Metal Toxicity and Allergy

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TOXIC METALS

.... may cause allergy and cancer either alone or by enhancing the effects of other agents through some additive or synergistic actions.

Therefore, it is important to study metal interactions.

Acute Cytotoxicity of (and Arsenic) in Control and CAsE Cells
Romach et al reported that chronic arsenite exposure for 18 weeks or more induced malignant transformation in TRL 1215 cells and that self tolerance to arsenic and cross-tolerance to nickel occurs concurrently with transformation (Romach et al., 2000; Zhao et al., 1997)
Environmental Toxins: the challenge of this century

- Toxic metals (lead, cadmium, mercury, arsenic etc) widely circulate in our environment.

- Humans are exposed to metals from numerous sources, including contaminated air, water, soil, food, cosmetics, medicines etc
Hypersensitive patients show increased reactions immunologically and toxicologically
Immunological response increases with exposure

- Nickel allergies used to be much more common among jewelry-wearing females. Cobalt and Nickel allergies were seen mostly in females due to ear-piercing.
- Increased wearing of jewelry among men has increased nickel and cobalt sensitivity.

Ear piercing, and nickel and cobalt sensitization, in 520 young Swedish men doing compulsory military service.

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Metal ion-induced toxic histamine release from human basophils and mast cells.

School of Dentistry, University of Vienna, Austria.

Recent data suggest that distinct metal ions can be released from dental alloys or other biomaterials, and may cause toxic effects on various cells.
Metals presently tested for immunological response are metals used in dentistry and implantology.

**Reason for testing:**

- to identify materials that do not (yet) cause immunological reactions
Metal (and Food) Allergy response is linked to (over)exposure and the body’s inability to deal with toxins and other stressors.
Mercury allergy in a contact dermatitis clinic in Northern Ireland
J. Havadley, D. Todd, D. Borrows
Department of Dermatology. Royal Victoria Hospital, Belfast N.Ireland

ABSTRACT

• Primary sensitization (294 female, 147 male) was most likely due to either inoculation with vaccines containing merthiolate preservatives or amalgam dental restorations.
A negative immunological response to a given metal does not suggest the metal causes no toxic effect.

A non-reactive Immune System does not suggest Health.
Common toxicological reactions to metal overexposure

- Enzyme dysfunction
- Cell death
Global Controversy - how much is safe?

- EPA has calculated a RfD* for methylmercury of 0.1ug/kg body weight/day = 1mcg/day for a child weighing 10kg.

- The World Health Organization (WHO) estimates that a RfD of 0.48 ug/kg bw/day is a more appropriate value = 5mcg/day for same child.

* A reference dose (RfD) is the amount of a substance that, if ingested daily over a lifetime, will have no adverse effect on human health.
Global vaccines currently containing Thiomersal (September 2003)

- Combined diphtheria and tetanus vaccine (CDT) ..... 50mcg
- Adult diphtheria and tetanus vaccine (ADT) ............ 50mcg
- Diphtheria vaccine .................................................. 50mcg
- Hepatitis B (Engerix B Adult) ..................................... 2mcg
- *Influenza vaccines (Fluarix, Influvac, Fluvax) ...... 50mcg
- Japanese encephalitis vaccine (JE Vax) ............... 35mcg
- Q fever vaccine (Q vax) ............................................ 50mcg
Fish may have methyl mercury levels in the 1 ppm range (=1000mcg/kg), if they swim in polluted waters.

Mercury levels for large fish generally remain between 0.5 and 1.5 ppm (500-1500mcg/kg), allowing for occasional consumption.

Hongkong average fish consumption is 673g/week.

This provides 673mcg Hg/week.

Allowed food intake = 35mcg/Hg/wk.
Symptoms of Mercury Intoxication
common symptoms seen in Allergy Patients

- Gastrointestinal disorders
- Renal dysfunction
- Hypertension
- Wide range of neurological disorders
- Memory loss
- Depression
- Insomnia
- Psychosis
- Metallic taste

Chronic poisoning results in atrophy and degeneration of the sensory cerebral cortex, hearing and visual impairment

Worbach MR, Nutriolische Medizin, Hädecke 1999
Inactivation of enzyme systems due to metal overexposure causes inflammation in various cell systems leading to cell death.
Nickel - Ni

Definition  By Mayo Clinic staff

Nickel allergy is one of the most common causes of allergic contact dermatitis — an itchy rash that appears when your skin touches a normally harmless substance.

