

*Mercury:
A metabolic perspective minus
the fear*

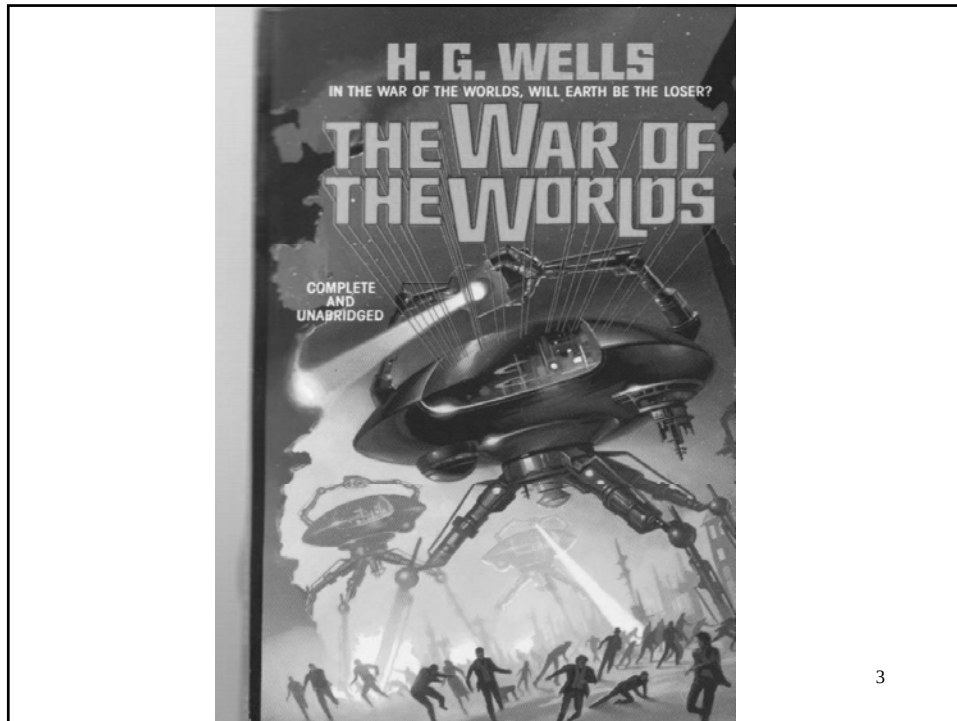


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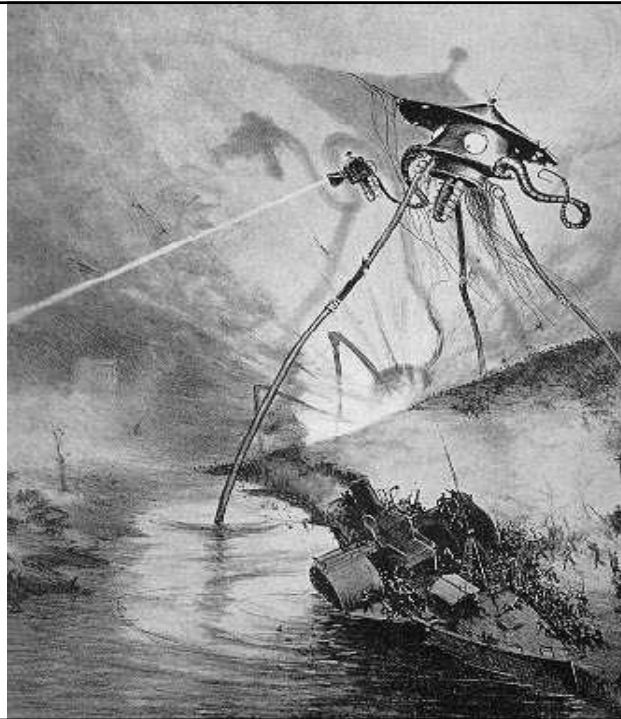
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- "...the Martians –*dead!* – slain by the putrefactive and disease bacteria against which their systems were unprepared; slain as the red weed was being slain; slain, after all man's devices had failed, by the humblest things that God, in his wisdom, has put upon this earth."
- "These germs of disease have taken toll of humanity since the beginning of things—taken toll of our prehuman ancestors since life began here. But by virtue of this natural selection of our kind we have developed resisting power; to no germs do we succumb without a struggle, and to many—those that cause putrefaction in dead matter, for instance—our frames are altogether immune."

4

- “That they did not bury any of their dead, and the reckless slaughter they perpetrated, point also to an entire ignorance of the putrefactive process.”
- “For so it had come about, as indeed I and many men might have foreseen had not terror and disaster blinded our minds.”

