transformation test originally toxicology test for beryllium sensitization in workers currently done by https://www.orthopedicanalysis.com
- MELISA- originally used for beryllium testing but adapted for mercury and many other metals only lab is in Germany: melisa.org
- IgG/IgM- for metals and dental materials by dental labs: Clifford Consulting and Research Labs http://www.ccrlab.com/downloads.html and Biocomp Labs- https://biocomplabs.com/about

  Dental material compatibility testing using IgM/IgG antibody responses

  Possible issue with IgG/IgM : Possible issues w false positives due to cross-over reactions with metal haptens
- ACT/ELISA- lymphocyte activation test developed by Russell Jaffe MD and available through ELISA/ACT technologies but no separate metal panel
- Provocation/Neutralization Intradermal Allergy Testing- subdermal testing done in office by allergy/environmental med docs www.aaem.org

PATCH TESTING

- Gold standard in allergy testing
- If sensitization has already occurred reactions can be significant and test metal materials are absorbed into circulation.
- Concordance with lymphocyte transformation test (MELISA) was good although Stejskal found false negatives when head-to-head testing modalities compared in same population.

Neuro Endocrinol Lett 2006; 27 (Suppl 1): 7–16.

LYMPHOCYTE TRANSFORMATION TESTING MELISA TEST

IMAJ • VOL 16 • DECEMBER 2014

Metals as a Common Trigger of Inflammation Resulting in Non-Specific Symptoms: Diagnosis and Treatment

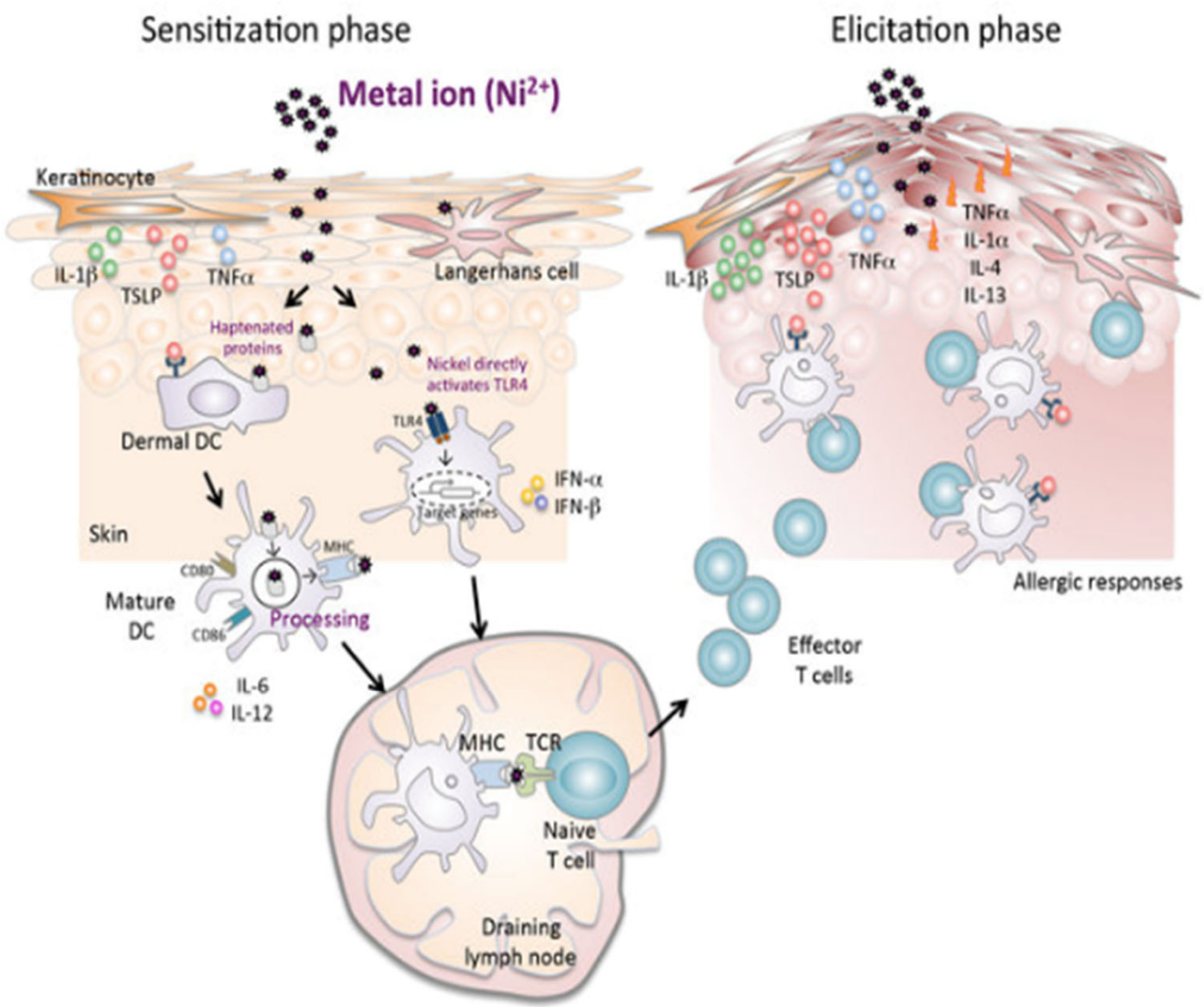
Vera Stejskal PhD

Wenner-Gren Institute for Experimental Biology, University of Stockholm, Stockholm, Sweden

IMAJ 2014; 16: 753–758.

TESTING FOR METAL SENSITIVITY

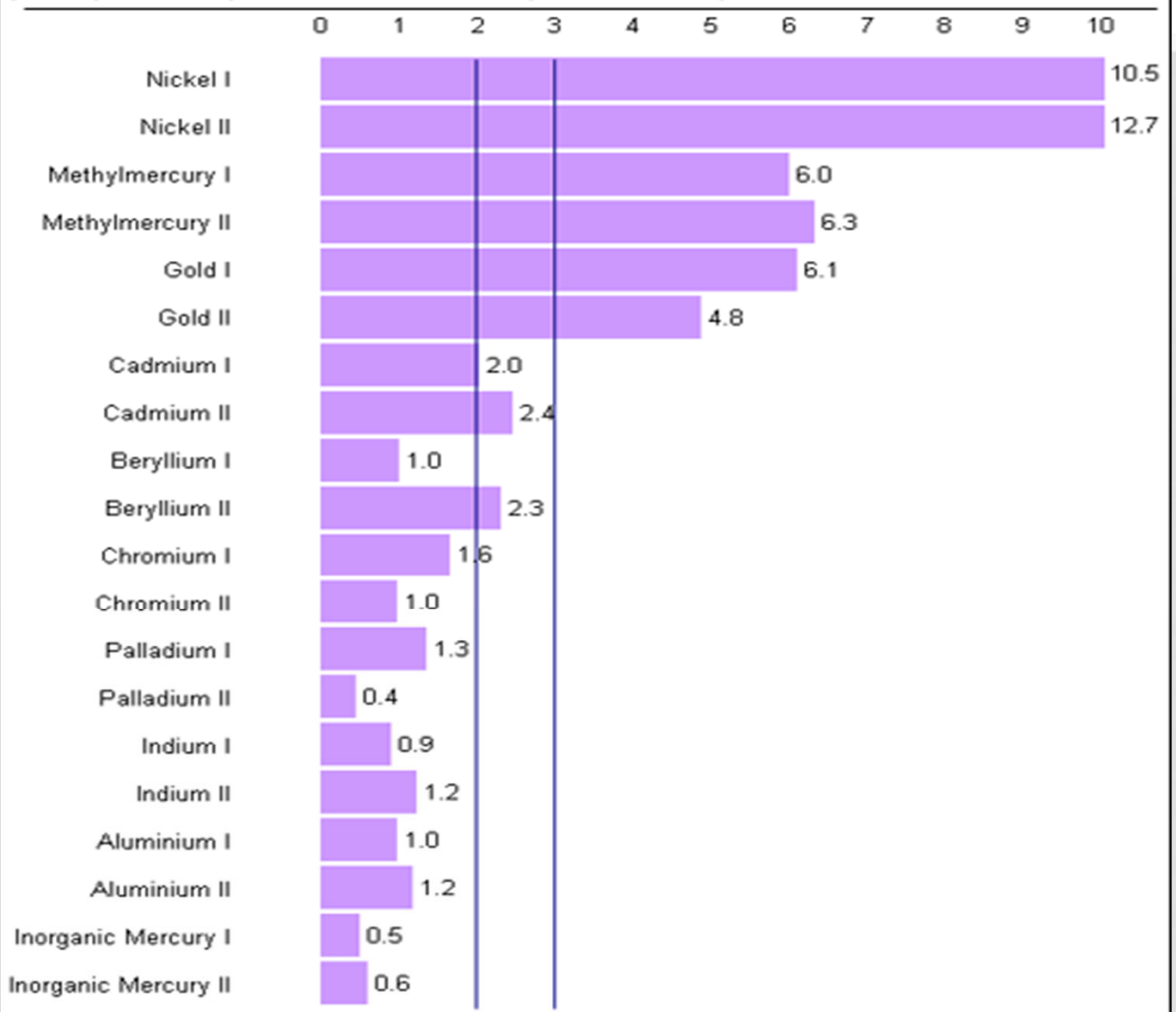
- LTT-MELISA: This test uses the property of memory cells to be re-stimulated by a specific allergen *in vitro*. If memory cells are present in the blood, they start to divide and differentiate to so-called lymphoblasts. When allergens are low-molecular substances, allergen-specific memory cells are found in the blood of patients experiencing exposure-related clinical symptoms but not in the majority of healthy subjects
- lymphocytes are isolated from the blood and cultivated with different metal salts in tissue culture medium containing 10% inactivated human AB+ serum or autologous serum. After 5 days, the presence of metal-reactive lymphocytes are measured by isotope labelling of newly formed DNA in growing lymphoblasts and evaluated by calculating the Stimulation Index.