Nickel allergy can affect people of all ages, and may occur after a single exposure to nickel or after repeated or prolonged exposure.
Figure 1: Patches of eczematous dermatitis on patient's face (left) in areas that came into contact with the headset of his cellphone (right)
Nickel compounds: well-established human carcinogens (Costa and Klein, 1999; Salnikow et al., 1999)

Nickel impairs cellular defense mechanisms against peroxidation by depleting free-radical scavengers including glutathione (GSH), or by inhibiting catalase, superoxide dismutase, glutathione peroxidase, glutathione S-transferase, or other enzymes that protect against free-radical injury (Donskoy et al., 1986; Sunderman, 1989).

Nickel exposure disrupts cellular redox status as part of its adverse effects.
Nickel may damage the developing fetus. Nickel and other toxins found in smoke increase allergy and asthma risk.
Induction of apoptotic cell death by particulate lead chromate: differential effects of vitamins C and E on genotoxicity and survival.

All of the cells killed by treatments with lead chromate particles underwent apoptosis.

Cell survival assays showed that ascorbate, but not alpha-tocopherol, protected cells from apoptosis induced by sodium chromate.

Blankenship LJ, Carlisle DL, Wise JP, Orenstein JM, Dye LE 3rd, Patierno SR. Genetics, The George Washington University Medical Center, Washington, DC 20037, USA.
Eryptosis – death program of erythrocytes

Conditions with excessive eryptosis include:

- iron deficiency
- lead or mercury intoxication
- sickle cell anemia
- thalassemia
- malaria and infection with hemolysin-forming pathogens i.e. bacterial, fungal
Lead absorption and renal dysfunction in a South African battery factory.

CONCLUSION: An exposure-response relation between Pb and renal dysfunction across the range from < 40 to > 70 micrograms/dl blood Pb was found in this workforce, with conventional measures of short and long term Pb exposure and of renal function. The findings probably reflect a higher cumulative renal burden of Pb absorption in this workforce. The results also confirm the need for strategies to reduce Pb exposure among industrial workers in South Africa.
Biochemical basis for Pb toxicity

- Only 8-12% of orally ingested lead is absorbed by small intestines
- Reacts easily with sulfhydryl groups in enzymes, thereby inactivating them
- Hematological manifestations are mainly due to inactivating Delta-aminolevulinic acid (ALA-) dehydratase and ALA synthetase
Metal overexposure and inability to properly detoxify
Symptoms of Lead Intoxication

- Anemias
- Blue-black lead line near gingival margin of teeth
- Weakness
- Headaches
- Energy loss
- Bone & muscle pain
- Abdominal pain & digestive disorders
- Anorexia
- Alopecia

- Large range of neurological disorders
- Loss of concentration (affects ability to learn)
- Irritability
- Depression
- Anxiety and fear neurosis
- Restlessness & sleep disorders
- Tremor
Other Lead Risks (noncancer)

- Aplastic anemia risk increases
- High level exposure in man damages sperm production
Early metal exposure can be linked to increased allergy responses, Autism and related diseases
Rapid cell death induced by methyl mercury in suspension of cerebellar granule neurons.


Sarafian T, Hagler J, Vartavian L, Verity MA.
Department of Pathology, UCLA Center for the Health Sciences 90024-1732
Hg in Brain Tissue

AA and Neutronactivation Analysis of brain tissue (gray vs white matter from 83 adult cadavers) demonstrated a positive correlation between occlusal surfaces of dental amalgam and mercury level of brain.

Eggleston DW, Nylander M. Univ.So.Calif., School of Dentistry, LA and Karolinska Institute, Stockholm, Sweden

Correlation of dental amalgam with mercury in brain tissue.
Journal of Prosthetic Dentistry, dec '87 www.nvbt.nl/hot-metalen4
Cardiology News: Mercury's Link To Heart Disease Begins In Blood Vessel Walls

Research recently published in a the International Journal of Toxicology and supported by the National Institutes of Health suggests mercury's link to heart disease can be traced to activation of a relatively obscure, misunderstood enzyme, which triggers a process leading to plaque buildup in blood vessel walls.

The study examined three forms of mercury, matching its characteristics in the environment. Each form of mercury caused changes in the behavior of cells that line the blood vessel walls and that can lead to cardiovascular diseases.
Recent etiological study in twins (Tanner et al. 1999) strongly suggests that environmental factors play an important role in typical, non-familial Parkinson's disease (PD), beginning after age 50.

Journal of Neurochemistry
Volume 76 Page 1010 - February 2001
doi:10.1046/j.1471-4159.2001.00096.x

Issue 4 molecular mechanism Hong S. Chun,* Gary E. Gibson,* Lorraine A. DeGiorgio,* H. Zhang,* Vincent J. Kidd† and Jin H. Son*
Trace elements and skin diseases-
Metal allergy and metal carcinogenesis (Arsenic and skin cancer)-

ITO MASATOSHI (Toho Univ., Sch. of Med.)  Journal Title; Biomed Res Trace Elem
VOL.16; NO.1; PAGE.1-8(2005)
Arsenic

Long term exposure increases risk of liver cancer

The risk is increased in smokers infected with hepatitis B or C

Cancer Research UK 2006
Arsenic Trioxide

U.S. Brand Names   Trisenox®

Antineoplastic Agent, Miscellaneous

Symptoms:
Dangerous, fast heartbeats can occur.

