Natural Detoxification

The human body is wonderfully capable of mitigating toxic exposures by means of natural detoxification at all levels. The biological basis for it is the three phase scheme of cellular excretion, familiar to everyone who has studied medicine and physiology,

The same three-phase process is at work all over the body. It moves endogenous toxins, like bilirubin, and exogenous ones like pesticides, drugs, and mercury, out of cells and toward their final route of elimination through the liver and the kidneys.

Understanding the three phase process of cellular excretion is essential to understanding the clinical practice of detox medicine.

Scheme and Process

Scheme

- Phase I – Activation
- Phase II – Conjugation
- Phase III – Transport

Process

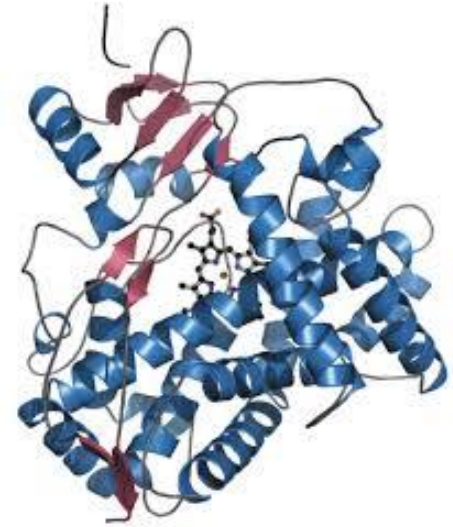
Phase I

Natural Pathways of Excretion

Phase I - Activation (cytochrome p450 enzymes)

- Necessary for organic molecules, not for ionized metal toxins like mercury
- Oxidative process
- Creates free radicals

Cytochrome P-450 with porphyrin active site in the middle:



The great family of cytochrome p-450 enzymes exists in all cells, oxidizing non-polar molecules, such as used-up steroid hormones, so they can be excreted by downstream reactions. If the next reactions are blocked, the phase I products can build up and become destructive free radicals. Mercury, like other metals, is already so reactive that it does not require p-450 activity to be ready for conjugation.

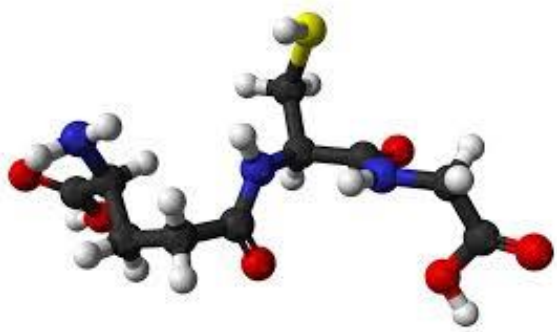
Phase II

Natural Pathways of Excretion

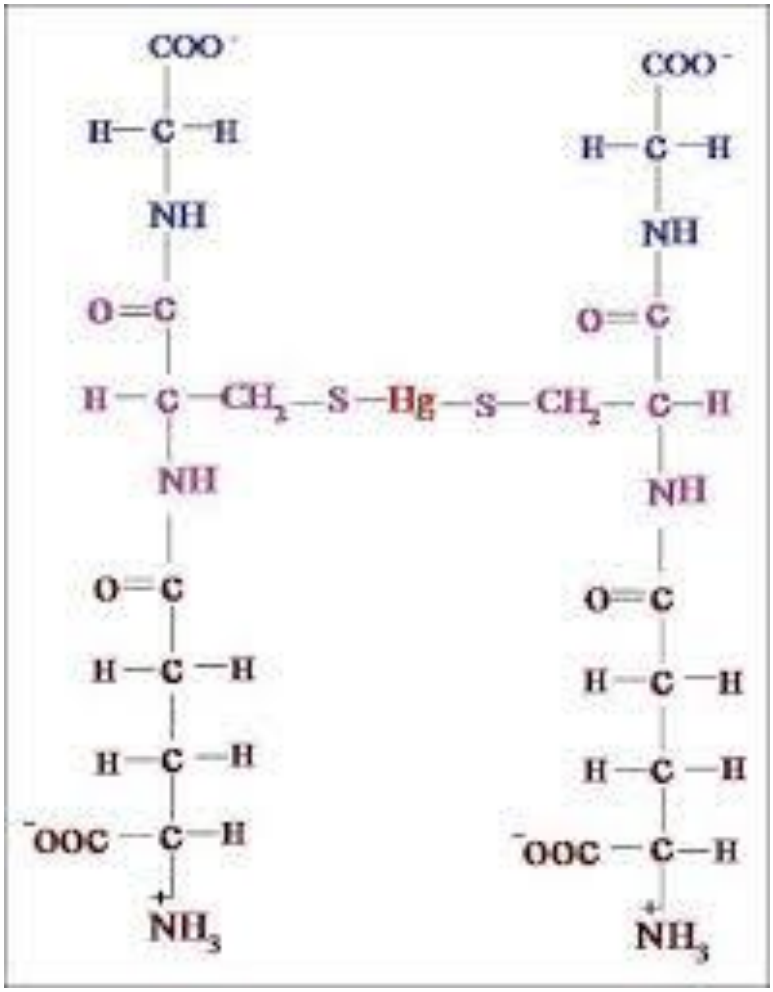
Phase II - Conjugation (glutathione, glycine, glucuronic acid, sulfate, etc.)

