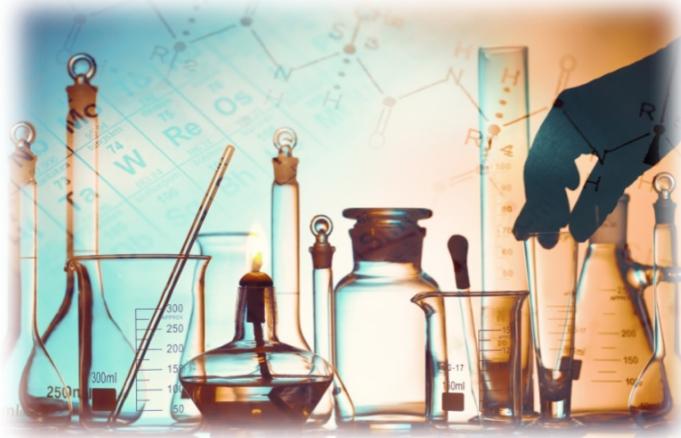


# Assessment for Toxic Elements in the Human Body



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# **Faculty Disclosure**

- Relationship with commercial interests - None
- Disclosure of Commercial Support – None
- Conflict of interest – None

# **Overview**

## **I. Significance of Toxic Elements**

## **II. Testing for toxic element contamination**

- Objectives of testing
- Who, how, when, to test
- Mechanics of testing
- Safety issues and other important considerations
- When & how to arrange treatment

## **III. Questions & Controversies**

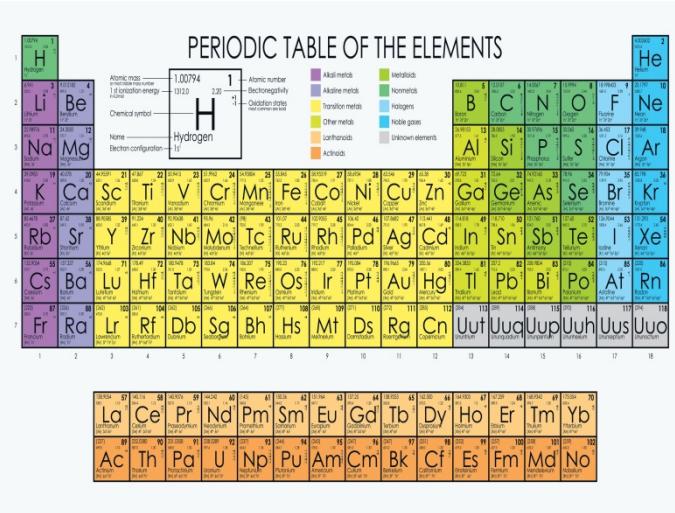


# Significance of Toxic Elements

An element is a substance (natural or man-made) that is made entirely from one type of atom. Of the known elements, nearly 80% are either metals or metalloids.  
(based on physical properties)

Some essential elements such as zinc are required by the body in small doses for normal function

Other elements have no physiological concentrations that are beneficial; some have the potential to cause enormous toxicity.



# Whole array of toxic elements

- **Mercury, Lead, Cadmium, Aluminum, Arsenic** (well-known)
- **Gadolinium** – often post MRI
- **Platinum** – post-chemo
- **Thallium** – electronics and glass industry – has seeped into kale and cruciferous veggies – cabbage, broccoli, cauliflower, collard in regions of California lately
- **Nickel** – occupational, proximity to industrial sources, food processing industry
- **Antimony** – used in some materials as a flame retardant
- etc.



# Each toxic element behaves in a unique way

1. Distribution
2. Storage
  - e.g. Cadmium: widely distributed, but mainly kidney then liver
  - e.g. Lead – stores primarily in bones, teeth and brain
  - e.g. Mercury – stores in brain and kidneys
3. Elimination process and half-life
4. Toxicology & mechanisms of damage



# What do toxic elements do?

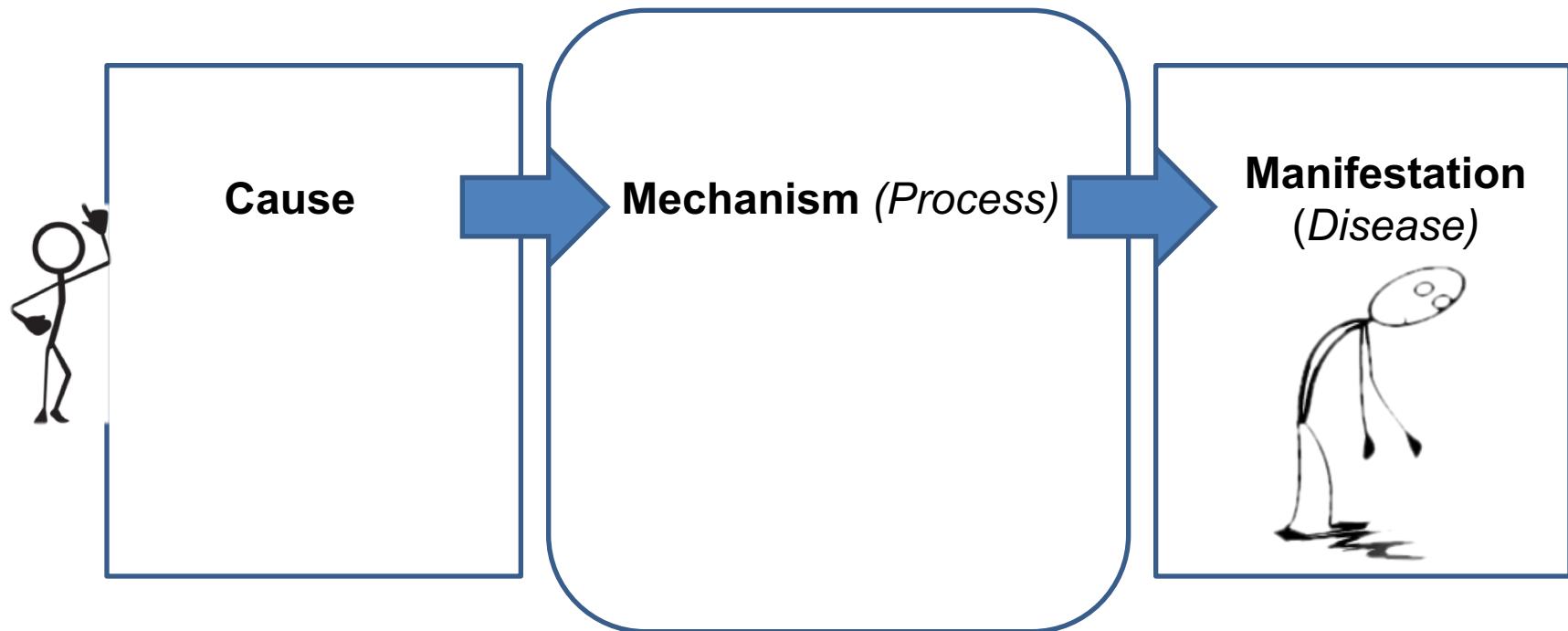
## e.g. disrupt biochemistry and physiology

- Toxic elements have potential to disrupt metabolic pathways in many ways
- Anything that would interfere with normal metabolism and biochemistry may result in malfunction – which will manifest as illness
- To improve health, must thus consider what is happening at biochemical pathway level