5



6



*Obligatory, fear based
introduction to mercury*

8

Key points

- The issue of environment mercury did not start with dentists and the industrial revolution.
- Because the relationship between all life on earth and mercury has been so intimate, the laws of nature have allowed most all living beings to develop a fairly sophisticated detoxification system to efficiently deal with the mercury.

9

Key points

- While the anti-mercury militia (chelation, amalgam removal) has its place, we are best served when we facilitate the laws of nature through optimizing endogenous detoxification mechanisms via good nutrition, supplements, healthy lifestyle modifications and, of course, practical mercury avoidance measures.

10

Key points - amalgam

- The world would be best served if all amalgam placement ceased immediately – ***in most situations.***
- We need to address patients who currently have several large amalgams with our hearts as well as our intellect – ***but minus the fear.***

11

Environmental Medicine | Article

Perceived Treatment Efficacy for Conventional and Alternative Therapies Reported by Persons with Multiple Chemical Sensitivity

Pamela Reed Gibson, Amy Nicole-Marie Elms, and Lisa Ann Ruding
School of Psychology, James Madison University, Harrisonburg, Virginia, USA

Multiple chemical sensitivity (MCS) is a condition in which persons experience negative health effects in multiple organ systems from exposure to low levels of common chemicals. Although symptoms experienced from particular chemicals vary across persons, they are generally stable within persons. The sensitivities often spread over time, first to related chemicals and then to other classes of chemicals. This study examined self-reported perceived treatment efficacy of 181 treatments used by 917 persons with self-reported MCS. Treatments examined included environmental medicine techniques, holistic therapies, individual nutritional supplements, detoxification techniques, body therapies, Eastern-origin techniques, newer therapies, prescription items, and others. The three most highly used treatments were creating a chemical-free living space, chemical avoidance, and prayer. Both creating a chemical-free living space and chemical avoidance were rated by 95% of respondents as helpful. Results for most therapies were mixed. Participants had assessed a mean of 12 health care providers and spent over one-third of their annual income on health care costs. We discuss this data on personal treatment and describe respondents' attitudes toward the possibility of healing from MCS. **Key words:** chemical hypersensitivity, chemical injury, environmental allergy, environmental illness, environmental toxicology, multiple chemical sensitivity. *Environ Health Perspect* 111:1498–1504 (2003). doi:10.1289/ehp.6233 [Online 9 April 2003]

Although some progress has been made in the development of a clear definition for multiple chemical sensitivity (MCS) (Bartha et al. 1999) and in elucidating symptom profiles (Jeffries et al. 2001), we still lack a widely accepted treatment protocol for the condition. Consequently, patients experience with a wide variety of both conventional and holistic health treatments. Although practitioners of environmental medicine have a systematic approach for working with MCS, there is no common MCS treatment protocol accepted across medical disciplines. The field of environmental medicine espouses guidelines and techniques for addressing MCS, but critics maintain that the techniques have not been efficacious in double-blind trials. Because research on treatments for MCS is sparse, people have few data on which to rely when choosing interventions. Physicians have described health findings from patient samples (Bell et al. 1993; Galland 1987; Heuser et al. 1992; Lieberman and Cason 1998; Ross 1992a) and suggested treatment strategies (Jewett 1992; Ross 1992b; Zinn 1992), but only a small number of published studies describe MCS treatment and follow-up (Lax and Henningsen 1995). In addition, only three studies to date have examined patients' assessment of a large number of health interventions for MCS (Gibson 2000; Johnson 1996, 1997a, 1997b, 1998; Leroy et al. 1996). All three studies found that chemical avoidance measures were rated as very highly effective, whereas prescription drugs were rated the least effective of all treatments. Life impact research shows that people with MCS tend to spend a considerable amount of

their incomes on large numbers of treatments, find that spending all annual income \$35,000 to \$40,000 is not developing 8.6 percent of respondents report health and experience

Our purpose was to investigate perceived efficacy of those treatments. The study was not limited to conventional techniques. Rather, we sought to gather data on any techniques that respondents had tried, in an effort to understand the experience of seeking medical treatment for a poorly understood condition. We chose to evaluate retrospective reports from patients to assess the large number of treatment methods used by this population of considerable size. Results may be helpful to patients, providers, and advocates in making decisions about resource allocation.