- Mercury conjugates with glutathione (GSH)
- Requires GST, glutathione-S-transferase enzymes
- Polymorphisms of GST can affect rate of conjugation, thereby affecting efficiency of excretion
- Availability of cysteine precursor limits the production of glutathione; therefore, protein nutrition is required

glutathione molecule:



mercury atom held tightly by the sulfur atoms of two glutathione molecules:



GSTs, glutathione-S-transferases, are the enzymes that attach mercury and many phase I products to glutathione for transport out of the cell. GSTs comprise a very large family of enzymes, with different varieties found in cytosol, mitochondria and microsomes. They can be as much as 10% of cytosolic protein in liver cells.

Many polymorphisms of GSTs exist, which means that some GSTs are less efficient than others. The result is that some individual people are more or less efficient at excreting those toxins, one of the many reasons why **some people seem to be uniquely susceptible** to the effects of toxic exposures.

The glutathione system is itself a complex, interconnected universe of many functions, with many enzyme systems using and affecting their critical currency, the glutathione molecule.

Glutathione system:

- Synthetases (synthesize GSH from precursors)
- Transpeptidases (take apart and reassemble)
- Transferases (Phase II conjugation)
- Peroxidases (radical quenching)
- Reductases (repair after quenching)
- Redoxins (using GSH as reducing equivalent for protein repair)
- Glutathionylation - protection of proteins

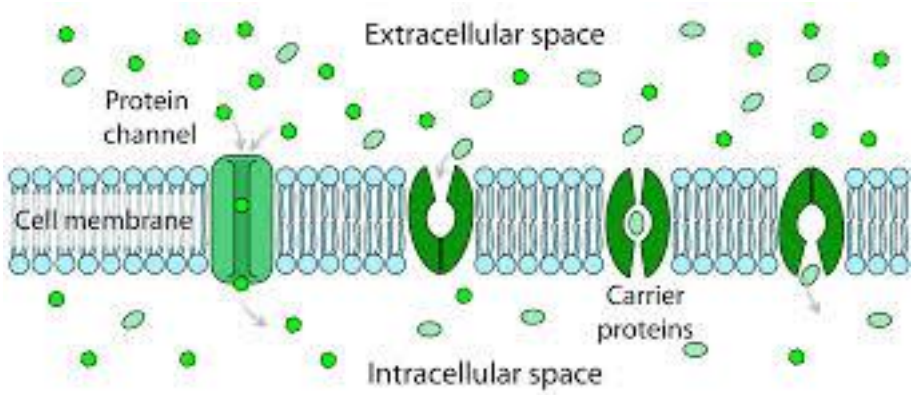
Phase III

Natural Pathways of Excretion

Phase III - Transport (membrane transport proteins: MRPs, OATs)

- Relatively few proteins are used to transport all the myriad conjugated products across cell membranes
- Polymorphisms of MRPs affect rate of excretion vs. retention (cit. Environ Health Perspect; DOI:10.1289/ehp.1204951)

Membrane transporter model:



The third phase of natural detoxification has been worked out only since the 1990s, as drug companies sought the source of resistance to their metabolic poisons. It turns out that those individuals with more efficient cell membrane transporters could deactivate drugs faster. Thus the name of the protein class: Multiple Drug Resistance Proteins, or MRPs.

The same process applies to all toxins, including mercury. These MRPs and their co-workers, the Organic Anion Transporters, or OATs, are responsible for moving conjugated products into and out of cells and into interstitial spaces, or into the lumen of bile ducts and renal tubules.

Inflammation

Inflammation is a major inhibitor of natural pathways of excretion.

Mercury swallowed from amalgam fillings is very pro-inflammatory in the gut, and a strong promoter of systemic inflammation.

Intestinal inflammation inhibits Phase III membrane transporters, which:

- Feeds back to inhibit Phase II conjugation,
- Allows a build-up of Phase I products, harmful free radicals!

While we usually focus on amalgam derived mercury that is absorbed by the lungs and distributed by the blood circulation, the mercury that is swallowed is a powerful ecological and pro-inflammatory influence in the gut. Intestinal inflammation exerts a powerful negative influence on the whole phase II -III system, inhibiting natural cellular excretion. This is another argument for the whole body approach, because all the methods that are used by physicians to reduce intestinal inflammation, whether it's addressing food sensitivities, gluten, parasites, dysbiosis, or reducing toxic metals in the gut, will tend to unlock natural detox function.

Measuring Mercury in the Body

What would lead a doctor to suspect metal toxicity in a patient? A wise old dentist once said, “Look in the mouth. If you have dentistry, you have a problem!” Naturally it’s much more extensive than that.

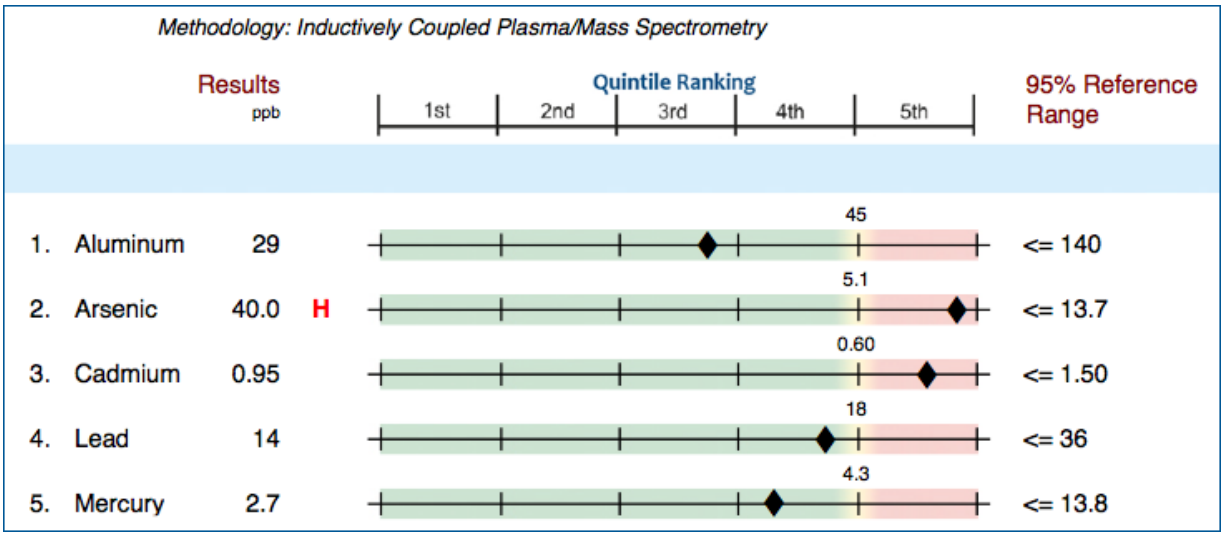
Many chronic conditions such as fatigue, fibromyalgia, digestive ailments, autoimmunity, neurodegenerative disorders, and others can have a component of metal toxicity, and should be evaluated for an underlying toxic influence.