International Journal of Molecular Sciences 2016;17(2):202

Test report for	Neg. control	Test date	Referred by
Mrs Mary Smith	1,621	May 20, 2007	Integrated Medical Centre

Graph for
MELISA Stimulation Index



METALS TRIGGER INFLAMMATION
INFLAMMATION TRIGGERS AUTOIMMUNITY

Metal-induced inflammation triggers fibromyalgia in metal-allergic patients

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Key words: **fibromyalgia; delayed type hypersensitivity; inflammation; lymphocyte transformation test; MELISA; mercury; metals; nickel**

Neuroendocrinol Lett 2013; **34**(6):559–565 **PMID:** 24378456 NEL340613A10 ©2013 Neuroendocrinology Letters • **www.nel.edu**

15 FEMALE FM PATIENTS 10 CONTROLS

- All FM patients tested positive to at least one of the metals tested. The most frequent reactions were to nickel, followed by inorganic mercury, cadmium and lead.
- Reduction of metal exposure in the FM patients was achieved by replacement of dental metal fillings and by avoidance of known sources of metal exposure.
- Objective examination 5 years later showed that half of the patients no longer fulfilled the FM diagnosis, 20% had improved and the remaining 30% still had FM.
- Metal sensitivity: most common-Ni, Hg (inorganic mercury)
- These findings were confirmed in two other larger studies in women with FM/CFS and confirmed in patch testing studies in FM patients.

Neuroendocrinol Lett 2013; 34(6):559–565.

CASES

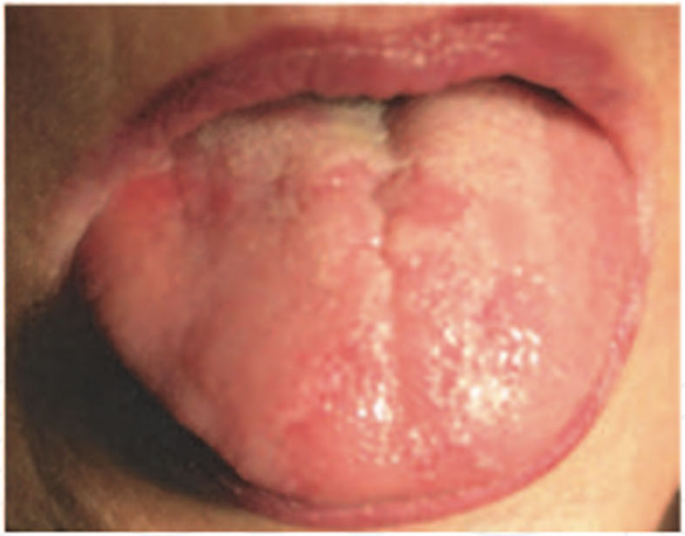


Fig. 5. Depapillation of the tongue, mimicking a geographical tongue, associated with a contact allergy to mercury and gold.

GALLSTONES AND METALS

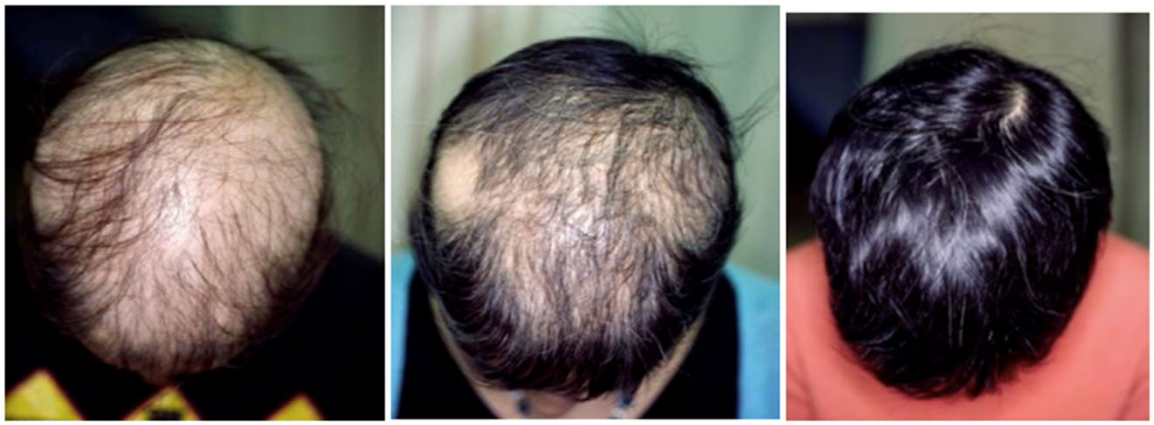
- A 52 year old woman had a history of numerous rashes, hives and recurrent mouth ulcers after having dental work (cavities filled with dental amalgams) at age 10.
- After a tubal ligation with metal clips at age 30, she experienced onset of IBS and subsequent diagnosis of gallstones. She had multiple metal/ceramic crowns placed prior to this diagnosis and at 45 became severely fatigued and was eventually diagnosed with CFS and fibromyalgia.
- MELISA testing was positive for inorganic mercury, palladium, gold, and tin.
- Treatment: removal of metal crowns, amalgams replacement w composites and ceramics.

IMAJ 2014; 16: 753–758.

GALLSTONES AND METALS

- EDX of one of the dental metal ceramic crowns showed that it was made of more than 75% nickel.
- She had GB removal and her nickel-containing clips were removed at that time.
- 3 months post removal of dental materials and ligation clips her oral ulcers and CFS/FM were in full remission, and remained for 3 years of follow-up.
- Her gallstones were analyzed w ICP-MS and were found to contain: nickel (0.1 ppm), mercury (0.1 ppm), tin (0.8 ppm) and molybdenum (0.3 ppm).

IMAJ 2014; 16: 753–758.



6a 6b 6c

- A 44-year-old female **alopecia diffusa** lost her hair in a period of 4 months.
- Corticosteroid injections had been ineffective, she was patch tested and was positive to nickel. Serum ANA was negative, serum γ-globulin was elevated at 21.2%. Serum IgE was 435 IU/ml. She had 3 dental metals in the oral cavity including nickel. After their removal and replacement with ceramics, her hair started to regrow- 6 months later, her alopecia was almost completely remitted and has been in remission for 4 years of follow up.
- **if being ANA positive at 160-320 times serum dilution is a sign of autoimmunity, about 10% of severe alopecia areata should be considered as autoimmunity. (author's comment)

Clin Dermatol Res J 2018;3:1.

7a 7b 7c

- A 28-year-old female with reticular **alopecia areata** x 18 months.
- A patch test showed that she was strongly sensitized to Ni and weak towards Co. Serum ANA was positive at 1:40 (wnl)
- Serum IgE was 840 IU/ml, however, RAST to metals was negative. There were 9 dental metals, and analysis of dental metals showed that Ni and Co were not contained in them, rather 3 out of 5 metallic pans and pots used every day contained Ni and Co at more than 1%. Scratch corrosion was seen on these pans and pots, suggesting the supply of metal allergens to the patient. Removal and replacement with ceramic cooking utensils initiated full recovery.

Clin Dermatol Res J 2018;3:1.

CASE: MISDIAGNOSIS

- While in Argentina in November 2006, a 23-year-old female contracted high fever, extreme fatigue, cervical adenopathies, and transient thrombocytopenia. At the time she was diagnosed with dengue fever; a lymph node biopsy reported ‘reactive hyperplasia’ only.
- In May 2007 she had another 104 degree fever episode, extreme fatigue and general malaise, multiple bilateral cervical adenopathy, and hepatosplenomegaly. Labs: Hgb 8.1 g/dL, WBC 2,500 cells/mm3), positive ANA 1:40 with a speckled pattern, AST 94 IU/L, ALT 33 IU/L, LDH 1,357 IU/L.