Methods

Participants. Participants were 917 persons contacted through the Chemical Injury Information Network (CIIN, White Sulphur Springs, MT; ciin.org) and through MCS support groups. People learn about and become members of CIIN and other support groups through other persons with MCS, physicians' offices, email media, and the

Internet. Most groups publish newsletters with resources and informational support for persons with MCS and other interested parties. Respondents were 82% women and 18% men. Participants' ages ranged from 20 to 82 years, with a mean age of 53 years. Respondents' characteristics are presented in detail in Table 1. When asked to identify the severity of their condition, 7% identified their MCS as mild, 32% as moderate, 45% as severe, and 13% as totally disabling.

Procedure. This research, including the survey instrument, was reviewed by the James Madison University Institutional Review Board. All members of CIIN were invited to respond via e-mail; sources that authorized

Gibson PR et al. Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity, *Environ Health Perspectives*, Vol. 111, No. 12, pp. 1498-1504, September 2003.

from the three efficacy studies done to date (Gibson 2000; Johnson 1996, 1997a, 1997b, 1998; Leroy et al. 1996), elements of environmental medicine protocol, widely used nutritional supplements, well-known body therapies and other holistic therapies, and other current treatments described to us by persons with MCS. Treatments were grouped into the following nine categories: environmental medicine/toxic techniques, holistic

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We thank C. Wilson and J. Wilson of the Chemical Injury Information Network for their support in survey distribution and funding. We also appreciate the efforts of all respondents who completed surveys.

This research was supported in part by a grant from the Chemical Injury Information Network and a James Madison University Faculty Summer Research grant.

The authors declare they have no conflict of interest. Received 17 June 2002; accepted 16 December 2002.

12

- “Respondents were 82% women and 95% Caucasian. Participants’ ages ranged from 20 to 82 years, with a mean age of 53 years.”
- “When asked to identify the severity of their condition, 7% identified their MCS as mild, 32% as moderate, 45% as severe, and 13% as totally disabling.”

13

Milk thistle				
# tried	Harmed	No effect	Helped	HH ratio
458	9.7	41.6	48.7	5.0
Remove mercury dental fillings				
425	9.2	47.1	43.8	4.8
Hulda Clark’s parasite program				
87	28.0	36.4	35.5	1.3
Coffee enemas				
146	19.7	32.0	48.3	2.5
Colonics				
222	13.2	28.2	58.6	4.4

14

A look at the realities of large scale amalgam removal and replacement

- “Biological side-effects of composites may be caused by toxic or allergic reactions to various components of the materials. These components may be residual impurities from the manufacturing processes, chemicals formed during polymerization or degradation, e.g., formaldehyde, or chemicals released from the material because of incomplete polymerization, e.g. methacrylate.

Horsted-Bindslev P et al, *Dental Amalgam - A Health Hazard*, 1991, Copenhagen, Denmark, Munksgaard.

15

A look at the realities of large scale amalgam removal and replacement

- “Also the risk of mucosal reactions to composites and the chemicals used for improved bonding to tooth substance should be considered.”

Horsted-Bindslev P et al, *Dental Amalgam - A Health Hazard*, 1991, Copenhagen, Denmark, Munksgaard.

16

A look at the realities of large scale amalgam removal and replacement

- “The prevalence of gold sensitivity in individuals with gold dental restorations is approximately 33.8%. This is significantly greater than the 10.8% prevalence seen in individuals without gold dental appliances as well as greater than the 3-year rate from the Oregon Health Sciences University Contact Dermatitis Clinic.”

Schaffran RM et al. Prevalence of gold sensitivity in asymptomatic individuals with gold dental restorations, *Am J Contact Dermat*, 1999, Vol. 10, No. 4, pp. 201-8.