A diagnosis of mercury toxicity is still a matter of clinical judgment. Clinical tests plus clinical symptoms paint a picture. The presence of a mercury body burden, measures of mercury retention, along with associated symptoms suggest the diagnosis.

Click to view some anecdotally derived symptom surveys that have been used to indicate mercury toxicity. (Note: you will also find these in the supplementary reading materials.)

Whole Blood Analysis

The most basic screen for toxic metals is in whole blood. Below is a sample of a report like that. In this case, the doctor should investigate where the patient would be getting so much exposure to arsenic and cadmium, and find out why they are retaining so much heavy metal.



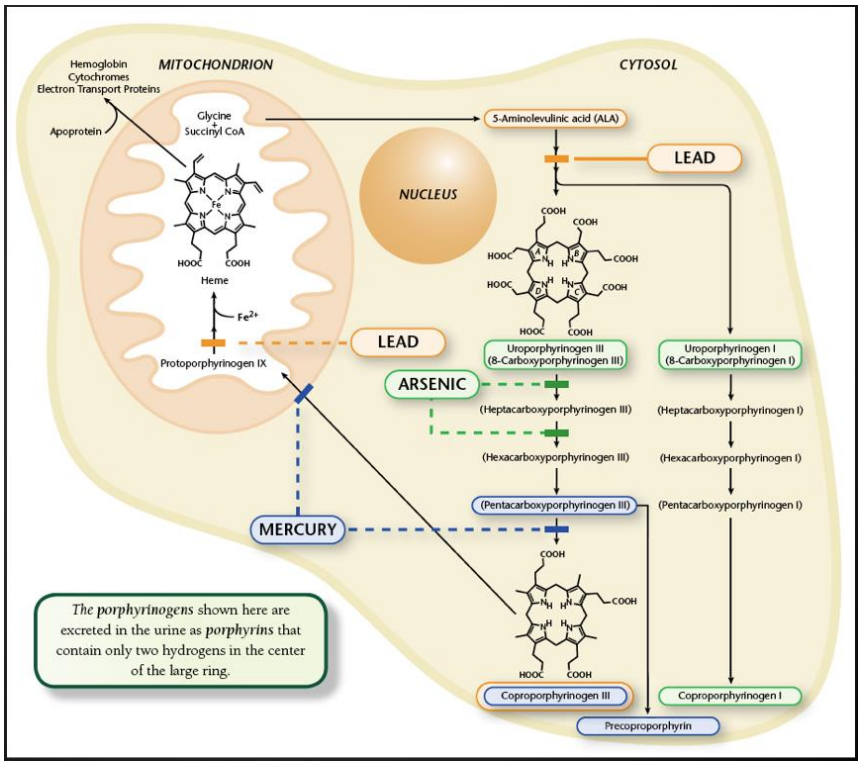
from Genova diagnostics, www.gdx.net

Porphyrin Profile Test

Beyond whole blood analysis, there are many more functional tests that can reveal toxic load. One that is particularly relevant to mercury is the Urinary Porphyrin Profile test.

The porphyrin pathway, involved in the synthesis of heme and cytochromes, turns out to have enzymatic steps that are inhibited in specific ways by a variety of toxins. Urine testing for by-products of this system can reveal evidence of toxic exposure.

Precoproporphyrin, highlighted on the bottom of the following illustration, is a non-functioning intermediary that is produced when mercury blocks the indicated enzyme. Its presence is considered to be a specific sign of mercury exposure.



from https://www.gdx.net/core/interpretive-guides/Porphyrins-IG.pdf

Precoproporphyrin is number 5 on the following chart. Together with number 9, the ratio of precoproporphyrin to its precursors, it is a strong signal of mercury exposure for this patient.

0060 Porphyrins Profile - Urine

Methodology: UPLC/Fluorescence detection, Colorimetry

Ranges are for ages 13 and over

Compound Tested	Results nmol/g creatinine		Quintile Ranking 1st 2nd 3rd 4th 5th	95% Reference Range
Porphyrin Pathway Intermediates				
1. Uroporphyrin I & III	7.1		16.6	<= 27.2
2. Heptacarboxyporphyrin	2.6		5.9	<= 11.2
3. Hexacarboxyporphyrin	<DL			<= 3.3
4. Pentacarboxyporphyrin	<DL		2.1	<= 5.4
5. Precoproporphyrin*	7.2		7.5	<= 14.8
6. Coproporphyrin I	16		33	<= 56
7. Coproporphyrin III	35		89	<= 159
Calculated Values				
8. Total Porphyrins	61		143	<= 233
9. Precopro/Uro I & III	1.01	H	0.64	<= 1.11
10. Copro I/Copro III	0.46		0.53	<= 0.87