Autoimmun Highlights (2013) 4:33–38.

CASE: MISDIAGNOSIS

- She was diagnosed with Adult Onset Still's disease, a diagnosis of exclusion. Episodes of high fever, anemia, muscle and joint pain, and high ferritin occurred in 2008 and 2010 when she lowered her prednisone to 10 mg. or below but responded to IV prednisone.
- MISSING HISTORY: At the age of 19, the patient underwent eye surgery for myopic correction and an abdominal liposuction. At age 22, before all symptoms began in Argentina, she had a nickel–titanium chin implant for cosmetic reasons.
- In Jan 2010 she elected to have implant removed and subsequently went into remission and in 3 months was off of all medication with no symptoms and a ferritin of 25.6 and remained asymptomatic as of follow-up in June 2012.

NICKEL, PALLADIUM, PLATINUM AND SJOGRENS

- A 65 year old woman presented with periodontitis, profound fatigue, atrial fibrillation, lichen planus, cardiomyopathy and Sjögren's syndrome. She had a diagnosis of chronic fatigue syndrome and had daily fainting episodes.
- She had received multiple mercury-containing vaccines in the past, and had several dental amalgams, gold crowns and a metal ceramic crown.
- She reported hypersensitivity to nickel and certain types of jewelry.

IMAJ 2014; 16: 753–758.

NICKEL, PALLADIUM, PLATINUM AND SJOGRENS

- MELISA testing showed a strong reaction to nickel and palladium, and a positive reaction to platinum.
- Her amalgam fillings and crowns were removed and replaced by metal-free alternatives. EDX analysis of four metal ceramic crowns showed that the crown contained 52% palladium.
- After dental restorations and a low-nickel diet all symptoms eventually went into remission including remission of daily fainting episodes and return to normal heart rhythms.

IMAJ 2014; 16: 753–758.

TITANIUM ALLERGY

Kim *et al. International Journal of Implant Dentistry* (2019) 5:10
https://doi.org/10.1186/s40729-019-0162-x

International Journal of Implant Dentistry

REVIEW Open Access

General review of titanium toxicity

Kyeong Tae Kim[1†], Mi Young Eo[2†], Truc Thi Hoang Nguyen[2] and Soung Min Kim[1,2,3*]

"the allergy response to dental implant materials and toxicity of the particles released from implant system are reported to have a role in implant failure."

TREATMENT

- Whenever possible remove the metals from the body
- If that is impossible, measures to desensitize the immune system is recommended: provocation neutralization therapy.
- Zinc supplementation suppresses Th17 development

And T cell activation in relapsing experimental autoimmune encephalomyelitis in SJL/J mice.

-
-

Pers comm Stephanie McCarter MD/Internatl Immunol 2012;22:375–386./ Biometals 2012;25:529–539

This information is current as of January 16, 2020.

Magnesium Decreases Inflammatory Cytokine Production: A Novel Innate Immunomodulatory Mechanism

Jun Sugimoto, Andrea M. Romani, Alice M. Valentin-Torres, Angel A. Luciano, Christina M. Ramirez Kitchen, Nicholas Funderburg, Sam Mesiano and Helene B. Bernstein

J Immunol 2012; 188:6338-6346; Prepublished online 18 May 2012;
doi: 10.4049/jimmunol.1101765
http://www.jimmunol.org/content/188/12/6338

In both mother and neonate-reduced maternal TNF-a and IL-6 production by 60% following in vivo MgSO4 treatment.

These findings establish a new paradigm for innate immunoregulation, whereby magnesium plays a critical regulatory role in NF-kB activation, cytokine production, and disease pathogenesis.

Neuroendocrinology Letters Volume 27 Suppl. 1 2006

Removal of dental amalgam decreases anti-TPO and anti-Tg autoantibodies in patients with autoimmune thyroiditis

Ivan Sterzl[1,2*], Jarmila Prochazkova[3], Pavlina Hrda[1,2], Petr Matucha[2], Jirina Bartova[3] & Vera D.M. Stejskal[1]

- small pilot study of 39 women dx autoimmune thyroiditis
- all underwent MELISA testing for sensitivity to INORGANIC MERCURY (Hg+2).
- group was then divided in those who were MELISA positive for mercury hypersensitivity (n=27)
- and those who were MELISA negative (n=12)
- 15 patients in the MELISA positive group had all amalgam fillings removed and replaced with composite fillings
- Anti-thyroid, anti-Tg, anti-TPO antibodies were measured at baseline and 6 months post-dental restoration

OBJECTIVES: The impact of dental amalgam removal on the levels of anti- thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibodies was studied in patients with autoimmune thyroiditis (AT) with and without mercury allergy.
METHODS: Thirty-nine patients with AT were tested by an optimized lymphocyte proliferation test, MELISA® for allergy (hypersensitivity) to inorganic mercury. Patients were divided into two groups: Group I (n = 12) with no hypersensitivity to mercury and Group II (n = 27) with hypersensitivity to mercury. Amalgam fillings were removed f[illegible] with hyperensitivity to mercury ([illegible]p IIA) and left in place in the remaining 12 p[illegible]ts (Group IIB). T[illegible] laboratory markers of AT, anti-TPO and anti-Tg autoantibod[illegible]ere d[illegible]rmined in all groups at the beginning of the study and six months later.
RESULTS: Compared to levels at the beginning of the study, only patients with mercury hypersensitivity who underwent amalgam replacement (Group IIA) showed a significant decrease in the levels of both anti-Tg (p=0.001) and anti-TPO (p=0.0007) autoantibodies. The levels of autoantibodies in patients with or without mercury hypersensitivity (Group I and Group IIB) who did not replace amalgam did not change.
C[illegible]NCLUSION: Removal of mercury-containing dental amalgam in patients wit[illegible] merc[illegible] hypersensitivity may contribute to successful treatment of autoi[illegible]une thyroiditis.

Removal of dental amalgam and other metal alloys supported by antioxidant therapy alleviates symptoms and improves quality of life in patients with amalgam-associated ill health

Ulf Lindh[1,2], Romuald Hudecek[2,3], Antero Danersund[2], Sture Eriksson[2] & Anders Lindvall[2]

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2. Centre for Metal Biology in Uppsala, Rudbeck Laboratory, Uppsala, SWEDEN.
3. Biomedical Dental Centre, Wallingatan 10, Uppsala, SWEDEN.

Correspondence to: Ulf Lindh
Centre for Metal Biology
Rudbeck Laboratory
Uppsala
SWEDEN

769 patients all referred to the Biomedical Dental Centre due to chronic ill health (chronic fatigue and general “unwellness”)
463 had all metal alloys and dental amalgam in their mouths replaced with non-metal fillings and crowns and follow-up for up to 5 years between 1991-1996. All patients had MELISA testing and were positive for metal allergies. They also had plasma levels of metals drawn before amalgam and crown removal.

Neuroendocrinol Lett 2013; 34(6):559–565

IN ADDITION TO REMOVAL:

- Antioxidant treatment:
- Vit. C 1900 mg. qd
- B-complex (30 mg B1,B2, 150 mg. pantothenic acid, niacin)
- Vit. E 400-600 IU qd
- Selenium as sodium selenite 400 mcg/day
- For those with low B12 in CSF:
- B12 10 mg s.c. per week
- Folic acid- 10 mg. qd

Neuroendocrinol Lett 2013; 34(6):559–565

MOST IMPROVED SYMPTOMS (P<.001) IN 70% OF COHORT

- Muscle pain or discomfort
- Memory impairment
- Inability to concentrate
- Sleep impairment
- Dizziness
- Intestinal symptoms
- “Heart problems” (palpitations, arrhythmias)

GADOLINIUM ENHANCED MRI: SAFETY CONCERNS

- Gadolinium (Gd^{3+}) significantly improves imaging.
  - Inflammation; multiple MRIs common with MS/CNS issues
- Ionic Gd is very toxic- therefore bound to DTPA (*linear* agent), or real chelating agents (macrocyclic) for enhancement of imaging.
- Concern about disassociation, especially w/ **impaired renal function** and **acidosis** (severe hepatic necrosis-free Gd)
- Numerous cases of Nephrogenic Systemic Fibrosis (NSF) with mild to moderate renal insufficiency (GFR> 30 to < 89), but most cases with severe renal failure (GFR < 30), and ***linear*** Gd-complexes
- **ASSESS GFR prior to Gd-enhanced MRIs**

Neth J Med(2008)66:416-22
Magn Reso Imaging(2007)26:1190-7
Brit J Radiol(2010)83:590-5