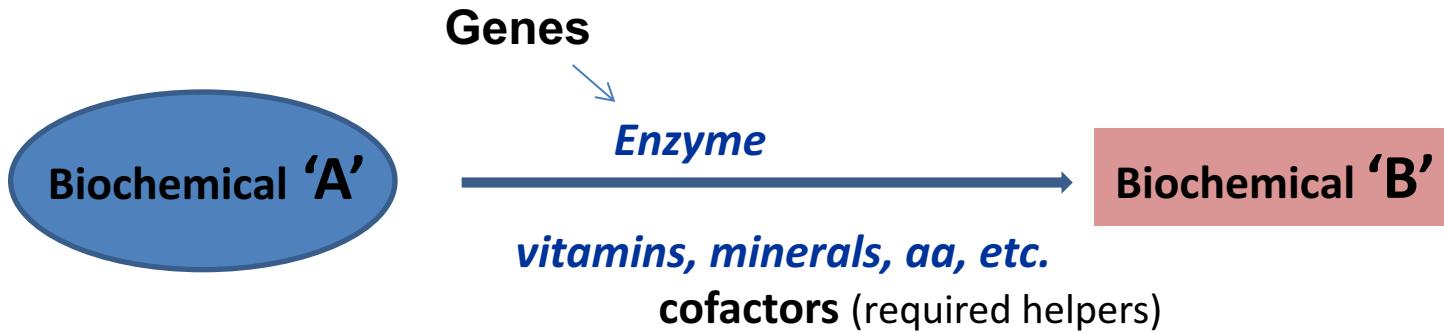


# Toxic Elements: a potential determinant of illness

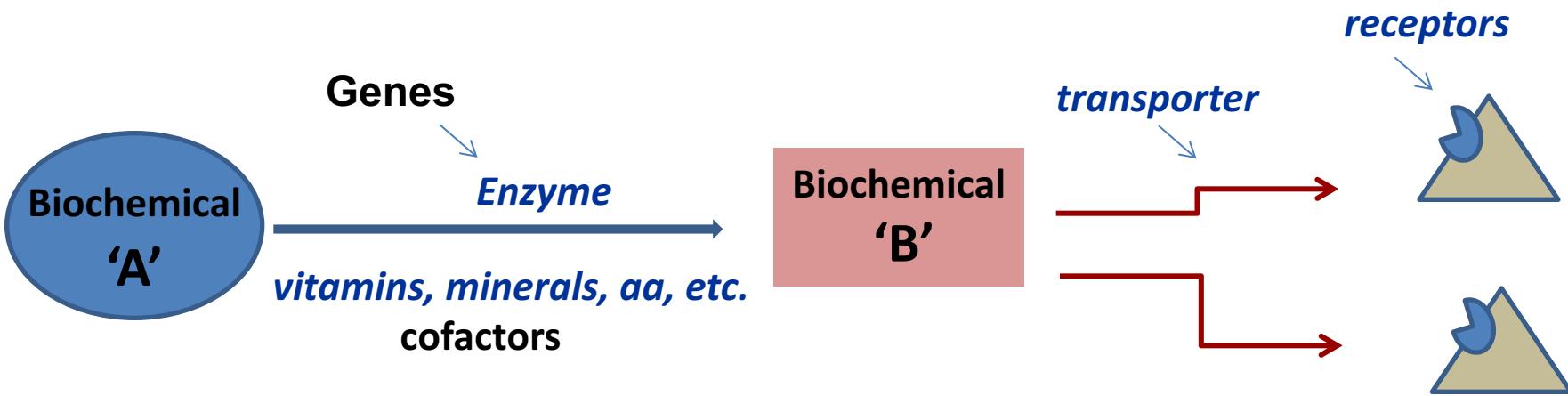
## Pathway to illness

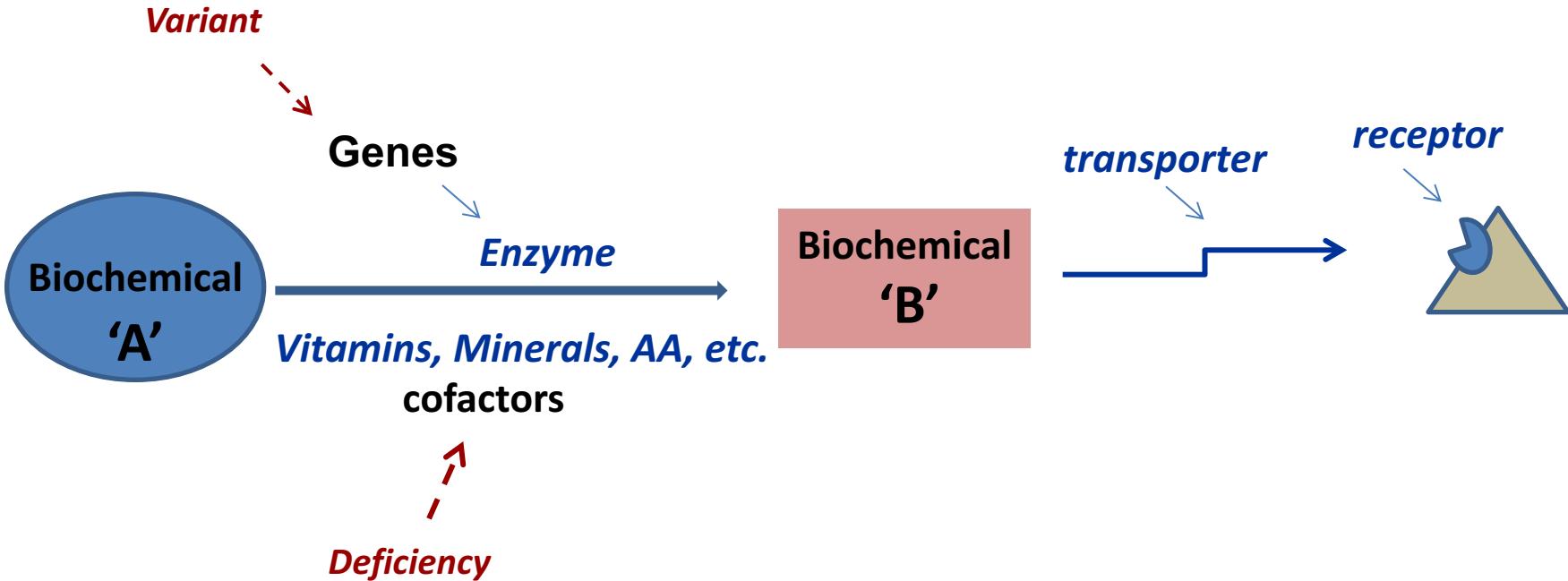


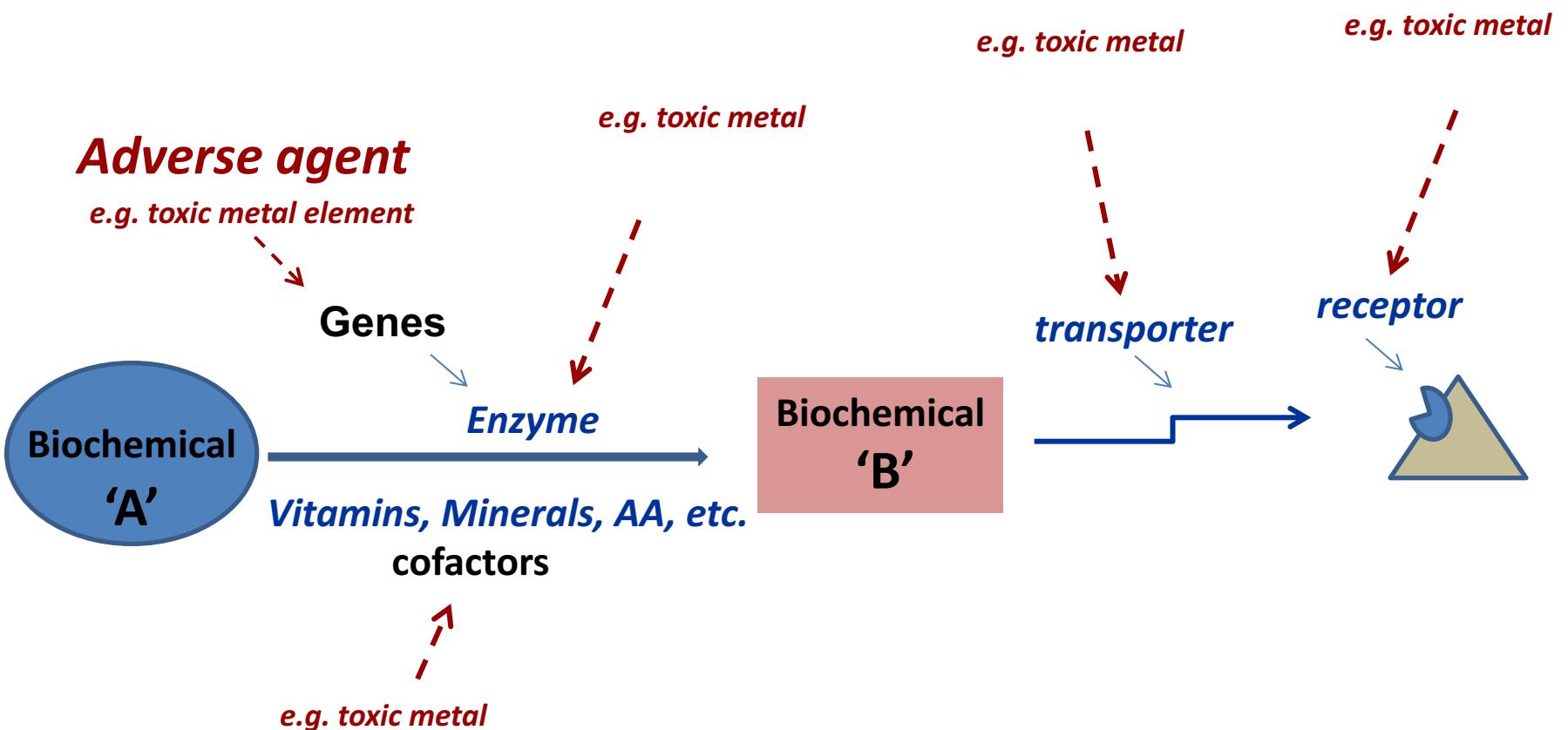
# Biochemical Manufacturing Plant



# Delivery to Receptor Sites for Activity







# Toxicants (e.g. heavy metals) can disrupt human biochemistry in many ways

CELLULAR TOXICITY		PATHOPHYSIOLOGY
Damage to Cell Structures -e.g. DNA, mitochondria		Endocrine Disruption
Oxidative Stress		Inflammation
Receptor and Transporter Dysregulation		Immune Dysregulation
Epigenetic Change		Pathway Impairment
Cellular Detoxification Impairment		Biome Alteration
Dysregulation of Signalling		ANS Dysregulation
Plaque Formation		Neurotransmission Dysfunction
Displacement		Nutritional Compromise
Other Mechanisms of Cellular Toxicity		Other Pathophysiological Mechanisms

# e.g. Toxic metals interfere with detoxification

Phase I – Activation of Xenobiotic (enzyme impairment)

- via cytochrome P450 enzymes, Impaired by Hg, Pb, As, Cd – perhaps others

Phase II – Conjugation of activated xenobiotic (enzyme impairment)

- via mechanisms including GSH-S-Transferase, Impaired by Hg, Pb, As, Cd

Phase III – Elimination of xenobiotic complex – (transport, microbiome damage)

- Various toxic metals alter microbiome which is intimately involved in elimination