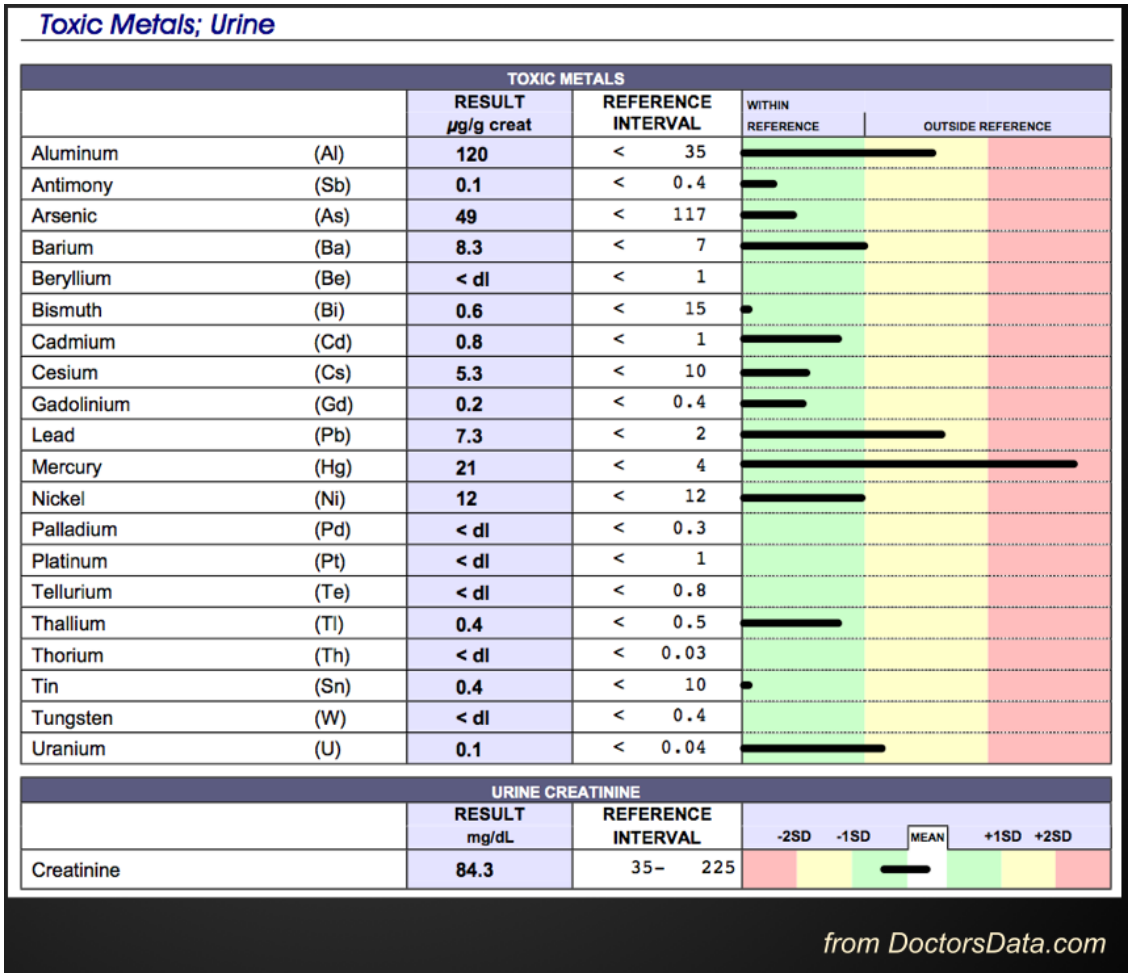
Creatinine = 175 mg/dL

<DL = less than detection limit

from Genova Diagnostics, gdx.net

Provoked Urine Test

Medicine has traditionally used urine mercury to assess levels of toxicity. Many have criticized plain urine mercury levels as being an unreliable measure of toxic load, and advocate the “stimulated” or “provoked” urine test. A baseline 6 or 24 hour urine sample is taken, followed by a dose of a chelating drug such as DMPS or DMSA. Another urine collection is taken immediately after. The degree of elevation of the second over the first urine level is taken as a better indication of the body burden of mercury.



Toxic Metals; Urine

TOXIC METALS		RESULT µg/g creat	REFERENCE INTERVAL	WITHIN REFERENCE / OUTSIDE REFERENCE
Aluminum	(Al)	120	< 35	
Antimony	(Sb)	0.1	< 0.4	
Arsenic	(As)	49	< 117	
Barium	(Ba)	8.3	< 7	
Beryllium	(Be)	< dl	< 1	
Bismuth	(Bi)	0.6	< 15	
Cadmium	(Cd)	0.8	< 1	
Cesium	(Cs)	5.3	< 10	
Gadolinium	(Gd)	0.2	< 0.4	
Lead	(Pb)	7.3	< 2	
Mercury	(Hg)	21	< 4	
Nickel	(Ni)	12	< 12	
Palladium	(Pd)	< dl	< 0.3	
Platinum	(Pt)	< dl	< 1	
Tellurium	(Te)	< dl	< 0.8	
Thallium	(Tl)	0.4	< 0.5	
Thorium	(Th)	< dl	< 0.03	
Tin	(Sn)	0.4	< 10	
Tungsten	(W)	< dl	< 0.4	
Uranium	(U)	0.1	< 0.04	