POTENTIAL TOXIC EFFECTS OF EXCESS GD IN THE BODY (*NORMAL RENAL FUNCTION*)

- General- mineral deposits in capillaries (lungs, kidneys), liver & spleen necrosis, mineralization of gastric mucosa, thrombocytopenia, prolonged prothrombin time, blocks calcium channels, inhibits GABA and glutamate receptors, **accumulates in the brain** (after *linear* Gd-complexes)
- Hepatic-
  - $GdCl_3$ inhibits *phagocytosis* by macrophages *and* decreases *number* of Kupffer cells
  - Impedes biotransformation of xenobiotics (CYP 450s)
  - Inhibits glutathione-S-transferases (Phase II)
  - Inhibits heme biosynthesis & stimulates heme catabolism

Radiology(2015)275:772-82 Acta Biochem Polonica(2000)47:1107-14

CLINICAL MANAGEMENT

Before MRI Imaging

- Question *absolute necessity* for use of a Gd-enhancing agent
- If required consider a **macrocyclic Gd-chelate** (Gadoteridol)
- **Check urine level of cystatin C** ***(or creatinine clearance test)***
- tech will ask "if you have kidney problems, or allergy to Gd" (signed release)

Post-Imaging Support Phases I&II detoxification processes

- Consider pre- and post Ca-EDTA urine Gd at least **96** hrs. after imaging
- Consider IV chelation (Ca-EDTA)- Concern about redistribution?

Neth J Med(2008)66:416-22
* personal communication with Dr. J Hickey (3/29/16)

Slide elements courtesy David Quig PhD

ADD THESE QUESTIONS TO YOUR PATIENT INTAKE FORM

- Do you currently or have you in the past had the following dental procedures: fillings, root canals, bridges, dentures, implants or braces? How many and when?
- OR, if you don't want to do a dental history- work with a dentist who is trained in this area (iaomt.org)

- Have you had any surgical procedures involving: stents, joint replacements, repair of broken bones or fractures, or implantation of silicone, saline, or metal devices (clips, tubal ligation, IUD, etc.)? What and when?

TAKE AWAY

- Removal of device/implant/metal IS the treatment
- If not then chelation and provocation/neutralization therapy has shown efficacy in some of these cases but not all of them

Pers. comm Stephanie McCarter MD

POST-AVOIDANCE TREATMENT

WHEN IS CHELATION NECESSARY?

- Mercury- inorganic mercury (amalgams), methylmercury (from fish) and ethylmercury (vaccines) have long half-lives in brain and kidneys. If patient has significant body burden and is poor detoxifier they may not improve without chelation of mercury (DMSA or DMPS)
- Lead/cadmium are stored in bone and also have long half-lives in organs (bone/liver/kidneys). Lifetime body burdens lead to vascular disease, etc. that may improve with chelation therapy (TACT Trial results) using NaEDTA and magnesium/B vits.

PHARMACOLOGIC ACTION OF CHELATING AGENTS

- Restricted to **extracellular** compartments
- EDTA, DMSA, DMPS cannot cross **healthy** blood-brain barrier
- Provocation levels of elements in urine do not reflect brain levels
- There is significant removal of metals from **kidney tissue** with provocation (1st compartment)
- Optimal nutrient status improves excretion of metals.

Clin Toxicol 2009;47:841-58. J Pediatr 1997;130:996-971. Occup Environ Med 1995;52:13-19. Fund Appl Toxicol 1995;25:233-40. J Pharmacol Exp Ther 1987;243:804.

Metal	1st Choice	2nd Choice
Inorg. Hg	DMPS	DMSA
Org. Hg	DMSA/ DMPS	
Pb	DMSA/EDTA	DMPS
As	DMPS	DMSA
Cd	EDTA	DMPS*
Sb	DMPS/DMSA	EDTA
Sn	DMPS,DMSA	EDTA
Tl	Prussian Blue (K ferric cyanoferrate II)	DMSA

Kemper(1990) Aposhian Toxicol (1995)97:23-38

EDTA STABILITY CONSTANTS: HIGHER = TIGHTER BOND = BETTER CHELATION

Metal	Log 10 K
Ca, Mg, Ba, Sr, Ag, Tl, Cs	< 10
Al, Cd, Zn, Co^{2}	16 – 16.5
Gd	17
Pb, Pd^{2}, Ni, Sn, Cu	18
Ti^{3}	21
Cr^{3} , V^{3} , Th^{4} , Mn^{3} , Fe^{3} , Sb^{3}	23-26
Co^{3}	**41**

www.dojindo.com/Images/Products%20Photo/Chelate Table of Stablity Constants.pdf

cem.msu.edu blamp.sites.trumen.edu

METALS/EDTA CHELATION

- Lead
- Cadmium
- Gadolinium
- Cobalt
- Nickel
- Titanium
- Antimony

CHELATION THERAPY FOR THE TREATMENT OF LEAD POISONING

The **CDC guidelines** for the use of $CaNa_2EDTA$ are as follows:

- Ca2NaEDTA can be administered either IM or IV with a total daily dose of 1,000 mg/m^2.
- The IM dose should be administered with procaine or lidocaine to decrease injection site pain, and the total daily dose is divided into IM injections every 8 to 12 hours.
- IV administration should be diluted in normal saline and given slowly to reduce adverse effects. $CaNa_2EDTA$ is incompatible with 10% dextrose and Lactated Ringer's solution.

CHELATION THERAPY FOR THE TREATMENT OF LEAD POISONING

The **CDC guidelines** for the use of $CaNa_2EDTA$ con't.

- The concentration should be <0.5% to avoid phlebitis.
- The total daily IV dose can be infused over a period of 8 to 12 hours. Treatment is given for 5 days, then is stopped for 2 to 4 days to allow the lead to redistribute.
- A second course of 5 days is then initiated in most cases. The number of courses is determined by the severity of the BLL and the adverse effects of the chelation therapy.
- The use of Ca2NaEDTA alone is not recommended in patients with encephalopathy or with a BLL >70 mcg/dL. It should be given with dimercaprol to decrease lead redistribution into the brain.

EDTA EXPERIMENTAL PROTOCOL FOR TACT TRIAL I AND II

- The TACT chelation infusion protocol includes disodium EDTA, 3 grams, [adjusted downward based on eGFRI] ascorbic acid, 7 grams; **magnesium chloride, 2 grams**; potassium chloride, 2 mEq; sodium bicarbonate, 840 mg; pantothenic acid, thiamine, pyridoxine; procaine, 100 mg; unfractionated heparin, 2500 U; sterile water to 500 mL
- infusion rate of 16.6 mg/min or less which results in only a slight lowering of serum ionizable calcium ion concentration and avoids hypocalcemic reactions.

Circulation: Cardiovascular Quality and Outcomes. 2014;7:15–24.

Enhanced vasculotoxic metal excretion in Post-MI patients after Edetate disodium therapy

Ivan A. Arenas,[1] MD, PhD, Ana Navas-Acien,[2] PhD, Gervasio A Lamas,[1] MD
[1] Columbia University Division of Cardiology, Mount Sinai Heart Institute, Miami Beach, Florida
[2] John Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Mount Sinai

Toxic metals have been ass
morbidity (1). The Trial to As
that treatment with an ed
cardiac events in post-MI pa
excretion of toxic metals e
disease as a possible mecha

Twenty four patients (post-M
were included. Urinary conc
urinary creatinine excretion
following a placebo infusio
dextrose, and for 6 hours fo
infusion as used in TACT (2)

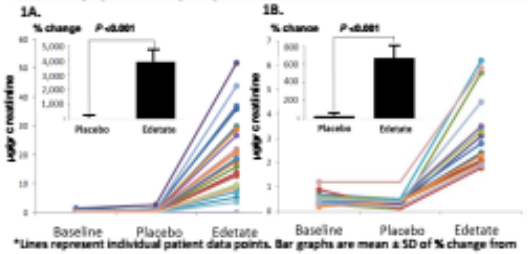
Mean age was 65 years (Ra
60% had history of diabete
Serum creatinine was 0.9
prevalent in the spontaneou
placebo infusion there was
with not significant changes
1.42 mg/g creatinine; 1.6%
total urinary metal excretio
mg/g creatinine; P<0.0001).
(3,887% increase) and Cd (6
moderate increase in Ni (1
(50%) (Figure 2). Gd appe
contrast MRI in the past.