17

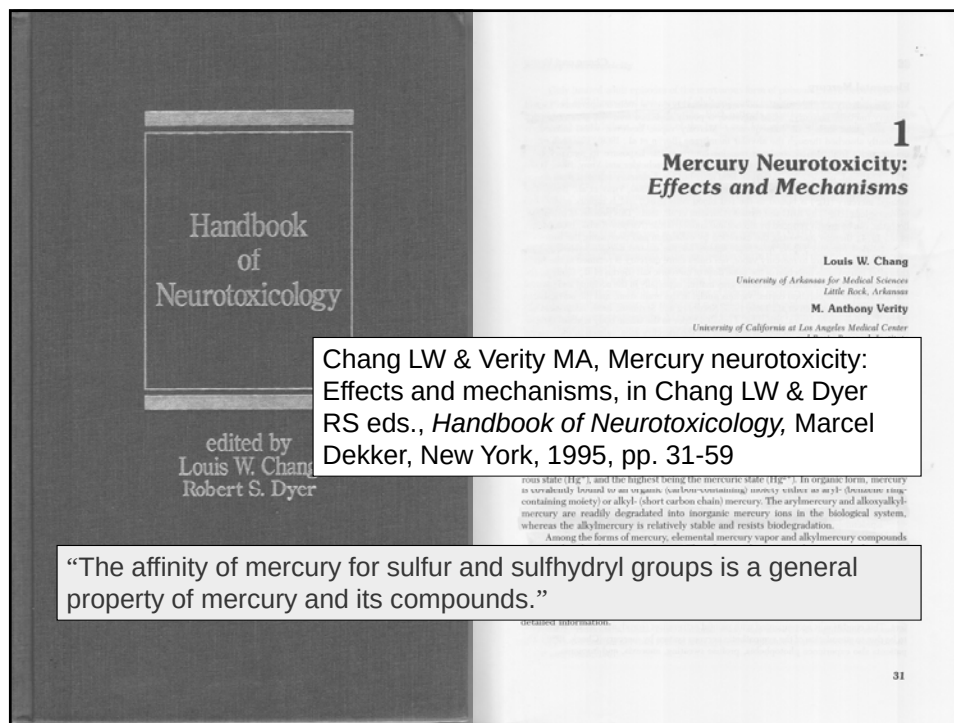
Controversies to be addressed

- Do we even have a mercury problem in this country?
- Who caused the mercury problem?
- Is there a direct relationship between levels of mercury in the body and the level of toxicity experienced by an individual?
- What form of mercury is most toxic?
- Can mercury levels in the body be ascertained via laboratory testing?
- What, specifically, is the best way to address elevated mercury levels in various patients?

18

*What does mercury do that
makes it so bad?*

19

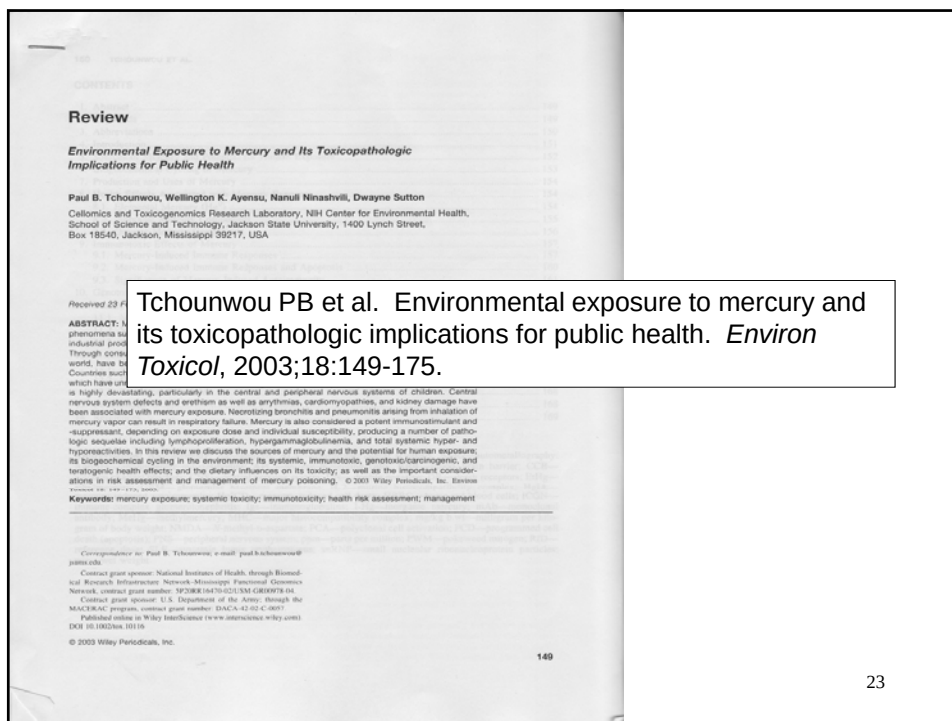


*Do we even have a mercury
problem in this country?*

21

The big picture

22



- “Between 2700 and 6000 tons of elemental mercury is released per year via natural means to the biosphere through degassing from the earth's crust and oceans.”
- “Volcanoes can be an important natural source.”
- “Industrial wastes and the combustion of fossil fuels add up to an additional 2000-3000 tons of mercury to the environment.”
- “Levels of mercury vapor in the ambient atmosphere are so low that intake from this source is negligible.”