URINE CREATININE		RESULT mg/dL	REFERENCE INTERVAL	-2SD -1SD MEAN +1SD +2SD
Creatinine		84.3	35– 225	

from DoctorsData.com

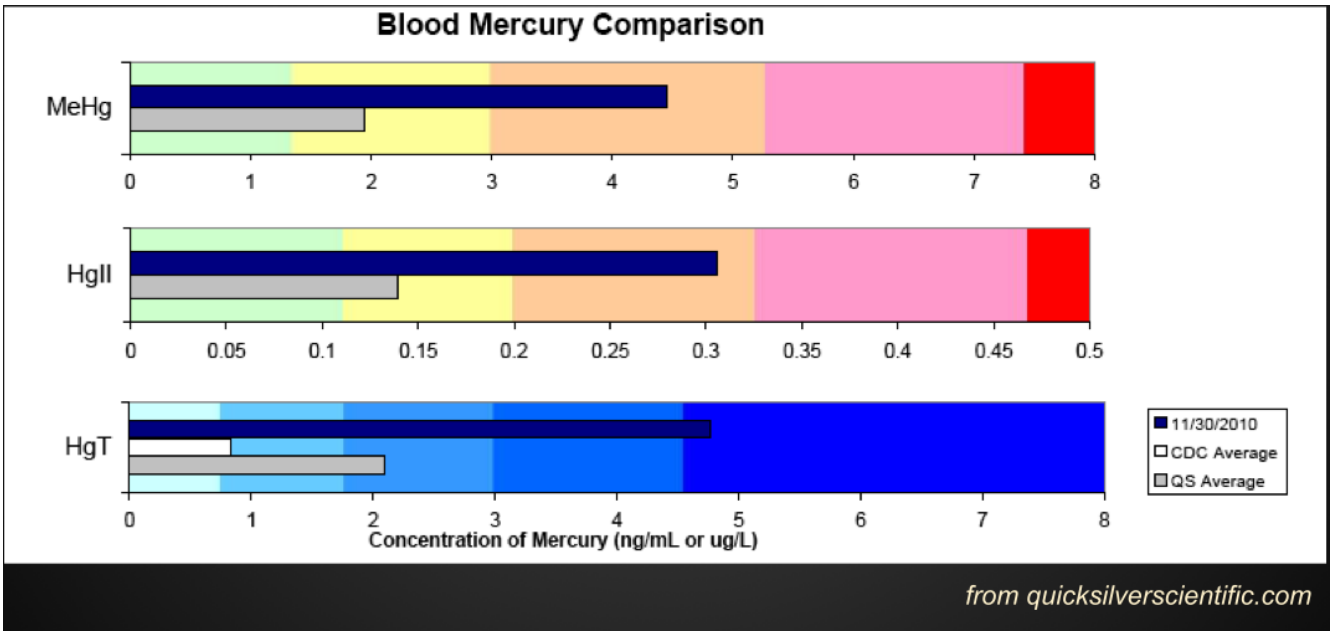
Quicksilver Tri-test

A newer test, the Quicksilver Tri-Test, uses samples of blood, hair, and urine. This test is innovative in that it provides a technology that “speciates” mercury. That is, it distinguishes between organic methyl mercury and inorganic mercury 2+ in the blood. This information leads us to a better understanding of the sources of mercury exposure, and the pathways of its excretory fate.

In general, methyl mercury in blood is derived from seafood, while inorganic mercury derives from amalgam fillings. And, for the most part, methyl mercury is excreted by the phase I-II-III systems in the liver, while inorganic mercury is excreted mostly by the kidneys.

Blood Mercury Comparison

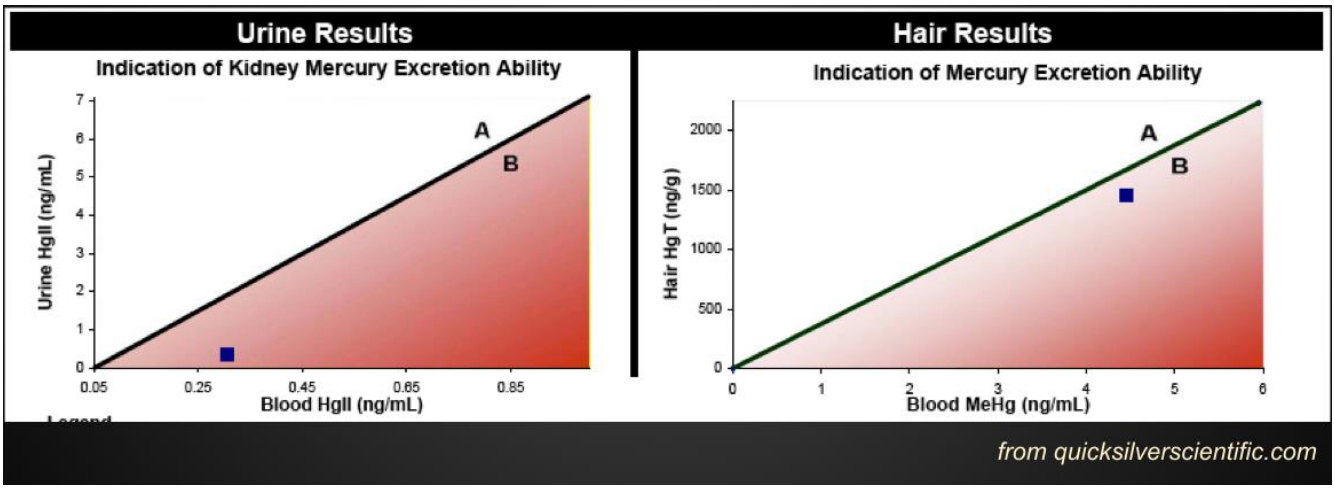
The following test results show the blood levels of organic, inorganic, and total mercury for a person with elevated levels of both mercury species.