Metal	Baseline urine	Placebo	EDTA
Aluminum (Al)	3.59(2.35–5.87)	4.23(2.95–6.06)	7.97(6.19–10.27)[b]
Antimony (Sb)	0.06(0.05–0.07)	0.07(0.06–0.09)	0.07(0.05–0.09)
Arsenic (As)	17.1(10.3–28.5)	21.5(12.9–35.9)	13.05(6.48–26.30)
Barium (Ba)	0.87(0.54–1.42)	0.74(0.46–1.16)	0.65(0.38–1.11)
Beryllium (Be)	< DL	< DL	< DL
Bismuth (Bi)	0.13(0.06–0.28)	0.17(0.07–0.39)	0.20(0.08–0.47)
Cadmium (Cd)	0.39(0.30–0.50)	0.37(0.30–0.47)	2.18(1.49–3.20)[c]
Cesium (Cs)	5.56(4.68–6.59)	5.84(4.65–7.34)	5.81(4.78–7.08)
Gadolinium (Gd)	0.05(0.04–0.07)	0.06(0.04–0.08)	0.52(0.18–1.54)[b]
Lead (Pb)	0.42(0.30–0.60)	0.43(0.31–0.59)	13.47(8.10–22.41)[c]
Mercury (Hg)	0.39(0.21–0.72)	0.54(0.38–0.76)	0.58(0.41–0.80)
Nickel (Ni)	3.40(2.36–4.90)	2.86(2.04–4.03)	7.52(5.81–9.73)[c]
Palladium (Pd)	< DL	< DL	< DL
Platinum (Pt)	< DL	0.08(0.04–0.15)	0.06(0.05–0.07)
Tellurium (Te)	< DL	< DL	< DL
Thallium (Tl)	0.14(0.10–0.20)	0.16(0.12–0.20)	0.20(0.16–0.26)[a]
Thorium (Th)	< DL	< DL	0.02(0.02–0.02)
Tin (Sn)	0.61(0.40–0.91)	0.59(0.39–0.89)	0.78(0.51–1.19)
Tungsten (W)	0.07(0.05–0.11)	0.07(0.05–0.10)	0.06(0.05–0.09)
Uranium (U)	< DL	0.04(0.04–0.04)	< DL

< DL: Below detection limit. Significant changes from baseline are underlined. Superscript letters indicate P-values for comparisons vs. Baseline:

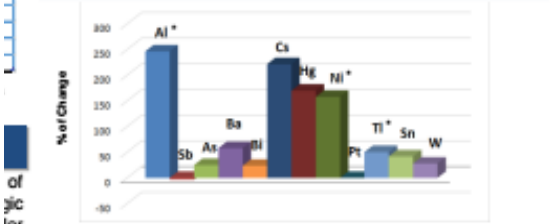
ULTS

Figure 1. Effect of placebo or edetate disodium on urinary lead (1A) and cadmium (1B) excretion* (n=24).



*Lines represent individual patient data points. Bar graphs are mean ± SD of % change from baseline.

Figure 2. Average % change from baseline urinary metal excretion after edetate disodium therapy (Excluding Pb, Cd and Gd; n=24). *P<0.05



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Author Disclosures: IAA: None; ANA: None; GAL: OWNERSHIP INTEREST/PARTNERSHIP/PRINCIPAL-Guided Delivery Systems, Inc

3887% Pb excretion post EDTA
670% Cd excretion post EDTA

246% Al excretion post EDTA
157% Ni excretion post EDTA
50% Tl excretion post EDTA

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DMSA

- **Indications:** FDA approved for the treatment of lead poisoning in pediatric patients with blood lead levels 25- 45 µg/dL
- **Contraindications:** Chemet should not be administered to patient with a history of allergy to the drug
- **Warnings:** Mild neutropenia has been reported in some patients receiving DMSA
  - Check CBC with differential prior to starting treatment

*U.S Department of Health and Human Services. Succimer approved for severe lead poisoning. FDA Medical Bulletin 1991; 21:5

DMSA- DOSING

DO NOT EXCEED 2250 MG TOTAL DAILY DOSE

- Treatment
  - different dosing regimens:
    - 5-10 mg/kg every 12 hours for 2 weeks on, then 2 weeks off
    - 10 mg/kg every 8 hours for 3 days, then 11 days off
    - 100 mg every night M-F, skip weekends
    - 500 mg 3x/day
    - 30 mg/kg divided into three doses/day for 5 days on, then 9 days off
    - 10 mg/kg divided into two or three doses/day for 3 days, then 11 days off (extremely sensitive patients do better with a lower dose and with more days off)
    - Suppository
  - Provide mineral replacement during treatment for all dosing schedules

BMC Clinical Pharmacology

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Research article

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Safety and efficacy of oral DMSA therapy for children with autism spectrum disorders: Part A - Medical results

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- Adams JB, et al.
- Phase I (N=65) [ages 3-8]
  - DMSA—10 mg/kg-dose, 3x/day, 3 days (DMSA compounded)
  - Urine collection after 1st and last dose. (High excretion→ Phase II)
- Phase II (N=49)
  - DMSA/placebo—3 days of DMSA/placebo and 11 days without DMSA/placebo (DMSA dose: 10 mg/kg-dose, 3x/day, 3 days) [tx group received topical GSH before phase I]
- DMSA is safe and effective in removing several toxic metals, normalizing RBC glutathione and platelet counts.

DMSA

- **Dosage and Administration:** (For assessing and treating a toxic heavy metal burden)
  - Ensure adequate hydration, normal kidney function, assessment of CBC, and bowel movements are regular (at least daily)
  - Whole blood lead and mercury and non-provoked heavy metal test prior to starting regimen (WHY?-to rule out current exposure)
  - DO NOT chelate a constipated patient (Phase 3 blockage). Check magnesium levels.
  - Check methylation SNP. Enhance methylation if impaired before starting
  - Ensure adequate GSH levels

DMSA

- **Precautions:** Ensure adequate hydration during treatment
- Transient mild elevations of serum transaminases have been observed in <10% of patients.
  - Check LFT prior to starting treatment
- **Drug Interactions:** None
- **Pregnancy:** Category C
- **Nursing mothers:** If treatment is necessary, mothers should be discouraged from nursing
- **Pediatric Use:** Safety in patients <1 yr has not been established

DMSA

- Adverse Reactions:
  - GI side effects—nausea, vomiting, diarrhea, metallic taste in mouth <10%. Most common: gas/bloating (Peppermint/ginger tea and peppermint tablets often can alleviate GI side effects)
  - Skin—mucocutaneous eruption, pruritus, uriticarial rash, erythematous rash
  - Neutropenia
  - Metabolic- in less than <10%: elevated transaminases (ALT, AST), Alkaline Phosphatase, Cholesterol

DMSA MALABSORPTION

- Unpublished data shows that individuals with positive antigliadin Ab (IgG) do not absorb DMSA efficiently *

The benefits of pre- and post-challenge urine heavy metal testing: Part 1.
Crinnion WJ. Altern Med Rev. 2009 Mar;14(1):3-8. PMID: 19364190

The benefit of pre- and post-challenge urine heavy metal testing: part 2.
Crinnion WJ. Altern Med Rev. 2009 Jun;14(2):103-8. PMID: 19594221

DMPS

- Indications: Used in Germany, Russia and China in acute and chronic poisoning with inorganic and organic mercury as well as metallic **mercury** and **arsenic**, and to a lesser degree—copper, antimony, chromium, cobalt.

- Not FDA approved

DMPS

- Explanation of non-FDA approved status:
  - Classified as safe by the FDA as a bulk ingredient in compounding.
  - Please see complete legal opinion written for College Pharmacy by Howard Hoffman of Duane Morris, LLP (he is a leading authority on FDA law and pharmacy compounding).
    - Ref. Compliance Policy Guide Sec.460.200 Pharmacy Compounding
- If DMPS is used, have patient sign an informed consent.

DMPS

- Contraindications
  - DMPS should not be administered to patients with a history of allergy to the drug.
- Warnings:
  - The urinary excretion of toxic metals as well as trace minerals should be checked regularly
    - Check Packed RBC minerals prior to starting treatment and periodically during treatment.
- Not recommended for use in patients with renal insufficiency (serum Cr > 2.5 mg/dL)

DMPS DOSING

Challenge:

- 5-10 mg/kg po 6 hr urine collection, iv 3 mg/kg 2 hr urine collection.
- pr 10 mg/kg, retained for 30-45 min, 8-12 hr urine collection.

Treatment:

- 1-2 mg/kg po, 3x/day for 3 days 11 days off
- 10 mg/kg, 1x/day pr, 3 days on 11 days off

Max dose: 250 mg IV, 600 mg. po

DMPS SIDE EFFECTS

- gastrointestinal discomfort, skin reactions, mild neutropenia, and elevated liver enzymes.
- Some patients, especially those with allergic asthma symptoms, may develop hypersensitivity to DMPS
- oral administration of DMPS did not adversely affect late gestation, parturition or lactation in mature mice and fetal and neonatal development do not appear to be adversely affected.