***Mercury pollution -
More than just an issue of amalgam***

- **“Although the natural degassing of the earth’s crust is the major source of environmental Hg, man-made release of Hg from mining, smelting, industrial discharge, such as chloralkali plants and paper pulp industries, burning fossil fuels, and other activities significantly contributes to the total global burden.**

Bagenstose LM et al, *Murine mercury-induced autoimmunity*. Immunologic Res, 1999. **20**(1): p. 67-78.

25

***Mercury pollution -
More than just an issue of amalgam***

- **Hg and Hg salts can be found in dental amalgam, creams, ointments, antiseptics, paints, foods, diuretics, cosmetics, and fumigants. Additionally, free Hg is found in barometers, thermometers, medical instruments, and certain types of lamps.”**

Bagenstose LM et al, *Murine mercury-induced autoimmunity*. Immunologic Res, 1999. **20**(1): p. 67-78.

26

Mercury pollution - More than just an issue of amalgam

- **“Large amounts of the metal are used in the production of chlorine and sodium hydroxide (chloralkali industries). The largest portion of the metal is used in electrical and electronic equipment, instruments, and apparatus. Compounds of mercury are employed as catalysts, pigments, and fungicides.”**

Schafer SG et al, *Metals*, in *Toxicology*, H. Marquardt et al, Editor. 1999, Academic Press: San Diego. p. 755-804.

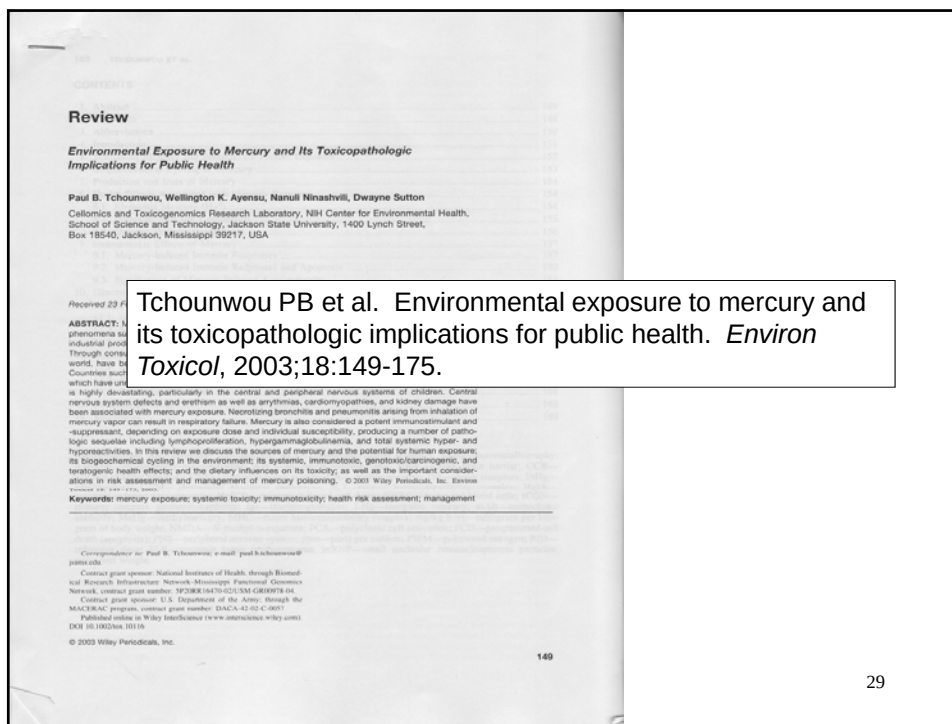
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Why is mercury so popular in industry?

- **“Mercury has been widely used in industrial processes because of its chemical and physical properties (for example, it conducts electricity, it responds to temperature and pressure changes, and it forms alloys with many metals.”**

Mahaffey, K.R., *Methylmercury: A new look at the risks*. Public Health Reports, 1999. **114**(5): p. 397-415.

28



29

“Mercury toxicity depends on exposure route, frequency, dose level, nutritional status, industrial susceptibility, and genetic predisposition.”

30

*What is the most important
source of mercury clinically?*

- ***It depends who you talk to!!***

31

- “It’s the dentists’ fault!
- “No, it’s the airborne polluters’ fault!!”
- “No, it’s the vaccine producers’ fault!!”

32

What is the most important source of mercury clinically?

- **“...the natural degassing of the earth’s crust is the major source of environmental Hg...”**

Bagenstose LM et al, *Murine mercury-induced autoimmunity*. Immunologic Res, 1999. **20**(1): p. 67-78.