## Result – facilitates bioaccumulation of all xenobiotics

- Breton J, et al. Ecotoxicology inside the gut: impact of heavy metals on the mouse microbiome. *BMC Pharmacol Toxicol* 2013;14:62.
- Maier A et al. Disruption of dioxin-inducible phase I and phase II gene expression patterns by cadmium, chromium, and arsenic. *Molec Carcinogenesis* 2000. 28:225-35
- Moore M . A commentary on the impacts of metals and metalloids in the environment upon the metabolism of drugs and chemicals. *Toxicol Letters*, 148, 2004, 153-158
- FM El-Demerdash, et al. Cadmium-induced changes in lipid peroxidation, blood hematatology, biochemical parameters and semen quality of male rats. *Food Chemical Toxicol*, 2004;42:1563-1571
- Y.C. Awasthi (2006). *Toxicology of Glutathionine S-transfseres*. CRC Press Inc..
- Bozcaarmutlu A.et.al.Effect of mercury, cadmium, nickel, chromium, and zinc on kinetic properties of NADPH cytochrome P450 reductase *in Vitro*,*Toxicol* 21: 2007, 408-416

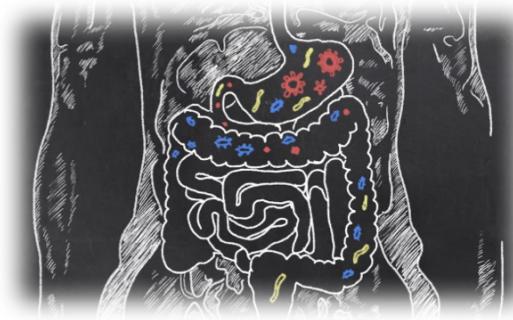
# e.g. Endocrine disrupting chemicals (EDC)

- Various heavy metals (many are xenoestrogens) are endocrine disruptors
- Can affect fertility, thyroid function, puberty, sexual development, and hormone sensitive organs such as prostate, breast, endometrium, etc. etc.



# e.g. Microbiome/Environment Interactions

- Toxic metals and other chemical agents can interfere with microbiome viability and function
- Disturbance of the microbiome by environmental chemicals can result in functional changes that lead to disease



Breton J, Massart S, Vandamme P, De Brandt E, Pot B, Foligne B. Ecotoxicology inside the gut: impact of heavy metals on the mouse microbiome. *BMC Pharmacol Toxicol* 2013;14:62.

# Potential Clinical Consequence of Toxic Element Exposure

Toxic metals metalloids associated with myriad types of physical and mental illnesses

- Autism
- Dementia
- Allergies
- Parkinson's
- Depression
- Sensitivity Related Illness (MCS, EHS)
- Cancer
- etc, etc, etc...



## **Prevalence: i) CDC & ii)American Red Cross - Cord Blood Samples:**

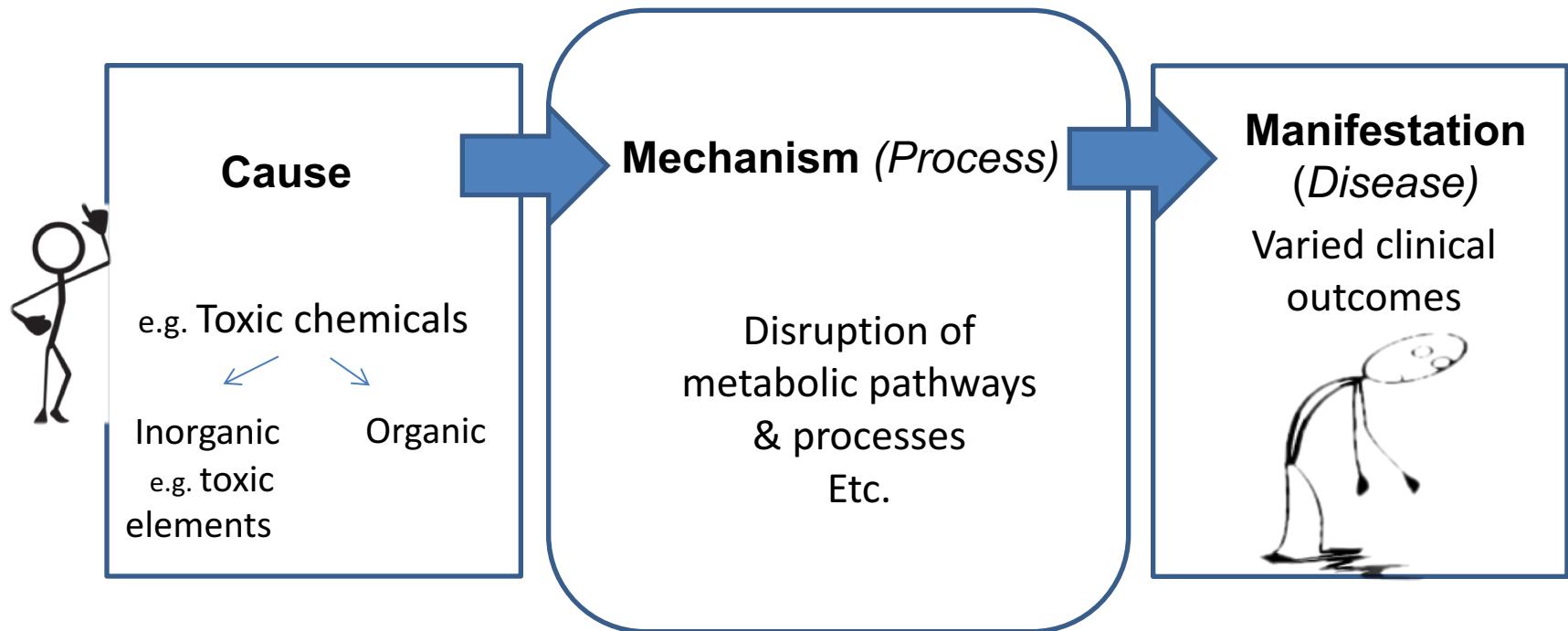
- Centers for Disease Control and Prevention: Department of Health and Human Services: Fourth National Report on Human Exposure to Environmental Chemicals. Atlanta: Georgia. Updated Tables. [ [http://www.cdc.gov/exposurereport/pdf/FourthReport\\_UpdatedTables\\_Mar2013.pdf](http://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Mar2013.pdf) ]

- Prenatal Exposure – impacting the pediatric population



Environmental Working Group. Body burden - the pollution in newborns A benchmark investigation of industrial chemicals, pollutants and pesticides in umbilical cord blood. (Executive Summary) July 14, 2005. [Accessed Sept 16, 2005] <http://ewg.org/reports/bodyburden2/execsumm.php> .

# A Common Pathway to illness

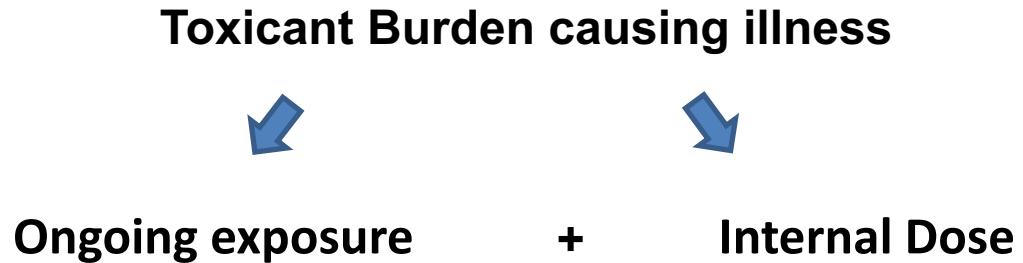


# Overall Clinical Approach with Toxic Metal Accrual

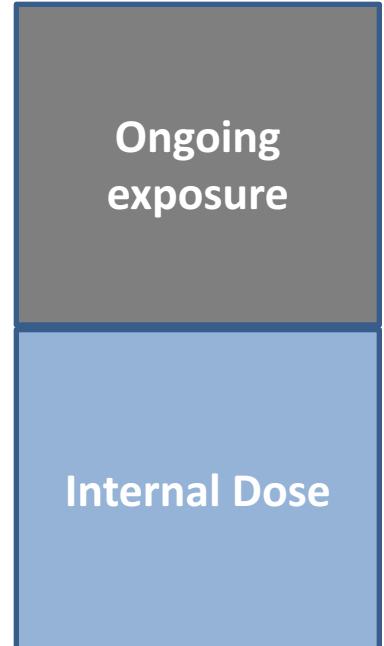
- Illness commences because of a cause
  - Illness persists because the cause persists
- To restore health must consider causation and intervene accordingly
- Toxic element contamination is a common cause of disrupted metabolism & illness
- Health providers need ability to assess for toxic metal contamination & a means to address it



## II) Assessing for Toxicants



Toxicant Burden



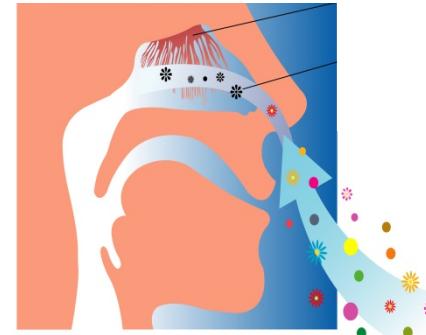
# Importance of Proper Assessment

Many people receiving Rx for internal dose while still experiencing ongoing exposure

Goes in much faster than it comes out

Assessment must include determination of ongoing exposures!