Flora SJ, Pachauri V. Chelation in metal intoxication. *Int J Environ Res Public Health*. 2010;7(7):2745–2788. doi:10.3390/ijerph7072745

TREATMENT: MAGNESIUM

- Magnesium lowered by lead, mercury, cadmium toxicity
- Magnesium levels decreased by cyp450 and NAD cytochrome reductase upregulation
- Decreased with needed production of GSH
- Decreased with ATP production
- Supplementation leads to increased cadmium, lead urinary excretion

Magnesium Res. 2004;17(3):183-8 /Proc Soc Exp Biol Med 1986;181:326-32/Med Sci Monit 2001;7(2):332-4

NUTRIENTS TO SUPPORT HEAVY METAL DETOXIFICATION

- N-acetyl-cysteine 1800 mg qd
- Magnesium bisglycinate or citrate/malate- 800-1200 mg.
- R-ALA - 300 mg. (potassium salt form)
- Zinc citrate (picolinate) 15-60 mg. bid
- Selenium- 200 mcg. qd
- Methionine- 150-600 mg.
- Potassium citrate- 2-3 grams daily as Urocit-K (10 mequiv bid to tid to achieve urinary pH of 7-7.5

Int J Environ Res Public Health. 2007 Jun;4(2):132-7
Environ Toxicol Pharmacol 2001;9:173-84./ *Cell Mol Biol (Noisy-le-grand)*. 2004;50 Online Pub:OL543–OL551.

ZINC

- Zinc (15-60 mg as Zinc citrate)
- Zinc supplementation increases the production of metallothionein in the body, providing protection for the kidneys from the movement of arsenic, cadmium, and mercury.
- Zinc deficiency leads to reduced GSH levels
- Co-administration of zinc (10 – 25 mg/kg) and CaEDTA enhances Pb mobilization.

Pharmacol Toxicol 1994;74:330-333. PMID: 7937565

MINERAL REPLETION

- Selenium (selenomethionine): 200 mcg. qd (400 mcg. per day in HIV/hepC)
- Molybdenum- necessary for complete sulfation- 1-2 mg. molybdenum glyinate qd if sulfite sensitive
- Iron (and zinc) are necessary for heme biosynthesis to allow for normal cytochrome production (cytochrome P450 function)

Drug Metab Rev(2011)43:1-26 Cell(2005)122:505-15

RESCUING MITOCHONDRIAL FUNCTION

- Rule out sleep apnea
- coQ10- 60 mg. bid higher for CVD
- R-ALA (R form of alpha lipoic acid) potassium salt- 300mg. bid
- Acetyl-L-carnitine- 500 mg tid
- Magnesium
- Selenium
- Zinc
- Resveratrol- 150-300 mg. qd
- Vit. C
- B complex with high dose B1/pantothenic acid

J Cerebral Blood Flow Metabol 1999;19:528-532/Nutrients. 2016 Mar 9;8(3):150. doi: 10.3390/nu8030150./Sci World J 2013 doi.org/10.1155/2013/219840

CASE: ARSENIC EXPOSURE

First seen in our clinic Feb 2004:

cc: 50 year old Causcasian male, BMI 18

- severe allergies to mold, pollen, food
- chronic sinus congestion
- chronic fatigue sleeps 12+ hours per night,
- depression x 25 yrs, can't stop Effexor or he winds up in bed for 2 weeks crying
- unable to exercise due to mm pain and severe post-exercise fatigue, on pain med for upper back pain
- IBS, multiple food intolerance, constipation/diarrhea
- Hashimoto's thyroiditis dx 2004 on Armour Thyroid

CASE: ARSENIC EXPOSURE

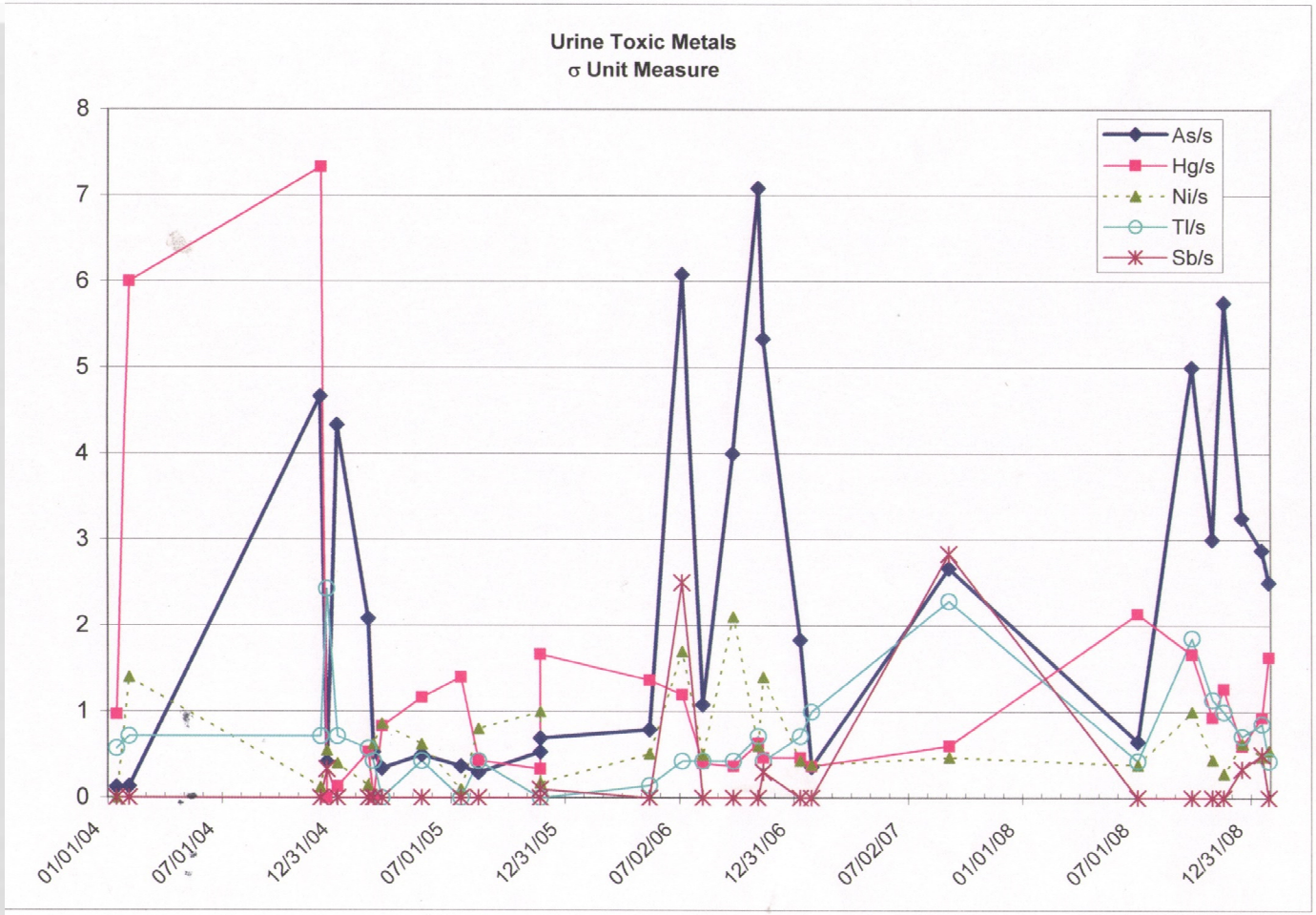
- HPI:
- Lived on golf course in Phoenix AZ for 8 years, had onset allergies and asthma shortly after moving there
- Onset of sx 25 yrs ago when living in Dallas TX, slowly worsening over last 3 years when exposed to forest fires
- Multiple amalgam fillings
- Occupational exposure to: solvents, epoxy, sodering fumes, diesel exhaust, varnishes, MEK
- SNPs: GSTM1-null, COMT+/+, MTHFR+/-(677C-T), NAT2 (I114T, R197Q, K268R) +/-)
- Hx single episode unexplained weight loss at age 32, was hospitalized and given IV nutrition BMI was 13 on admission released with BMI 15