33

What is the most important source of mercury clinically?

- **“Inorganic mercury is, due to dental amalgam fillings, the principal source of mercury exposure in the general population.”**

Hultman, P. and Hansson-Georgiadis H, *Methyl mercury-induced autoimmunity in mice*. Toxicol Appl Pharmacol, 1999. **154**(3): p. 203-11.

34

What is the most important source of mercury clinically?

- **“The major source of non-occupational exposure is dietary intake of methylmercury, with fish and seafood the main culprits because of their propensity to concentrate mercury from water.”**

Pless, R. and Resber JF, *Mercury, infant neurodevelopment, and vaccination*. J Pediatr, 2000. **136**(5): p. 571-3.

35

Why the difference in opinion?

Hypothesis:

- Different researchers, all of whom being human, are not totally free of prejudice.
- Different researchers are examining different populations.

36

Evidence of the latter point

- **“On the average, amalgam tooth fillings add 0.5-30 µg Hg/day to a dietary and environmental uptake of 1-6 (without fish) or 2-25 (with fish) µg Hg/day.”**

Schafer SG et al, *Metals*, in *Toxicology*, H. Marquardt et al, Editor. 1999, Academic Press: San Diego. p. 755-804.

37

Evidence of the latter point

- **“Available data on Hg vapor emission show very large interindividual variation.”**

Weiner, J.A. and Nylander M, *Aspects of health risks of mercury from dental amalgams*, in *Toxicology of Metals*, L.W. Chang et al, Editor. 1996, CRC Press: Boca Raton. p. 469-486.

38

Why the large variation?

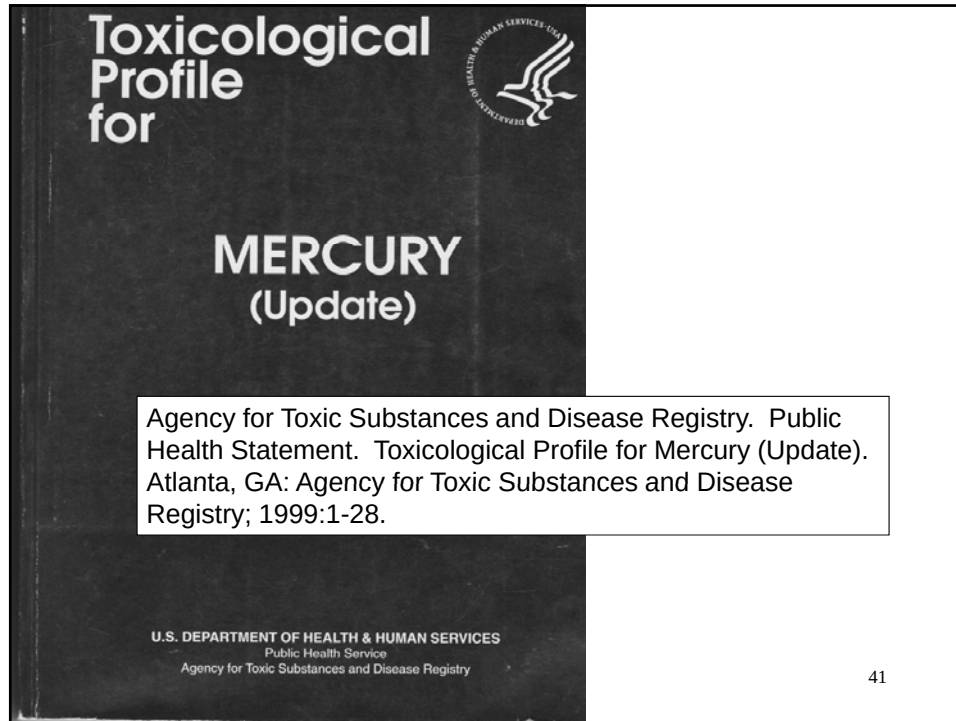
- **“It is generally believed that the dominant route of uptake of Hg from amalgam fillings is through pulmonary absorption of inhaled Hg vapor. A number of studies show that amalgam fillings continuously emit Hg vapor and that the emission increases as a result of chewing, toothbrushing, or with intake of hot beverages.”**

Weiner, J.A. and Nylander M, *Aspects of health risks of mercury from dental amalgams*, in *Toxicology of Metals*, L.W. Chang et al, Editor. 1996, CRC Press: Boca Raton. p. 469-486.