Tri-test Ratios

The second part of the Quicksilver report for the same patient gives us an indication of their ability to excrete mercury by the hepatic and the renal pathways. Hair mercury stands in for the liver, because the same cellular mechanisms are employed, and at least 95% of the mercury expressed in hair is from the organic fraction. By the same token, at least 95% of the mercury in urine is from the inorganic fraction.

So, in this case we have slightly low hair mercury relative to the methyl mercury in blood. This is an indication of stressed phase II and III function. But the urine mercury is severely low relative to the inorganic mercury in the blood, which indicates poor kidney function and leads to mercury retention. This type of information gives us a clue as to which areas of metabolism to direct our supportive therapies.

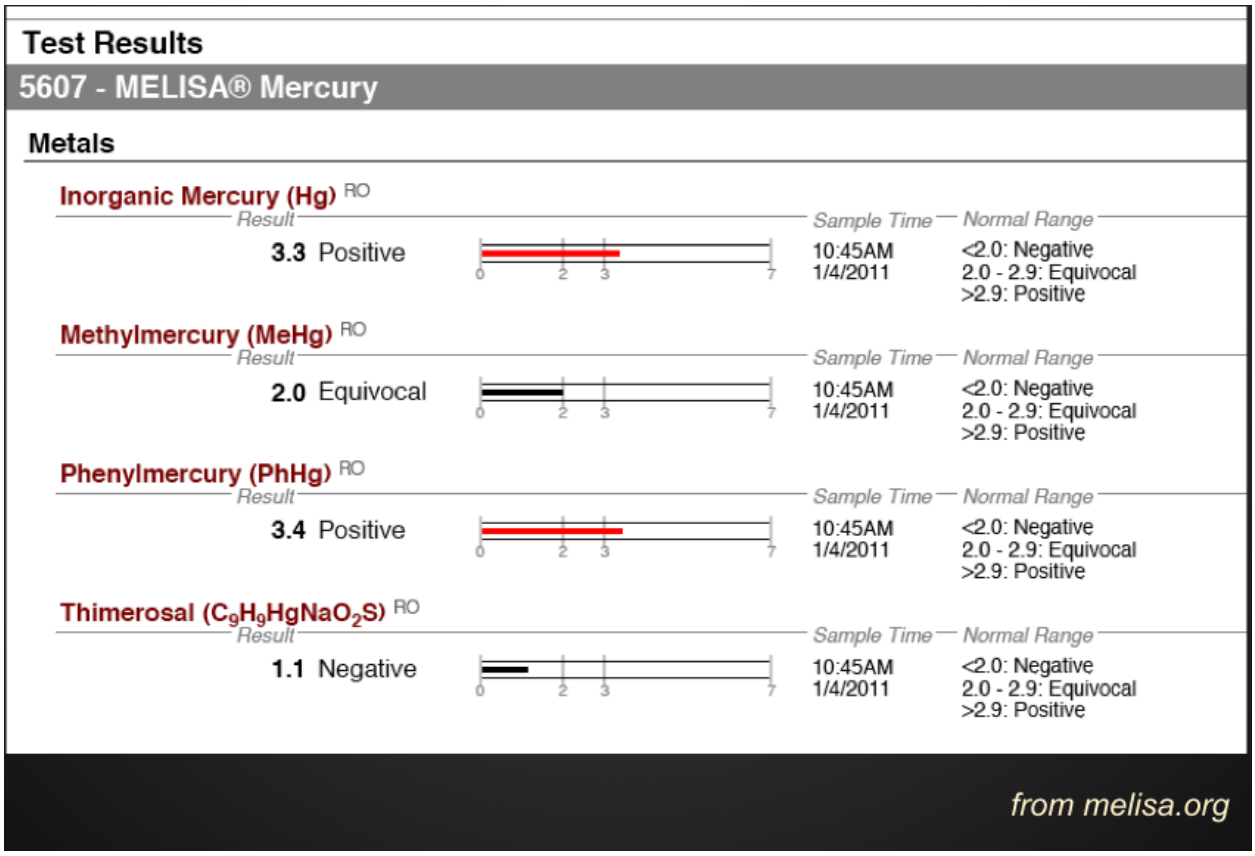


Immune System Testing

A completely different dimension of mercury toxicity is its ability to provoke an immune response. Mercury compounds can provoke the production of IgG and IgM antibodies, leading to type II and III antibody-dependent hypersensitivity. Mercury can distort normal biochemical molecules, and provoke autoimmunity, a process called “haptenization.” And it can provoke the insidious type IV delayed hypersensitivity, and generate long-term memory in lymphocytes.

A positive skin patch test would indicate delayed hypersensitivity, but it involves directly exposing the patient to the toxic substance, and has been known to cause severe reactions.

The MELISA test is a blood test that uses live lymphocyte cultures. It is currently the best method for evaluating delayed hypersensitivity to immunologically active metals.