**Lab testing is only part of the assessment**



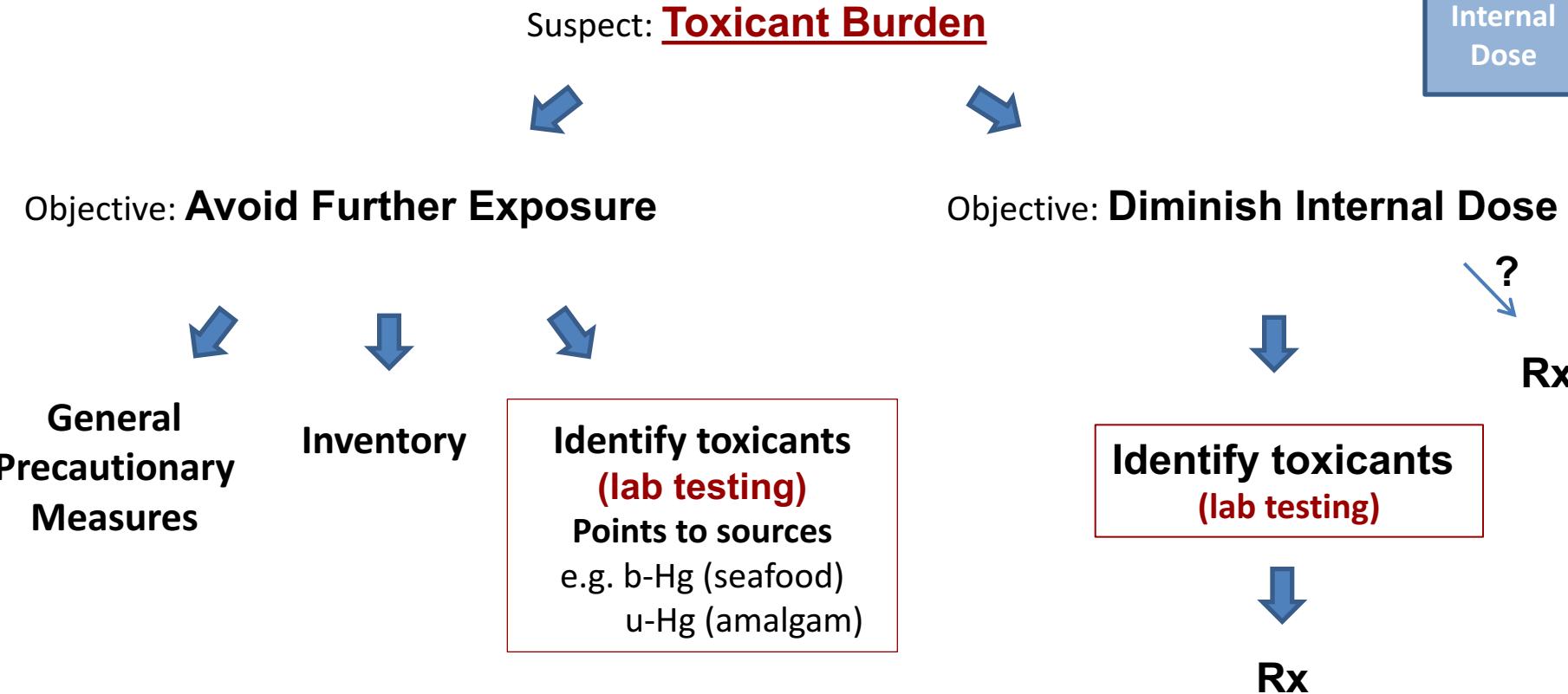
*Major pitfall: If ongoing exposure remains, lab testing and Rx usually insufficient*

# Case History

- 58y/o prior dentist with chronic pain (joints, fibromyalgia)
- Extensive nutritional training – ate incredibly well
- Involved with various holistic groups
- Assessment – lot of toxic metal; Rx implemented
- 9 months later – no clinical or lab improvement - ???
- Detailed questioning: had not disclosed about a herbal supplement
- Testing – herbals were daily source of metals
- Prompted further study on supplements



# Toxicants: Overall Strategy

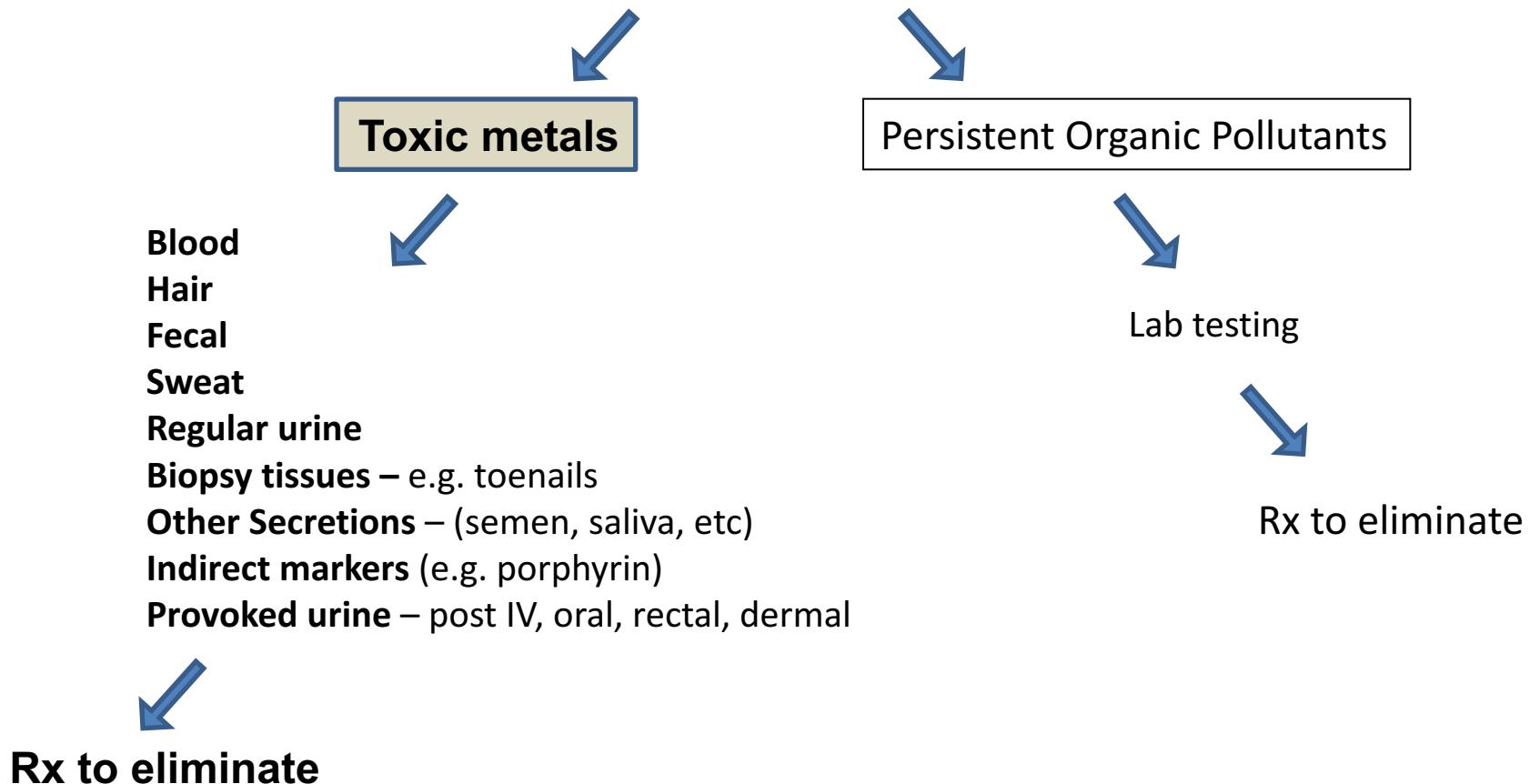


# I) Identify ongoing exposure: Assessment for toxic elements – Inventory

- Vehicle emissions – engine compartment e.g. Cd
- Emissions from computers – Hg, Pb, As, etc
- Some candles – wicks to slow rate of burning – e.g. Pb
- Some supplements – some sourced from polluted areas
- etc. etc...



## II) Laboratory Assessment for Internal Dose



# A) What is Provoked Testing? ('Challenge' test or 'Heavy Metal Challenge')

**Use of agents to mobilize toxic elements from storage sites**

and / or

**Use of agents to bind toxic elements, makes them more soluble and kidney filterable so they are dumped into proximal tubules where toxin conjugates move into the urine**

Objective – to enhance excretion to get a better idea of

- what metals are present
- the extent of the internal dose
- the ability to diminish the burden with treatment

## ➤ Mechanism of action with provoking (chelating) agent

- A chelating agent appears to bind and mobilize the most readily available toxic elements first – binds them and facilitates elimination
- With repeated doses the accessible “pools” of toxic elements will be depleted
- Re-equilibration between less accessible body compartments replenishes toxic elements into primary accessible sites.
- This is evident in the rebound of levels of some metals in the blood, following discontinuation of a chelator. (typical rebound increase in early stages)
- Overall internal burden continually diminishes
  - Precise pharmacodynamics not completely understood

Sears ME. Chelation: harnessing and enhancing heavy metal detoxification--a review. The Scientific World Journal. 2013;2013:219840.  
Graziano et al. 2,3-Dimercaptosuccinic acid as an antidote for lead intoxication.Clin Pharmacol Ther 1985 Apr;37(4):431-8

## B) Why is there an accrued internal dose (body burden)?

Depending on i) properties of the chemical  
ii) detoxification abilities of the individual

Some chemicals  
are eliminated

Some chemicals persist — why?