KEY PIECES OF PUZZLE

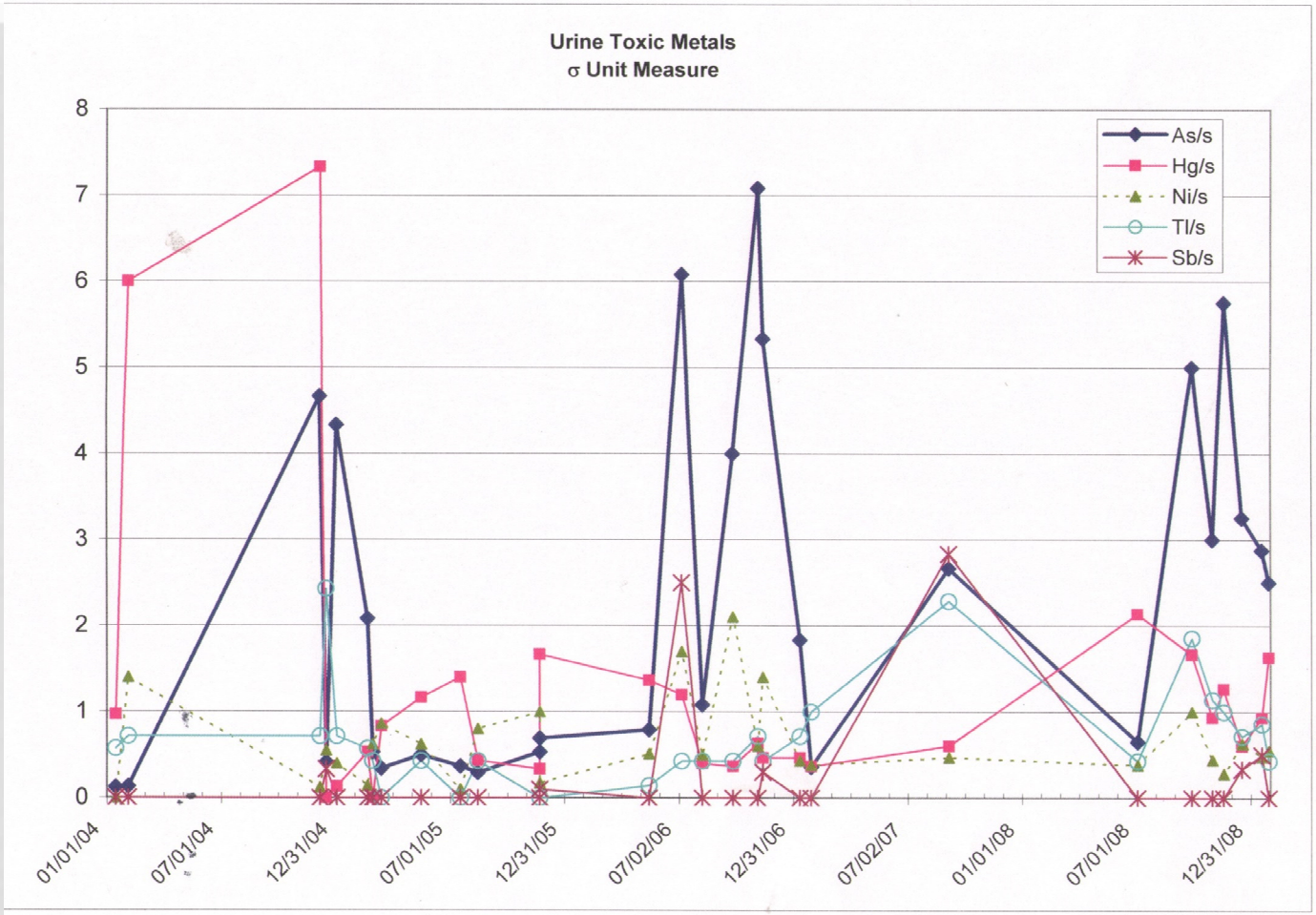
- Amalgam removal 11/04: complete remission of chronic shoulder pain (went off Neurontin that week) after amalgam removal by biologic dentist
- Referred to Environmental Health Center Dallas Nov. 2005 for allergies where he was diagnosed with cotton allergy, multiple food allergic responses based on P/N testing, given oxygen therapy (which he continued as outpatient)
- Told his body burden of PCBs was third highest EHCD has seen and supported to continue sauna therapy we had started him on in our clinic

KEY PIECES OF PUZZLE

- 2006-Home evaluation found mold in structural wood behind walls (leaky window sills), under house and high levels of mold and mold toxins in air testing throughout home
- IQ Air filter in home and remediation through moisture barriers, removal of available wood foundation and drying of structural wood gave him relief from fatigue and allergies
- Eventual diagnosis of chronic Klebsiella/Blastocystis enteritis and in 2006: SIBO tx with Rifaximin

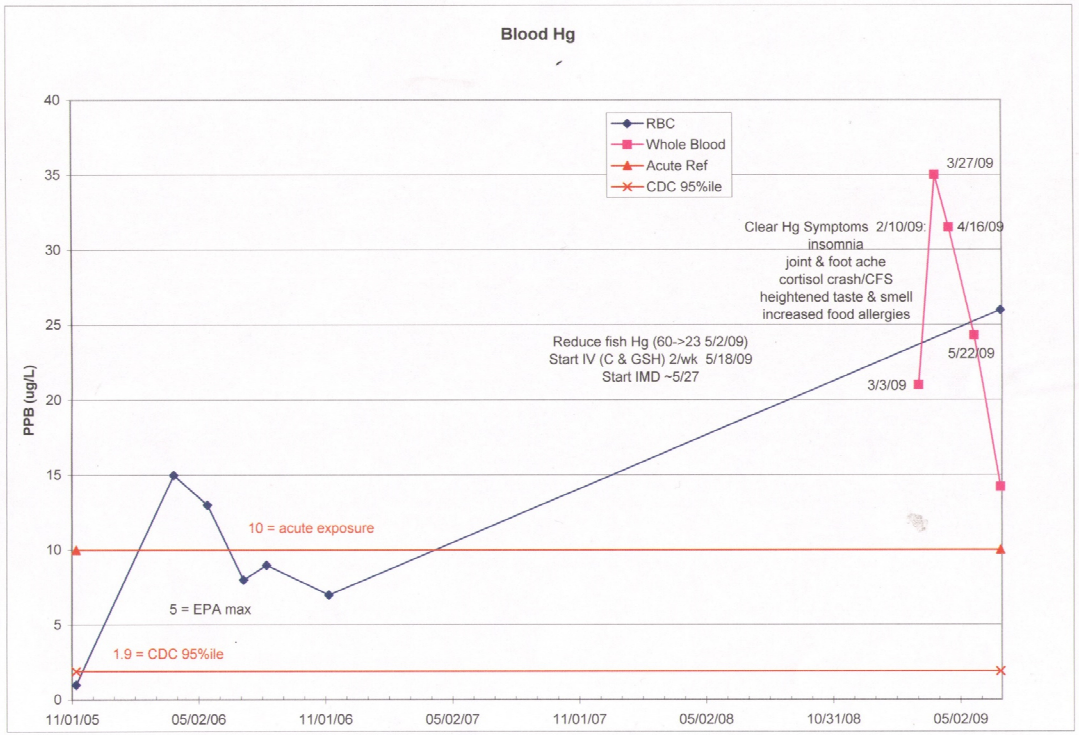

Urine Toxic Metals
σ Unit Measure
8
7
6
5
4
3
2
1
0
As/s
Hg/s
Ni/s
Tl/s
Sb/s
01/01/04
07/01/04
12/31/04
07/01/05
12/31/05
07/02/06
12/31/06
07/02/07
01/01/08
07/01/08
12/31/08

Initiation of Treatment Post-DMSA challenge- 12.04



DMSA PROTOCOL

- Arsenic speciated at Univ. Arizona by Dr. Aposhian and found to be >95% inorganic arsenic
- DMSA 10 mg/kg three times daily (total daily dose is 30 mg/kg max 2750 mg.) 3 days on 11 days off initiated 12.04 and continued intermittently due to complex nature of illness, dx mercury exposure from diet (dx 4.06) and symptoms that may or may not have been side effects from DMSA (fatigue, pain, etc.)
- Methylation support for arsenic removal (MTF, MethylB12, SAMe, liposomal GSH, IV vit. C 20 gms. bimonthly)
- multiple supplements (see supplement sheet)


Blood Hg
PPB (ug/L)
40
35
30
25
20
15
10
5
0
RBC
Whole Blood
Acute Ref
CDC 95%ile
3/27/09
4/16/09
Clear Hg Symptoms 2/10/09:
insomnia
joint & foot ache
cortisol crash/CFS
heightened taste & smell
increased food allergies
Reduce fish Hg (60->23 5/2/09)
Start IV (C & GSH) 2/wk 5/18/09
Start IMD ~5/27
5/22/09
3/3/09
10 = acute exposure
5 = EPA max
1.9 = CDC 95%ile
11/01/05
05/02/06
11/01/06
05/02/07
11/01/07
05/02/08
10/31/08
05/02/09

C:\Documents and Settings\Nick Bartol\My Documents\Medical\[Supplements.xls]Sheet2