Test Results

5607 - MELISA® Mercury

Metals

Inorganic Mercury (Hg) RO

Result	Sample Time	Normal Range
3.3 Positive	10:45AM 1/4/2011	<2.0: Negative 2.0 - 2.9: Equivocal >2.9: Positive

Methylmercury (MeHg) RO

Result	Sample Time	Normal Range
2.0 Equivocal	10:45AM 1/4/2011	<2.0: Negative 2.0 - 2.9: Equivocal >2.9: Positive

Phenylmercury (PhHg) RO

Result	Sample Time	Normal Range
3.4 Positive	10:45AM 1/4/2011	<2.0: Negative 2.0 - 2.9: Equivocal >2.9: Positive

Thimerosal ($C_9H_9HgNaO_2S$) RO

Result	Sample Time	Normal Range
1.1 Negative	10:45AM 1/4/2011	<2.0: Negative 2.0 - 2.9: Equivocal >2.9: Positive

from melisa.org

Results

Clinical Tests plus Clinical Symptoms Paint a Picture

"Findings are extremely variable and include tremors (shakes), salivation (excess saliva), stomatitis (inflammation of the mouth), loosening of teeth, blue lines on gums (tattoos), pain and numbness in the extremities (multiple sclerosis symptoms), nephritis (inflammation of the kidney), diarrhea, anxiety, headache, weight loss, anorexia, mental depression, insomnia, irritability, instability, hallucinations, and evidence of mental deterioration (Alzheimer-like symptoms)"

Hg Materials safety data sheet (MSDS) for acute exposure

Test Results that Best Correlate with Self-reported Symptoms

Test results in order of efficacy:

1. Retention of Hg II+ - (low urine/blood ratio in the Quicksilver test)

> 2. Retention of Me-Hg - (low hair/blood ratio in the Quicksilver test)

> 3. Total mercury - (similar to provoked urine mercury)

> 4. Porphyrin profile - (poor correlation with symptoms)

MELISA-positive status may correlate with symptoms, independent of other variables.

unpublished IAOMT study results

Conclusion

A General Conclusion

Chronic low level exposure and body burden of toxins, such as amalgam mercury, is stressful to the body, but the degree of toxic illness that results is a function of the body's ability, or lack of ability, to excrete the toxins.

A Corollary

A corollary and a feature of "retention toxicity":

A body burden of mercury stresses the kidneys, so that over time it reduces the body's ability to excrete the mercury by the urinary pathway. As that happens, toxic illness increases.

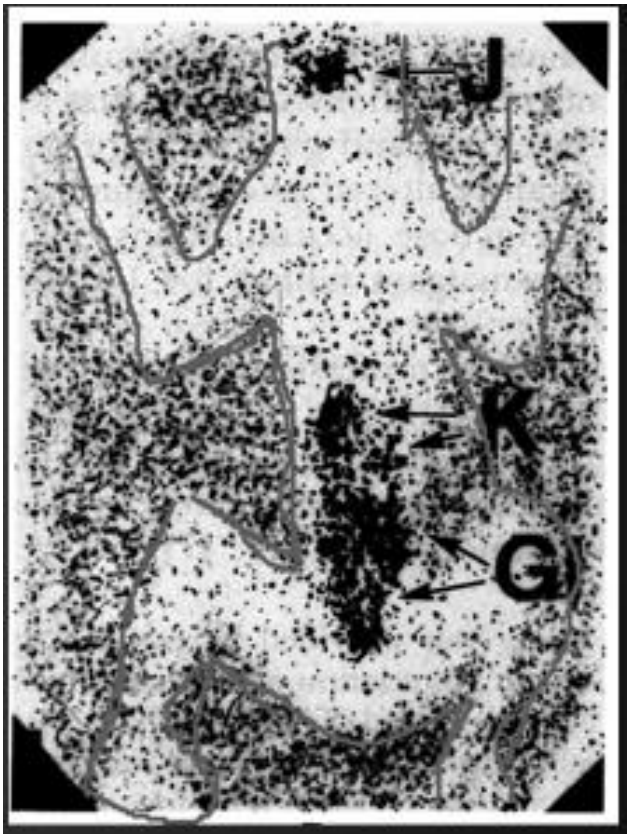
Promoting Natural Excretion

For some people, safely removing their mercury fillings can be enough to allow them to detox over time. For others, the fillings are just the tip of the iceberg. Many they need help to get their cellular excretory systems going effectively. If they lack an intact ability to excrete toxic metals just by normal excretory function, they will require extra help to detox over time.

Traditional methods of natural medicine can be very helpful. Intestinal cleansing, nutritional support, and herbal chelation can all lead to success. And let's not forget exercise, which we know positively affects everything about health!

Intestinal Cleansing

Animal studies of exposure to amalgam fillings have proven that much of the mercury gets stored in the digestive tract.



The gut is a chemical reaction vessel and when exposed to mercury, it becomes a reservoir of toxicity where complex interactions between human and microbial metabolisms take place. The bacteria can turn inorganic mercury into easily absorbed methyl mercury, and de-methylate it back to inorganic. They can take conjugated mercury that the liver has dumped into the bile, decouple the mercury from glutathione, and make it available to be reabsorbed back into the bloodstream. Reducing the mercury concentration of the bowel contents is a powerful healing method. It creates the conditions for a net reduction of mercury throughout the body.