- Enterohepatic circulation (EHC)
- Renal tubular reabsorption
- Impaired detoxification mechanisms
  - Organ dysfunction – e.g. liver, kidney
  - Deficient in nutrients for elimination
  - Polymorphisms
  - Toxicants interfering with elimination
  - Insufficient mechanisms in fetus

## C) Which test will accurately quantify internal dose?

Although considerable yield on testing suggests heavier burden

- e.g. Toxic metal body burden was assessed by measuring urinary excretion of toxic metals...Multiple positive correlations were found between the severity of autism and the level of provoked DMSA urinary excretion of toxic metals.

*But does not quantify internal dose*

Adams et al. J Toxicol. 2009;532640. doi: 10.1155/2009/532640.

The severity of autism is associated with toxic metal body burden and red blood cell glutathione levels.

# **Not aware of any single test to precisely quantify internal dose of the range of toxic elements**

- Blood and urine testing do not measure burden toxins accrued over lifetime
- Ongoing flux between compartments: various tissues, blood, lymph, air in the lungs, etc. - caloric status, activity, weight, hormonal changes, etc
- Different tissues store differently
- Provoked testing, different agents have different affinities for specific elements

*.....evidence of testing inaccuracy for burden assessment - 4 points*

## i. My observation: different tests/different results

In same patients around same time:

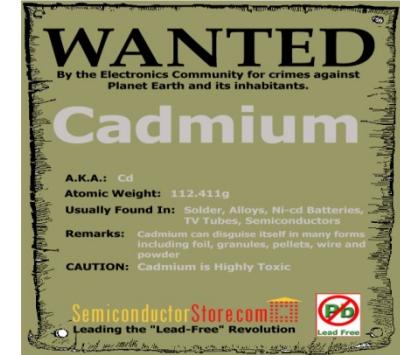
- blood
- unprovoked urine
- fecal samples
- hair
- sweat
- provoked urine



*Completely different results!!*

# Cadmium

- Blood: 10/20 participants had no detectable cadmium in their blood.
- Urine: Same 10/20 had no detectable cadmium in their urine.
- Conclusion – Cd not an issue...However:
- Of the 10 participants with no Cd in blood or urine, ***80% of these had notable levels in sweat***



## ii. My observation: inconsistent excretion

Observed in several patients - Rx 3 months apart:

- blood (none of metal 'A' present at baseline)
- unprovoked urine (none 'A' present at baseline)
- provoked urine – moderate amount

***3 months later: Substantial increase (>100%) in excreted amount:***

*(same protocol p. urine , same lab, no further exposure, but other concomitant interventions – sauna, exercise, improved nutrition, etc)*

### iii. Lack of established standards

Lack of established standards for population groups  
for most tests including provoked urine

*Hard to accurately interpret results in relation  
to internal dose*

*Cannot correlate level of results with specific  
clinical outcomes*



## iv) Speciation (members of family)

- Exposure and accrual of toxic elements can exist in different forms in the body

Marked variability in toxicity and behavior of different species of same element:

- Metabolized by the body in different ways



## e.g. Hg Speciation

- e.g. Hg: Organic – methylmercury, ethyl Hg, dimethyl Hg, Hg-oxalate, etc  
Inorganic – elemental mercury, mercuric chloride, divalent Hg,etc.
- Urine – reflects inorganic mercury – lot coming from amalgam
- Methylmercury often coming from fish is eliminated primarily through GI tract; found in blood and hair – not urine
- No single test will give overall internal dose of Hg

### Conclusion:

- Considerable yield suggests considerable burden
- Not aware of any single test to precisely quantify internal dose of the range of toxic elements

## D) Fundamental Query:

- If unable to accurately quantify internal dose, is there any value in lab testing for toxic metals?

**Yes!** *(in my view)*



# What is Objective of Laboratory Testing

- Recognizing that toxic elements alter biochemistry and cause illness...
- Results of informed testing - safely identify which specific agents are present & potentially disrupting biochemical function...
- Enable directed treatment to diminish burden of specific toxic agents that are contributing to ill-health
- Clinical observation and published literature confirms improvement with safe treatment



## **Case Series** (*QJM: An International Journal of Medicine* 2009 ;102(10):721-32.)

- **Use of oral DMSA in adult patients with inorganic lead poisoning.**
- Case series of 17 lead contaminated adults
- Blood testing confirmed in all 17 patients that there was a substantial burden of lead
- DMSA therapy (30mg/kg/day) markedly increased lead excretion
  - ***12 fold increase in excretion overall compared to pre-treatment level***
- Overall - rapidly reversed lead related symptoms (largely neurological and gastrointestinal)
- Oral DMSA 30 mg/kg/day is an effective antidote for lead poisoning

# E) Which test(s) are best to assess for toxic element status:

my preference

- My criteria:
  - very safe
  - non-invasive
  - minimal likelihood of complications
  - well tolerated - esp children
  - reliable
- I have found whole blood, provoked urine, and sweat analysis to be the most reliable tests for retained metals
- Each of these provides unique information; provide data to help determine if Rx is worthwhile



## i) Sweat testing

- Sweat is helpful for detection of metals
- Often more sensitive to accrued metals in tissues & detects metals not found on other tests
  - Of 10/20 participants with no Cd in blood or urine, 80% of these had notable levels in sweat
  - 3/20 participants had no detectable levels of Hg in blood, all of these had Hg in sweat
  - Confirms efficacy of sweat Rx as means to diminish burden in these individuals

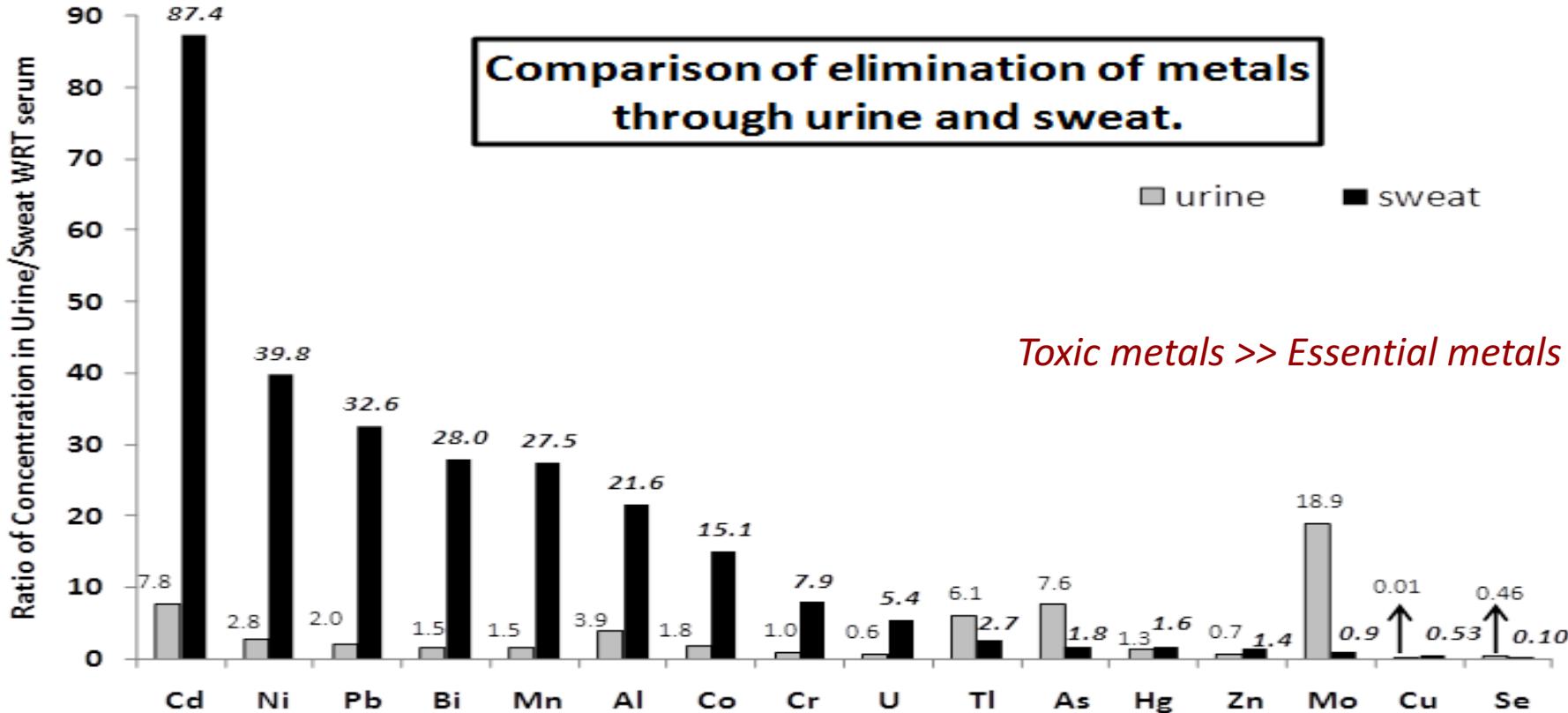


Genuis SJ, Birkholz D, Rodushkin I, Beesoon S. Blood, urine, and sweat (BUS) study: monitoring and elimination of bioaccumulated toxic elements. Archives of environmental contamination and toxicology. 2011;61(2):344-57.

# Sweat testing - Challenges

- Not yet available at most labs
- People heavily burdened often have ANS dysfunction & often do not sweat much – hard to collect
- Differential excretion rates between metals – higher amounts may reflect better elimination rather than higher accrued concentrations. e.g. Cd > Pb > Al > Hg





Genuis SJ, Birkholz D, Rodushkin I, Beeson S. Blood, urine, and sweat (BUS) study: monitoring and elimination of bioaccumulated toxic elements. Archives of environmental contamination and toxicology. 2011;61(2):344-57.