39

*Occupational
versus
chronic, low grade exposure*

40



Occupational vs chronic, low grade exposure

- "Workers are mostly exposed from breathing air that contains mercury vapors, but may also be exposed to other inorganic mercury compounds in the workplace."
- "Occupations that have a greater potential for mercury exposure include manufacturers of electrical equipment or automotive parts that contain mercury, chemical processing plants that use mercury, metal processing, construction where building parts contain mercury (e.g., electrical switchers, thermometers) and the medical professions (medical, dental, or other health services) where equipment may contain mercury (e.g., some devices that measure blood pressure contain liquid mercury)."

42

Occupational vs chronic, low grade exposure

- “Dentists and their assistants may be exposed to metallic mercury from breathing mercury vapor released from amalgam fillings and to a much lesser extent from skin contact with amalgam restorations.”
- “Family members of workers who have been exposed to mercury may also be exposed to mercury if the worker’s clothes are contaminated with mercury particles or liquid.”

43

THE NEW ENGLAND JOURNAL OF MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

The Toxicology of Mercury—Current Exposures and Clinical Manifestations

Thomas W. Clarkson, Ph.D., Lucile Magos, M.D., and Gary J. Myers, M.D.

MERCURY HAS BEEN USED COMMERCIALY AND MEDICALLY FOR CENTURIES. FROM THE DEPARTMENTS OF ENVIRONMENTAL HEALTH AND SAFETY, NATIONAL INSTITUTE FOR ENVIRONMENTAL HEALTH EFFECTS, AND THE DEPARTMENT OF ENVIRONMENTAL HEALTH, U.S. ENVIRONMENTAL PROTECTION AGENCY.

Mercury (quicksilver) still finds its way into homes, causing a risk of poisoning from the vapor and creating major cleanup costs. Humans are also exposed to two distinct but related organic forms, methyl mercury (CH_3Hg^+) and ethyl mercury ($\text{CH}_3\text{CH}_2\text{Hg}^+$). Fish are the main if not the only source of methyl mercury, since it is no longer used as a fungicide. In many countries, babies are exposed to ethyl mercury through ventilation, since this form is the active ingredient of the preservative thimerosal used in vaccines. Whereas removal of certain forms of mercury, such as that in blood-pressure cuffs, will not cause increased health risks, removal of each of the three major sources described in this article entails health risks and thus poses a dilemma to the health professional.

...urinary concentrations in people with amalgams (about 2 to 4 μg of mercury per liter) are well below concentrations found in people who are occupationally exposed to mercury (20 to 50 μg of mercury per liter) unless they are also excessive chewers.”

less fingers and toes in association with photophobia, irritability, anhedonia, and hypertension. It is believed to be a hypersensitivity reaction.

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44

The fate of atmospheric mercury

45

The fate of atmospheric mercury

- **“Mercury in the atmosphere has a complex fate. The mercury that is released into the air is mercury vapor or inorganic mercury. Mercury released into the atmosphere as a gas ultimately redeposits on the earth with precipitation. Once on the earth or in the waterways, it is incorporated into sludges or sediments, where it is methylated by microbial or abiotic processes into methylmercury.”**

Mahaffey, K.R., *Methylmercury: A new look at the risks*. Public Health Reports, 1999. 114(5): p. 397-415

46

The fate of atmospheric mercury

- “The plant and sedimentary materials are consumed by small fish and finally by humans. During the course of this progression a great increase in concentration occurs—known as bioaccumulation or bioconcentration. This increase can result in concentrations of mercury in fish tissues that are hundreds of thousands of times as high as the concentration of inorganic mercury in the water.

Mahaffey, K.R., *Methylmercury: A new look at the risks*. Public Health Reports, 1999. 114(5): p. 397-415

47

The fate of atmospheric mercury

- “It is this bioaccumulation that results in significant exposures through the aquatic food web. Inorganic mercury, which is less efficiently absorbed and more readily eliminated from the body than methylmercury, does not tend to bioaccumulate.”

Mahaffey, K.R., *Methylmercury: A new look at the risks*. Public Health Reports, 1999. 114(5): p. 397-415

48

The fate of atmospheric mercury

- **“Predators at the top of the aquatic food web generally have higher mercury concentrations than those lower in the food web.”**

Mahaffey, K.R., *Methylmercury: A new look at the risks*. Public Health Reports, 1999. 114(5): p. 397-415

49

The fate of atmospheric mercury

- **“In Minamata, Japan in 1953, neurologic manifestations including mental confusion, convulsions, and coma were reported in villagers who had eaten methylmercury-contaminated fish and shellfish (38% of them later died). Between 1953 and 1971, cerebral palsy, chorea, ataxia, tremors, seizures, and mental retardation were seen in the children of exposed mothers.”**

Molenareshari R et al. *Occupational exposure to mercury. What is a safe level?* Can Fam Physician, 1999. 45:p. 43-5.