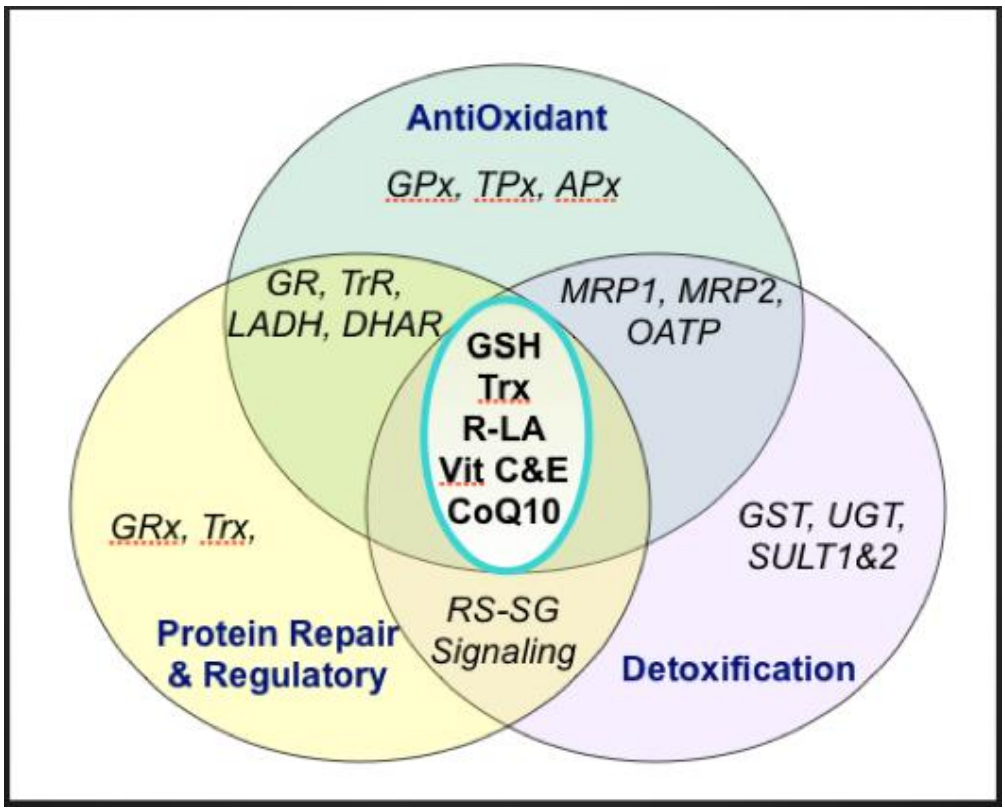
Intestinal cleaning to reduce entero-hepatic recirculation of toxins, gut inflammation, and systemic inflammation can be achieved using products such as:

- Charcoal
- Clay (bentonite, zeolite)
- Quicksilver IMD supplement

Up-regulation of the Cellular Detox System

The universe of cellular defenses is vast and complex with numerous points of vulnerability and strength. Each of the many proteins involved are subject to variability in efficiency due to genetic polymorphisms, as well as epigenetic influences. Likewise, there are many avenues available for nutrient support and targets for pharmaceutical action.

The collection of small molecules in the center of the following diagram, are molecules that are the common currencies of anti-oxidant and detox function: glutathione, thioredoxin, r-lipoic acid, vitamin C, vitamin E, coenzyme Q-10. They all can be augmented by nutrition.



The detox/antioxidant/cell repair “super system” can be up-regulated by many of the familiar healing herbs, such as:

- Boswellia
- Curcumin
- Resveratrol
- Takesumi
- St. John’s Wort
- Plant polyphenols, such as quercetin, etc.

The reparative super-system is under the overall control of the NRF-2 gene complex. Many of the well-known healing herbs act by promoting NRF-2 gene transcription. This increases the activity of the whole system, including phase II and phase III enzymes. It's interesting that so many herbs that are described as anti-inflammatory turn out to have this mechanism in common, acting to promote expression of these "good" genes.

The Nrf2 antioxidant response pathway is the primary cellular defense against the cytotoxic effects of oxidative stress.

Role of Clinical Nutrition

As always, good nutrition is essential to healing. Malnutrition increases susceptibility to toxicity. Clinical nutrition's role for good general health includes:

- Good hydration
- Promoting an alkaline body chemistry environment
- Reducing systemic inflammation
- Reducing food sensitivities
- Providing supportive cofactors

Supportive cofactors such as:

- Vitamin C, a-lipoic acid, etc.
- Amino acids
- Nutritional minerals: iron, copper, zinc, selenium, calcium, magnesium, etc.

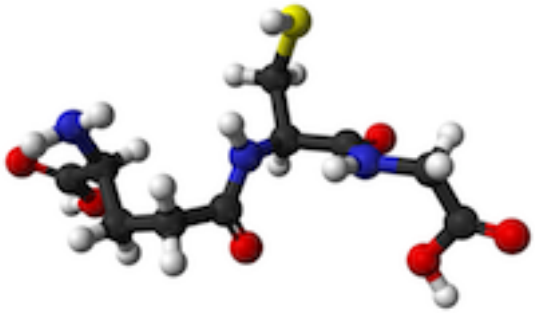
Raising the Levels of Glutathione

Many of the nutritional approaches to promotion of natural excretion are aimed at increasing reduced glutathione levels inside cells. Unfortunately, just feeding a person supplemental glutathione does not seem to work, because it is broken down in the digestive tract, or used up by the cells of the gut lining. Supplementing the building blocks of glutathione, especially n-acetyl cysteine or d,l-methionine, and the factors that help recharge the anti-oxidant systems is more efficient.

Some doctors have used IV glutathione with mixed results. The more recently developed method of packaging supplements in lipid nanospheres, or liposomes, allows them to be absorbed directly without being digested. Oral supplementation with liposomal glutathione may be the best way to deliver it to the cells.

To raise the levels of intracellular glutathione:

- Provide adequate protein
- Supplement with precursors: cysteine, methionine
- Supplement with recharge anti-oxidants: vitamin C, a-lipoic acid
- Promote good sleep to take stress off anti-oxidant systems
- Include *Liposomal* glutathione supplement for direct absorption



Exercise

Exercise as a detox method:

- Positively affects everything about health
- Encourages blood circulation and lymphatic drainage
- Engages the mechanism of sweat to excrete toxins
- Encourages replacement of mercury-toxic mitochondria

The only way to detox at a mitochondrial level is to replace the old mitochondria. The only way to encourage that is by exercise with adequate levels of intracellular glutathione present.