## ii) Whole Blood Elements

- Results generally indicate more recent or ongoing exposure
- Results tend to reveal metals more likely to stay longer in blood (e.g. cadmium)
- Less helpful for agents with shorter half-life – such as Pb – tends to sequester in tissues
- Helpful for several metals not easily found with DMSA provoked urine (Cd, Al, As)
- Some metals appear to be preferentially taken up into erythrocytes (e.g. methylmercury, thallium) – vs. serum



# Comprehensive Whole Blood Elements

- Caloric restriction may facilitate mobilized metals
  - (Pre and post fasting with some toxic elements e.g. Pb)
- If do comprehensive blood elements – get some indication of mineral status as well - helpful with regards to address nutritional issues



### iii) Provocation testing = Heavy metal challenge

Mobilizes some metals from tissues as they link to the chelator and maintains the chelate complex during circulation to the kidneys for excretion in the urine, and to the liver for excretion in the bile. Also binds some circulating toxic elements.

\* DMSA Rx (30mg/kg/day) ***12 fold increase in excretion overall compared to pre-treatment level***



1. Often reveal metals not readily seen in regular blood or unprovoked urine testing
2. Assesses efficacy as a trial of therapy

\* Bradberry et al. Use of oral dimercaptosuccinic acid (succimer) in adult patients with inorganic lead poisoning. Qjm. 2009;102(10):721-32.

e.g. of findings:

## Mercury (profile seen several times)

- None in hair
- None in blood
- Minimal in stool
- Minimal in unprovoked urine
- Lots in provoked urine
- Consistently present in sweat



Mercury can be stored in tissues and excreted via sweat or provoked urine with no evidence on other tests

*If provoked urine testing not done – may miss key determinant of illness*

# Approach to Provocation testing – Baseline testing

Comparison of baseline (no provocation) and provoked urine levels

- Allows you to see if the chelator is effective at the dose given
- Results may assist with management decisions
- Does not indicate amount eliminated in bile

# Review - So what is the value of lab testing?

- Lab testing indicates which particular metals are present
- Lab testing does not quantify precise burden but considerable yield suggests burden is heavier
- Provoked lab testing vs. unprovoked testing may
  - Confirm presence of metals not seen with regular urine
  - Confirms efficacy of intervention - a trial of therapy
  - Confirms huge increase in rate of elimination with provocation: basis for Rx



# Provoked urine – one technique that can be used (there are others)

- Use of oral DMSA 10 mg/kg with co-agents to increase yield  
(DMPS and EDTA do not absorb well po)



## Protocol Pre-test:

- Glycine (co-agent): Trial of 500 mg glycine on one day.
  - Some affinity for metals such as Hg, Al, Pb, Sb, etc. L-glycine can facilitate the movement of metals from within cells to extracellular compartment where the binding agents are restricted to.
- L Glutathione (co-agent): Trial of increasing dose of over a week (↗ 500 mg).
- DMSA: Trial of ~3 mg/kg on day 1; trial of ~6 mg/kg on day 2.

If, and only if, no problems with pre-test trial - Move on to testing.

# Provoked urine – one technique that can be used

## Protocol test day:

- Glycine boost 40 mg/kg (orally)
- 15 minutes later Liposomal Glutathione ~500 mg
- 2 hours later –
  - Use 5mg/kg DMSA;
  - Repeat another 5 mg/kg DMSA 30 minutes later
  - Void urine into toilet 30 minutes after last dose of DMSA
- Collect urine for next 4 hours and send to lab for testing
- Await results and make Rx decisions accordingly
  - If patient has evidence of considerable amount of toxic metal, may decide to facilitate Rx to diminish the burden

# Other Options (not my preference)

Respect and recognize that other approaches can work very well

Some people successfully use IV DMPS, EDTA (alone or in combination)

Some prefer not to use IVs in general - citing

- IV more invasive – esp for children...some plasticizer exposure
  - Concern re nephrotoxicity of rapid Cd release with abrupt higher dose
  - DMPS potentially more adverse reactions and more toxic
  - Does not provide any further information that I need to make clinical decisions
- 
- Some people use longer collections – I have not found any benefit



# Other Options (not met with success)

- Some people use p.r. EDTA – Although up to 30% reportedly absorbed, have not seen notable increase of any metals in urine collection over 6 hours post insertion
  - perhaps results with longer collection – but prefer short collection...more convenient, more compliance, less forget at work, etc)
- Some people use transdermal EDTA – (observation) have not seen notable increase of any metals in urine testing over 12 hours.(overnight)
- Some people use oral EDTA - Oral EDTA is only about 5% absorbed.



## vii) Arranging Treatment

- Asked to leave Rx approach for another talk
- If provoked test works, consider same approach to Rx



**If toxic element accrual is a concern:**

If not trained to do this

- Can refer to someone who is trained and experienced in this field
- Some practitioners from AAEM & ACAM undertake this work
- These organizations provide training courses which teach options for Rx.

### III. Questions & controversies

- No validity to provocation testing
- Provocation testing is harmful
- Everybody is contaminated – results useless
- Levels mean nothing
- Ultimately no benefit to patients
- Etc.



## i) Provocation testing – No validity!

- Since there are no established reference ranges for provoked urine samples, no reliable evidence to support a diagnostic value for the tests ... these tests should not be utilized (1)
- It is the position of the American College of Medical Toxicology that post-challenge urinary metal testing has not been scientifically validated, has no demonstrated benefit...when applied in the assessment and treatment of patients in whom there is concern for metal poisoning.(2)
  - Ruha AM. Recommendations for provoked challenge urine testing. J Med Toxicol. 2013;9(4):318-25.
  - American College of Medical T. American College of Medical Toxicology position statement on post-chelator challenge urinary metal testing. J Med Toxicol. 2010;6(1):74-5.

# Provocation testing - Not scientifically valid?

- 'No reference ranges for provoked testing'
  - True: provocation test not valid in quantifying body burden.

- Response:

Challenge this assertion – evidence confirms:

- Confirms that metals are present in the body – info that may not available on blood or regular urine testing
  - *"Blood and urine are poor surrogates to measure the toxins accrued over the lifetime (body burden)."*
- Confirms metals can be excreted at much faster rates than without Rx
  - *"12 fold increase in excretion overall"*
- Confirms that therapy will diminish body burden



## ii) Provocation testing - May be harmful!

- There is potential harm, these tests should not be utilized (1)
- It is the position of the American College of Medical Toxicology that post-challenge urinary metal testing ... may be harmful.(2)



- Ruha AM. Recommendations for provoked challenge urine testing. J Med Toxicol. 2013;9(4):318-25.
- American College of Medical T. American College of Medical Toxicology position statement on post-chelator challenge urinary metal testing. J Med Toxicol. 2010;6(1):74-5.

# Overall safety of provocation?



- WHO: “Use of DMSA...has resulted in few adverse effects.” (1)
- DMSA can be administered orally and has relatively low toxicity (2)
- Very low frequency of toxic side effects necessitating discontinued treatment. (3)
  1. Lowry JA, WHO Expert Committees. ORAL CHELATION THERAPY FOR PATIENTS WITH LEAD POISONING. [http://www.who.int/selection\\_medicines/committees/expert/18/applications/4\\_2\\_LeadOralChelators.pdf](http://www.who.int/selection_medicines/committees/expert/18/applications/4_2_LeadOralChelators.pdf). 2010.
  2. Cao et al. Chelation therapy in intoxications with mercury, lead and copper. J Trace Elem Med Biol. 2015;31:188-92
  3. Anderson O, Aaseth J. Molecular mechanisms of in vivo metal chelation: implications for clinical treatment of metal intoxications. Environ Health Perspect. 2002;110:887-890

# DMSA Overdose

- Only reported case of a DMSA overdose (I am aware of),
- a 3-year-old girl ingested approximately 2.4 g DMSA or 185 mg/kg body weight !!
- No apparent side effects and without clinical signs of intoxication



# **Chelating agents (what is used for provocation) established Rx:**

- Mayo clinic recommends ‘Chelation therapy’ for lead intoxication .  
<http://www.mayoclinic.org/diseases-conditions/lead-poisoning/diagnosis-treatment/treatment/txc-20275071>
- CDC –”Chelation therapy is considered a mainstay in the medical management” for Pb.  
[https://www.cdc.gov/nceh/lead/CaseManagement/caseManage\\_main.htm](https://www.cdc.gov/nceh/lead/CaseManagement/caseManage_main.htm)  
<https://www.cdc.gov/nceh/lead/publications/refugeetoolkit/pdfs/medicaltechnicalbrief.pdf>
- WHO – The final component of treatment once lead has entered the body is chelation therapy....” Lead removal should halt further toxicity and reverse previous effects”  
[http://www.who.int/selection\\_medicines/committees/expert/18/applications/4\\_2\\_LeadOralChelators.pdf](http://www.who.int/selection_medicines/committees/expert/18/applications/4_2_LeadOralChelators.pdf)
- Med lit: Chelation therapy has so far been used as the mainstay of the treatment that involves quenching of lead from different sites of the body and expels it through urine .\*

\*Flora G, Gupta D, Tiwari A. Toxicity of lead: A review with recent updates. Interdiscip Toxicol. 2012;5(2):47-58.