Supplement/Drug	5/21/2006 every	even	odd	5/25/2006 every	even	odd	8/13/2006 every	even	odd	9/12/2006 every	even	odd	9/19/2006 every	even	odd	10/13/2006 every	even	odd	rot 4
Cortef (mg)	5			5			5			5			5			5			
Effexor (mg)	112			112			112			112			112			112			
Armor Throid (mg)	30			30			30			30			30			30			
Basic Detox Nutrients	12			12			12			12			12			12			
Folic Acid, Biotech (mg)	100			100			100			100			100			100			
Folinic Acid																			
Mo Citrate (ug)	60			180			180			180			180			180			
CoQ10 (mg)	150			150			150			150			150			150			
Quercetone (Thorne, mg)		500			500			500			500			500			500		
Biotin (ug)	8,000			8,000			8,000			8,000			8,000			8,000			
Ultra B12-Folate																			
Adenosyl/Methyl cobalamin (ug)		2,000			2,000			2,000			2,000			2,000			2,000		
Folate (ug)		400			400			400			400			400			400		
B_2 (Riboflavin, mg)	400			400			400			400			400			400			
P-5-P (B_6 successor, Now, mg)							300			300			300			300			
B_6 has 8 metabolites (of which P-5-P is only one)																100			
Thiocid (Thorne, mg)			600			600													
R-Plus (lipoic acid, mg)		150			150		150			150			150			150			
Vit C (g)	5			5			5			5			5			5			
Vit E (IU)			2,400			2,400			2,400			2,400			2,400			2,400	
Chelated Ca (glycinate, mg)	1,500			1,500			1,500			1,500			1,500			1,500			
Chelated Mg (glycinate, mg)	600			600						400			400			400			
5-HTP (serotonin percursor, mg)	250			250			250			250			250			250			
Thyrosol (tabs)	2			2			2			2			2			2			
NAC (mg)	2,000			2,000			2,000			2,000			2,000			2,000			
Betaine HCl (Now)																			
Betaine HCl (mg)	9,720			9,720			9,720			9,720			9,720			9,720			
Pepsin (mg)	2,250			2,250			2,250			2,250			2,250			2,250			
Probiotics (cap v 1/8 tsp)							1			intermit			intermit			intermit			
Charcoal (mg)	1,120			1,120			1,120			1,120			1,120			intermit			
Melatonin (mg)	3			3			3			3			3			3			
Cu Sebacate (mg)	8			10			10			10			10			10			
Curcumin 97 (mg)	500			500			500			500			500			500			
MSM (Now, mg)	3,000			3,000			3,000			3,000			3,000			3,000			
Cr Picolinate (Klaire, µg)																			1,000
V Citrate (BioTech, mg)																			6.5
Acetyl-carnitine																			
L-Carnitine caps							soon			too many reactions			too many reactions			too many reactions			
α-ketoglutaric acid (mg)																600			
Cytra-K (3.3 g K-citrate, 1 g citric acid)																	4		
Tri-Salts (AEHF, tsp)																		1	
Tri-Salts (Ecol Formula, tsp)																		2	
L-Glutamine Powder Metab Maint (g)							soon			1			3			intermit			
Glucosamine																			
Butyric Acid																soon			
Hypo-Gest							soon			2/meal			3/meal			3/meal			
Pantethine (mg)							soon			soon			soon			soon			
Choline Citrate (mg)							soon			1,300			1,300			intermit			
Fiber Supplement (tsp)							start			too many reactions			wait: intest repair &						
IV $MgCl_2(H_2O)_6$ (g)									2			2			2				2
IV Vit C (g)									30			30			30				50
IM $MgSO_4(H2O)_7$ (g)									1	0.5			0.5			0.5			

Sauna:
α-ketoglutaric acid (mg): 300
Reduced L-glutathione (mg): 75
B3 (Niacin, mg): 100

08Jun 2009 16:17 FROM: LABC[illegible] LCLS BLK TO: 19702479579 LAB[illegible] P
Cedar Diagnostics
To:

Phone: 800-762-4344

Specimen Number	Patient ID	Control Number	Account Number	Account Phone Number	Route
[redacted]		CAW05648375			

Patient Last Name: [redacted]
Patient First Name: [redacted] Patient Middle Name:
Patient SS# | Patient Phone | Total Volume
Age (Y/M/D): 50/06/03 | Date of Birth: [redacted] | Sex: M | Fasting
Patient Address:

Account Address:
Cedar Diagnostics
575 Rivergate Lane #106
DURANGO CO 81301

Additional Information:

Date and Time Collected	Date Entered	Date and Time Reported	Physician Name	NPI	Physician ID
06/04/09 14:55	06/06/09	06/08/09 16:12ET			PATRICK,W

Tests Ordered:
Antiparietal Cell Antibody

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
Antiparietal Cell Antibody	36.3	High	Units	0.0 - 20.0	01
			Negative	0.0 - 20.0	
			Equivocal	20.1 - 24.9	
			Positive	>24.9	

Parietal Cell Antibodies are found in 90% of patients with pernicious anemia and 30% of first degree relatives with pernicious anemia.

01 BN LabCorp Burlington Dir: William F Hancock, MD
1447 York Court, Burlington, NC 27215-3361
For inquiries, the physician may contact Branch: 303-792-2600 Lab: 800-762-4344

11/18/09

\\PSF\Mac\Users\[redacted]ocuments\My Docs\Medical\[Supp[illegible]s.xls]Sheet2

Supplement/Drug	~6/20/2009 every	even	odd	wk	rot 4	~7/10/2009 every	even	odd	wk	rot 4	10/22/09 every	even	odd	wk	rot 4
Hydrocortisone Cortef (mg)	55.0					55.0					25				
Effexor (mg)	0					0					0				
Levothyroxine (ug)	125					125					125				
Armor Throid (mg)	105					105					105				
Testosterone IM (mg)				50					50						
Methyl-cobalomin IM (mg)	1														
$MgSO_4(H2O)_7$ IM (mg)															
Basic Detox Nutrients, Thorne (high grade multi-vitamin)	12					12					12				
B Vitamins															
Folic Acid, Biotech (mg)	100					100					100				
Biotin (ug)	8,000					8,000					8,000				
Ultra B12-Folate															
Adenosyl/Methyl cobalamin (ug)	2,000					2,000					2,000				
Folate (ug)	500					500					500				
Intrinsi B12/Folate (Metagenics)															
L-5-Methyl tetrahydrofolate & 5-formyl tetrahydrofolate)	800					800					800				
Cyanocobalomin	500					500					500				
5-MTHF (Thorne, mcg)	1,000					1,000					1,000				
B_2 (Riboflavin, AEHF, mg)		300					300					300			
B_2 (Riboflavin, Solaray, mg)			600					600					600		
P-5-P (Pyridoxal-5-Phosphate B_6 successor, Now, mg)															
P-5-P (Pyridoxal-5-Phosphate B_6 successor, Klaire, mg)			400					400					400		
P-5-P (Pyridoxal-5-Phosphate B_6 suc., Pure Encap, mg)		400					400					400			
B_6 Pyridoxine HCl	300					300					300				
B_6 has 8 metabolites (of which P-5-P is only one)															
Thiocid ((lipoic acid) Thorne, mg)	0					0					0				
Pantothenic Acid	500					500					500				
Other															
R-Plus (α-lipoic acid, mg)	0					0									300
IMD (intestinal metal detox, non-circulating GSH?) (scoops)		2					2					2			
CoQ10 (UBQH (reduced ubiquinol), 50 mg)			300					300					300		
Vit A															
GNLD Vit A water miscible Pollack Liver (IU)		30,000					30,000					30,000			
Bluebonnet fish liver oil (IU) w/D_3			25,000					25,000					25,000		
Vit C (buffered, bulk; ARG, BBonnet, g)	0					7,000									
Vit E (IU)			2,400			2,400					2,400				
Vit D_3 (IU)															
Thorne Vit D_3 (IU)			10,000					10,000					10,000		
Bluebonnet (w/vit A) Vit D_3 (IU)			1,000					1,000					1,000		
Pure Vit D_3 (IU)		5,000					5,000					5,000			
SAMe (mg)	0					0					0				
Minerals															
Chelated Ca (glycinate, mg)	500					500					500				
Chelated Mg (glycinate, mg)	1,200					1,200					1,200				
Iodoral (iodine, mg)			12.5					12.5					12.5		
Mo Citrate (ug)	180					180					180				
Cr Picolinate (Klaire, µg)					2,000					2,000					2,000

PROGRESS

- Pt went off of all high mercury fish meaning he went EXCLUSIVELY to wild Alaskan salmon, occ. shellfish and meat and stopped swordfish (main source of dietary mercury).
- Blood mercury came down to baseline in 2 months (w continued DMSA)
- In 2009 pt was recovered enough to start exercising on daily basis, was off hydrocortisone 8.09
- Currently asymptomatic started summiting 14'ers (mountains 14,000 feet high in Colorado) and continues to be advocate for environmental medicine