Trisenox can cause retinoic-acid-APL syndrome.
Severe problems can occur in some patients who develop this condition.
Symptoms of Arsenic toxicity

- Skin lesions, peripheral neuropathy, and anemia are hallmarks of chronic arsenic ingestion.

- Arsenic is strongly associated with lung and skin cancer in humans, and may cause other internal cancers as well.
Verburgh-van der Zwan N, van Ketel WG.

Contact allergy to an arsenic-containing drug administered intravaginally
[Article in Dutch]
Other risks of As-exposure

- Inhaled or ingested arsenic can injure pregnant women or their unborn babies
- Smoking should be avoided around pregnant women and young children
Cadmium – Cd

toxic to all body systems

- Exposure to cadmium happens mostly in the workplace where cadmium products are made.
- The general population is exposed from breathing cigarette smoke or eating cadmium contaminated foods.
Symptoms of Cadmium intoxication

- Weakness
- Anorexia
- Loss of taste & smell
- Alopecia
- Dry skin (quick aging as seen in smokers)
- Liver problems
- Anemia due to disturbed iron metabolism
- Osteoporosis
- Kidney dysfunction
- Nephrocalcinosis due to disturbed renal calcium clearance
- High blood pressure
- Pulmonary irritation
- Lung Emphysema

Werbach MR, Nutriolische Medizin, Hädecke 1999
Cadmium Distribution in Body Tissues

- Bone
- Brain
- Skin
- Hair
- Muscle
- Heart
- Colon
- Liver
- Kidneys

mcg/kg

Cadmium
Lymphocyte Damage

- Cadmium at low and high concentration kills CEM-C12 cells by apoptosis and necrosis, respectively.

- The apoptotic effect of cadmium suggests a possible mechanism for lymphocyte damage.
Cadmium and Suppression of Cell Death

In a significant 1998 study, researchers found that cadmium appears to block programmed cell death, or apoptosis. By stopping this process, cells that would otherwise die, including those with damaged DNA, may continue to live and divide. This probably results in increasing numbers of cells with altered DNA, which can eventually lead to the development of tumors.

The researchers believe that the suppression of apoptosis may be a significant aspect of cadmium's carcinogenic mechanism.

*Journal of Toxicology and Environmental Health 22 May 1998 issue.*
Acute toxicity of metal ions in cultures of osteogenic cells derived from bone marrow stromal cells

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Center for Biomedical Engineering, University of Kentucky, Lexington, Kentucky

Bone marrow cultures were examined for effects of cytotoxicity by measuring total cell number, total cell protein, and mitochondrial activity.

- Cr$^{6+}$ was grossly cytotoxic;
- Mo$^{6+}$, Fe$^{3+}$ were moderately cytotoxic;
- Ti$^{4+}$, Al$^{3+}$, V$^{5+}$, and Mn$^{2+}$ were minimally toxic
Cadmium- and chromium-induced oxidative stress, DNA damage, and apoptotic cell death in cultured human chronic myelogenous leukemic K562 cells, promyelocytic leukemic HL-60 cells, and normal human peripheral blood mononuclear cells

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2Cell Biology and Anatomy, University of Nebraska Medical Center, Omaha, NE 68198
Sodium dichromate [Cr(VI)] and cadmium chloride [Cd(II)] are both cytotoxic and mutagenic.

Results demonstrate that both cations in combination are highly toxic, producing oxidative tissue damage and apoptosis.

More drastic effects were observed on Leukemia cells as compared with normal human peripheral blood mononuclear cells.
Causes of Metal allergy and Metal Toxicity

- ENVIRONMENTAL OVEREXPOSURE through Diet, Water, Smoke, Metal-containing Medication and Cosmetics, Amalgams, Implants etc
- DIGESTIVE & RENAL INABILITY TO PROPERLY EXCRETE
- GENETIC INABILITY TO PROPERLY EXCRETE
PRENATAL EXPOSURE at important developmental stages
The concentrations of cadmium, lead and total mercury were determined in maternal blood and umbilical cord blood collected during the III-rd stage of term delivery from 56 mother-neonate pairs.

The obtained results support the opinion that human placenta does not form an effective barrier to toxic metal intake by the fetus.
Conclusion:
AVOIDANCE, *EARLY DETECTION* and DETOXIFICATION LEADS TO A HEALTHY LIFE (without allergies)

Thank you!

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