## ➤ ‘Deaths have been reported with use of provocation agents!’

- Three deaths associated with chelation therapy have been reported
- Related to hypocalcemia with use of Na<sub>2</sub>EDTA (rather than CaNa<sub>2</sub>EDTA) - Drug error – gave wrong agent
- Estimated pharmaceutical-related annual mortality in America includes 7,000 deaths/year related to medication mishaps!
- Drug errors are tragic events – not reflective of properly done provocation testing



Centers for Disease Control and Prevention (CDC), “Deaths associated with hypocalcemia from chelation therapy—Texas, Pennsylvania, and Oregon, 2003–2005,” Morbidity & Mortality Weekly Report, vol. 55, pp. 204–207, 2006.

Phillips DP, Christenfeld N, Glynn LM (1998) Increase in US medication-error deaths between 1983 and 1993. Lancet 351: 643–644.

➤ ‘Provocation might cause harm if no metals present’



- Two studies on rats published in 2007 by this group
  - Used very high dose: i) 50mg/kg DMSA ii) daily for 3 consecutive weeks
  - Remarkable benefits – reversal of cognitive dysfunction in rats with lead burden – previously considered irreversible!
  - Animals with no heavy metals – receiving high dose DMSA daily x 3 weeks – appeared to produce cognitive decline (absolutely suggest do not do this)
  - *Likely related to deficiency as DMSA may be diminishing required elements in absence of toxic elements*
  - Protocol very different than single, low dose, in those with evidence of metal intoxication on blood testing
- 
- Stangle DE, Smith DR, Beaudin SA, Strawderman MS, Levitsky DA, Strupp BJ. Succimer chelation improves learning, attention, and arousal regulation in lead-exposed rats but produces lasting cognitive impairment in the absence of lead exposure. *Environ Health Perspect.* 2007;115(2):201-9.
  - Beaudin SA, Stangle DE, Smith DR, Levitsky DA, Strupp BJ. Succimer chelation normalizes reactivity to reward omission and errors in lead-exposed rats. *Neurotoxicol Teratol.* 2007;29(2):188-202.

➤ ‘Provocation agents dump good elements required by the body and causes mineral depletion’

- DMSA causes a significant increase in urine copper and zinc excretion.
- Response: Secure mineral sufficiency and hydration prior to testing
- Cautions
  - if used with other interventions that may deplete nutrients – purified water; other detox methods – e.g. sweating,
  - Avoid until after Rx mineral depletion on comprehensive element testing,
  - Hydration status impaired - caffeine & alcohol can deplete – impact on ADH
  - Adrenal disorder - mineralocorticoid aldosterone – regulates blood levels of electrolytes – sodium, potassium - do mineral status prior to testing

Smith et al. (2000) Succimer and the urinary excretion of essential elements in a primate model of childhood lead exposure. *Toxicol Sci* 54(2):473–480

Bradberry et al. Use of oral dimercaptosuccinic acid (succimer) in adult patients with inorganic lead poisoning. *Qjm*. 2009;102(10):721-32.

# Mineral insufficiency may impair elimination

- [Flora SJ. Hum Exp Toxicol.](#) 1991 Sep;10(5):331-6. Influence of simultaneous supplementation of **zinc and copper** during chelation of lead in rats.
- **The simultaneous supplementation of zinc and copper increased urinary lead excretion by (CaNa2EDTA) compared to treatment with CaNa2EDTA alone.**
- **Combination therapy was effective in potentiating the depletion of blood and renal lead by CaNa2EDTA and (DMSA).**
- **Combination therapy was also more effective in reducing hepatic lead by CaNa2EDTA and blood lead by (DMPS).**



## ➤ ‘Using provoked testing can make people feel awful’

- People with high levels of metals can experience worsening of symptoms if the dose of provocation agent is too aggressive.
- Much more likely with high dose, IV injection, & DMPS
  - May relate to enhanced mobilization of metals in circulation
  - May be sulfur sensitivity
  - May be in part related to shifts in essential minerals esp with higher dose
  - Some toxicant burdens (e.g. Hg-Cd synergy) may block kidney transport proteins – retention of metal-DMSA conjugates
  - If renal incapacity to handle large load, may be unable to excrete.
- ‘A gentle touch is necessary’ - Pre-test trial; low dose

## ➤ ‘Use of chelators causes redistribution into other tissues?’

- Alleged: Toxic elements stored in bone and other tissues are not immobilized; they can shift back into the bloodstream and potentially to other tissues
  - *esp CNS & Renal* - where they may exert toxic effects.
- Many things may induce redistribution – fever, weight loss, exercise, caloric restriction, hormonal changes, use of chelators, etc



# DMSA – CNS redistribution

- Animal studies suggest that DMSA does not redistribute i) lead or ii) arsenic to the central nervous system (CNS).
- Animal work: DMSA and DMPS diminish brain and kidney concentrations of iii) Hg



Goldfrank's Toxicologic Emergencies, Ninth Edition. Lewis S. Nelson, Neal A. Lewin, Mary Ann Howland, Robert S. Hoffman, Lewis R. Goldfrank, Neal E. Flomenbaum. 2006 by The McGraw-Hill Companies, Inc.

Aposhian H et al. Vitamin C, glutathione, or lipoic acid did not decrease brain or kidney mercury in rats exposed to mercury vapor. J Toxicol Clin Toxicol. 2003;41(4):339-47.

# Redistribution & Cerebral toxicity



- Rather than worsening situation, long been recognized that rapid reversal of cerebral toxicity occurs with EDTA & DMSA Rx for lead encephalopathy (i-iii)

- i) Byers RK, Maloof C. Edathamil calcium-disodium (versenate) in treatment of lead poisoning in children, Am J Dis Child , 1954, vol. 87 .559-69).
- ii) Whitfield CL, Ch'ien LT, Whitehead JD. Lead encephalopathy in adults, Am J Med , 1972,52:289-98.
- iii) Bradberry et al. Use of oral dimercaptosuccinic acid (succimer) in adult patients with inorganic lead poisoning. Qjm. 2009;102(10):721-32.

# Overall CNS Safety Perspective

- Human: Remarkable clinical improvement in various domains including neurological and psychiatric area - compelling
  - Improvement in conditions thought to be irreversible neurologically
  - Even with repeated or prolonged high dosing



# Children: CNS risk?



Several studies: Evidence for sustained improvement with interventions to diminish the load of toxic elements

Oral DMSA in children with autism:

In one study, 74% of ASD children reported improved with removal of toxic metals

- Patel et al. 2007. A comprehensive approach to treating autism and attention-deficit hyperactivity disorder: a prepiilot study. J Alternative and complementary medicine13(10):1091-1097.
- Adams JB et al. 2009. Safety and efficacy of oral DMSA therapy for children with autism spectrum disorders: part A-medical results. BMC Clin Pharmacol 9:16.
- Adams JB, et al. 2009 Safety and efficacy of oral DMSA therapy for children with autism spectrum disorders: part B - behavioral results. BMC Clin Pharmacol 9:17.
- Kidd PM. Autism, an extreme challenge to integrative medicine. Part II: Medical management. Alternative Medicine Review 2002;7:472-99
- Rossignol DA. Novel and emerging treatments for autism spectrum disorders: a systematic review. Ann Clin Psychiatry. 2009;21(4):213-36.

# Adults: Case Series (*QJM: An International Journal of Medicine* 2009; 102(10):721-32.)

- **Use of oral DMSA in adult patients with inorganic lead poisoning.**
- Case series of 17 lead contaminated adults
- DMSA therapy (30mg/kg/day) for at least 5 consecutive days markedly increased lead excretion
  - 12 fold increase in excretion overall compared to pre-treatment level
- Overall - **rapidly reversed lead related symptoms (largely neurological)** and gastrointestinal)
- DMSA was generally well tolerated by all - one course was discontinued after 2 days due to a severe mucocutaneous reaction.
- Oral DMSA 30 mg/kg/day is an effective antidote for lead poisoning

# 'Redistribution damage to the kidney?'

1. Rapid dumping of cadmium with high dose Rx may be associated with renal toxicity - DMSA does not have marked affinity to Cadmium
  2. NEJM: "A concern with chelation therapy is that renal insufficiency may be a contraindication for therapy. The opposite appears to be the case. In a randomized, controlled study of 64 patients with chronic renal insufficiency with elevated body burden of lead and without diabetes, three months of CaNa<sub>2</sub>EDTA weekly infusions resulted in slowing or reversing degeneration in the chelation group. Following 24 further months of treatment in 32 patients with elevated body lead burdens, glomerular filtration rate improved among the treatment group and decreased in controls."
- Nordberg GF. Chelating agents and cadmium toxicity: problems and prospects. Environ Health Perspect. 1984;54:213-8
  - Lin et al. Environmental lead exposure and progression of chronic renal diseases in patients without diabetes. NEJM 2003 Jan 23;348(4):277-86.

# Overall safety of provocation?



Theoretical redistribution concerns continue to be discussed – exercise caution

- ***\*Avoid in pregnancy and lactation\**** (will discuss)
- Proceed slowly to avoid mobilizing large pool, and to avoid overwhelming the body with large dose of mobilized metal

Lowry JA, WHO Expert Committees. ORAL CHELATION THERAPY FOR PATIENTS WITH LEAD POISONING.  
[http://www.who.int/selection\\_medicines/committees/expert/18/applications/4\\_2\\_LeadOralChelators.pdf](http://www.who.int/selection_medicines/committees/expert/18/applications/4_2_LeadOralChelators.pdf). 2010.

Cao et al. Chelation therapy in intoxications with mercury, lead and copper. J Trace Elem Med Biol. 2015;31:188-92.

### iii) Everybody is contaminated – results useless?

- Most people have been exposed to myriad toxic chemical agents (including toxic metals) in the contemporary world. Multiple sources confirm this: CDC, Health Canada, Cord blood studies, FIGO, etc.
- No results linking testing point to specific level where treatment should begin or end



Centers for Disease Control. NHANES – Fourth National Report on Exposure to Environmental Chemical Exposures, 2012. Available at  
<http://www.cdc.gov/exposurereport/pdf/FourthReport.pdf> Accessed November 24, 2012.

# Results may result in intervention

When you diagnose that a person has a considerable amount of any toxic agent – diminishing burden appears to be beneficial for the body

Diagnosis and Rx may have profound benefit

- Extensive evidence linking toxic exposure and accrual to adverse clinical outcomes even in asymptomatic patients (e.g. Cancer)
  - Linked birth addresses of children (1-15 y/o) who died of childhood malignancy over a 15 year period with sites of toxic emissions from industrial sites
  - Would be worthwhile for health profession to have discussion on role of screening for toxic agents

# Sauna bathing is inversely associated with dementia and Alzheimer's disease in middle-aged Finnish men.

- Prospective cohort study of 2,315 apparently healthy men aged 42-60 years at baseline,
- Median follow-up of 20.7 years

Compared to 1 sauna/week

HR (hazard ratio) for dementia was 0.78 for 2-3 sauna sessions per week

HR for dementia was 0.34 for 4-7 sauna sessions per week.



#### **iv) What about testing hair, nails, other tissues & secretions, porphyrins, etc**

##### Tissues & Secretions

- Toxic elements store differently in different tissues.
- Insufficient study researching levels in many tissues and different secretions (nails, semen, breast milk, etc) – need more research
- Testing may be useful if positive, but unreliable if negative. e.g Hg – toxic inorganic Hg (amalgam) does not go into hair well – might be negative with huge burden of Hg
- Biopsy results for some toxins also vary between different sites of same tissue.

##### Energy testing

- many claims and anecdotes; no credible published evidence seen in peer review PubMed indexed lit.

Ho G, et al Blood, urine, and hair kinetic analysis following an acute lead intoxication. Journal of analytical toxicology. 2011;35(1):60-4.

Yu GW, Laseter J, Mylender C. Persistent organic pollutants in serum and several different fat compartments in humans. J Environ Public Health. 2011;2011:417980.

# Hair testing

- Tends to represent blood over recent time period
- DN show very recent exposure
- DN show bioaccumulated burden
- Not reliable - often under-represents range of metal exposures
- Speciation differences even with same element
- Subject to external contamination – hair dyes, etc
- Many examples of low levels on hair, with abundant in provoked urine or sweat



# Porphyrin testing

- *Porphyrins* are naturally occurring proteins essential for the production and function of heme – a component of hemoglobin
- Some toxic metals affect metabolic pathway of porphyrin production  
Porphyrins in the urine, can be an indicator of heavy metal poisoning - e.g. Pb, Hg
- Not specific – may also be affected by POPs (PCBs, various pesticides, etc)
- Other confounders - infections, EMR, some medications, oxidative stress, some malignancies, etc. may also cause porphyriuria



## v) Laboratory test: Who to test? Can you test children?

- Anyone may be contaminated – from children to seniors
- Success in children with ASD
- Thus toxic elements should always be considered as a determinant of illness
- I routinely incorporate laboratory testing for toxic elements in workup with almost all patients with chronic illness
- But special mentions



# I avoid testing or Rx in gestation and lactation

- Redistribution with mobilization may increase vertical transmission
- Potential to endanger offspring
- Insufficient research



# Exquisite Fetal Vulnerability

Placenta does not filter many agents

Liver immature and unable to efficiently detoxify

Inadequate serum binding proteins

Inability to excrete – ongoing re-exposure

Rapidly growing organs

Proportionately, high toxicant – weight ratio



# I recommend Preconception care

*Review Article*

**Preconception Care: A New Standard of Care within  
Maternal Health Services**

Stephen J. Genuis and Rebecca A. Genuis



## vi) When to test patient for metals in the work-up?

- Initial blood metals assessment
- Follow up urine provocation after
  - Detailed history & physical examination
  - Assessment of metabolic function, renal function, etc
  - Results of toxicological screen & blood metal results
  - I often perform challenge in patients with
    - patient is stable,
    - pretest is OK,
    - ready to commence Rx

## vii. Provocation testing does not assess brain levels



- Common provocative agents (DMSA, DMPS, Ca EDTA) reported to not appreciably cross a healthy blood brain barrier
- Agents too hydrophilic to provide direct information about metals in the lipid-rich CNS.

### Response:

- Yet, many accounts in literature indicate improvement in neuropsychiatric problems with Rx with agents used in provocation therapy
  - e.g. improved neurological symptoms in >50% patients within 2 days of higher dose chelation.

Bradberry et al. Use of oral dimercaptosuccinic acid (succimer) in adult patients with inorganic lead poisoning. Qjm. 2009;102(10):721-32.

## (viii) ‘Are there other cautions?’ – *some that come to mind:*

- Caution with sulfur sensitivity ...GSH, DMSA, DMPS
- I prefer to avoid higher doses - no need to push – DN add anything
- Seniors - Proceed cautiously if overall health concerns (may use even lower dose 2-4 mg/kg)
- I always do trial of agents before full test
- Cautious when other medications on board – that may be disrupting metabolism
  - esp polypharmacy. Minimize use of unnecessary meds, v. low dosing, no need to push
- ***If uncertain about provocation in a specific situation – avoid and use sweating and GI interventions (GSH, chlorella, MCP, etc) as means to diminish toxic element burden***

## (ix) ‘Ultimately, some health officials state there is absolutely no benefit to provoked urine testing!’

Contention: It is the position of the American College of Medical Toxicology that post-challenge urinary metal testing ... has no demonstrated benefit.

Response:

- As blood and unprovoked urine are poor indicators of a lifetime of accrued toxic elements – provides a mechanism to assess that people have accrued metals
- Provoked urine excretes stored metal – well established...
  - American College of Medical Toxicology position statement on post-chelator challenge urinary metal testing. J Med Toxicol. 2010;6(1):74-5.



# Response

- Not assessing & Rx people damaged by toxic elements leaves sick and vulnerable people uncared for with their chronic affliction
- Leaves contaminated people at risk for long term adverse sequelae
- Not assessing women in preconception period, secures that transmission will be delivered to developing fetus with potential impact on children



# Children with ASD

- In a randomized, double-blind controlled trial, reductions in measures of the severity of autism were associated with urinary excretion of toxic metals following treatment with DMSA
- In another study, 74% of ASD children improved with removal of toxic metals



Adams et al. Safety and efficacy of oral DMSA therapy for children with autism spectrum disorders: part B - behavioral results. BMC Clin Pharmacol. 2009;9:17.  
Rossignol DA. Novel and emerging treatments for autism spectrum disorders: a systematic review. Ann Clin Psychiatry. 2009;21(4):213-36.

# Science

- Chronic toxicity from exposure to toxic elements pose significant morbidity and mortality if they are not recognized
- ***Is it scientific or ethical to ignore the etiology of chronic illness in people who have toxic element contamination?***



\*Molecular, Clinical and Environmental Toxicology. Vol 2. Clinical Toxicology. Berlin: Birkhauser Verlag. 2010. p 387.

# **Why is there such reservation about provocation testing?**

- Focus in toxicology training has been on acute poisoning which shows in ordinary blood tests
- The concern regarding accrual of low dose exposures and marked bioaccumulation in tissues that does not show on regular testing – often not recognized
- Many publications - asked to keynote at tox conference (toxicologists and public health officials) – frank discussion

# Conclude with Case History: Man with Bipolar Disease & Progressive Dementia

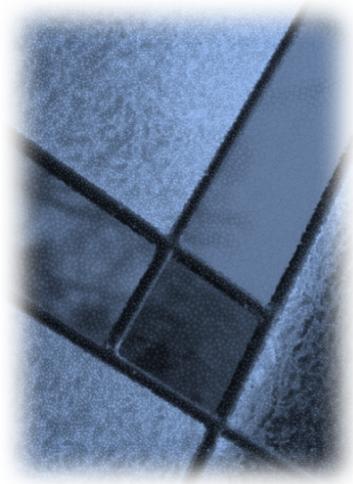
- 62 year old with 33 year history of bipolar illness.  
Recent development of progressive dementia.
- Memory, comprehension, communication and reasoning - rapidly declining.
- “Irreversible, degenerative condition.”
- Recommendation: chronic care placement.



Genuis SJ, Kelln KL. Toxicant exposure and bioaccumulation: a common and potentially reversible cause of cognitive dysfunction and dementia. Behav Neurol. 2015;2015:620143.

# Case: Man with Bipolar Disease & Progressive Dementia

- Assessment: History of work with stained glass in confined space – lead exposure
- Massive amounts of lead on challenge test; minimal levels on blood testing
- Repeated blood and unprovoked urine by other MD – no Pb
- Pb detoxification: over 9 months, astonishing recovery in mentation & mood
- Good sense of humor. “Great to have the man I married back in my life.”



Genuis SJ, Kelln KL. Toxicant exposure and bioaccumulation: a common and potentially reversible cause of cognitive dysfunction and dementia. Behav Neurol. 2015;2015:620143

# Bottom line

- Toxic elements do not belong in the body and are associated with harm
- Many recognized and documented mechanisms of harm associated with toxic element accrual
- In most cases, testing can help identify which toxic elements are involved and whether Rx will facilitate removal
- If diminish burden, considerable evidence that patients improve clinically – an immeasurable win for everyone



# Assessment for Toxic Elements in the Human Body

[www.stephengenuis.com](http://www.stephengenuis.com)

- videos & medical papers with associated references



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