50

The fate of atmospheric mercury

- **“The infants had not eaten contaminated fish, so the neurologic symptoms must have resulted from toxicity in utero.**

In 1964, an epidemic similar to the one in Minamata occurred in Niigata, Japan. The source of methylmercury was traced to ingestion of fish contaminated by mercury from industrial discharge.”

Molenafshari R et al. *Occupational exposure to mercury. What is a safe level?* Can Fam Physician, 1999. 45:p. 43-5.

51

The fate of atmospheric mercury

- **“In 1971, a widespread epidemic with similar symptoms occurred in Iraq. The source was barley and wheat grain treated with methylmercury for defumigation and distributed in error among Iraqi farmers.”**

Molenafshari R et al. *Occupational exposure to mercury. What is a safe level?* Can Fam Physician, 1999. 45:p. 43-5.

52

*Is environmental mercury a
concern in the U.S.?*

- “But some of the mercury in Massachusetts comes from incinerators and power plants in states to the west, which underlies the need for the EPA to adopt a national standard, said Gina McCarthy, an assistant secretary a the state’s Executive office of Environmental Affairs.”

Daily Hampshire Gazette, Sept. 19, 2000

53

**‘We must do no
less than clean
the rain’**

54

Sources of mercury and the forms of mercury involved

55

The Three Modern Faces of Mercury

Thomas W. Clarkson

Department of Environmental Medicine, University of Rochester School of Medicine, Rochester, New York, USA

The three modern "faces" of mercury are our perceptions of risk from the exposure of billions of people to methyl mercury in fish, mercury vapor from amalgam tooth fillings, and ethyl mercury in the form of diethyl added as an antiseptic to widely used vaccines. In this article I review human exposure to and the toxicology of each of these three species of mercury. Mechanisms of action are discussed where possible. Key gaps in our current knowledge are identified from the point of view both of risk assessment and of mechanisms of action. Key words: amalgam, ethyl mercury, mercury, methyl mercury, thimerosal. *Environ Health Perspect* 110(suppl 1):11-23 (2002).

http://ehpnet1.niehs.nih.gov/docs/2002/suppl_1/11-23/clarkson/abstract.html

Several reviews of the toxicology of mercury have appeared recently (1-6). In this present review I do not repeat all the material presented in these extensive reviews. Instead I focus on three chemical species of mercury that are currently the source of interest to public health experts.

Public health concerns about methyl mercury in edible tissues of fish suddenly

emerged in 1960

St. Clair benthic

have high levels. It

caused in this review

health concerns of

In 1997, the U.S. EPA

Agency (U.S. EPA)

sets limits of methyl

mercury in fish

about five (5) times

higher to new levels.

The U.S. EPA recommended safe intake

level is referred to as the reference dose and

is defined as that dose that can be absorbed

daily for a lifetime without a significant risk

of adverse effects. The new reference dose

was estimated in 1997 to be 0.1 µg methyl

mercury/kg body weight/day. This dose

implies that the amount of methyl mercury

ingested in just one 7-oz can of tuna fish per

week would equal or even slightly exceed the

safe limit.

Mercury vapor remained in the air of the and

entry apprehended and even exceeded occupa-

tional health limits. The debate has now

reached new heights (a) but, depending on

the side of the argument) with claims that

chronic degenerative diseases of the nervous

system such as Parkinson's disease and

Alzheimer's disease are caused or exacerbated

by mercury released from amalgam.

Methyl Mercury in Fish

History of Human Exposure

The first methyl mercury compounds were synthesized in a chemical laboratory in London in the 1860s (8). Two of the laboratory technicians died of methyl mercury poisoning. This was the first chemical confirmation that methyl mercury compounds were given a wide berth for the rest of the century. However, early in the twentieth century the potent neurotoxic properties of the short-chain alkyl mercury compounds were discovered, leading to application to seed grains, especially for cereal crops. The widespread global use of these mercury compounds was found to be highly proximate of seed grain from what otherwise would be devastating fungal infections and the loss of the grain harvest.

Clarkson TW et al. The three modern faces of mercury, *Environ Health Perspectives*, 2002; 110(Suppl 1):11;23

"Today...exposure of the general population comes from three major sources: fish consumption, dental amalgams, and vaccines. Each has its own characteristic form of mercury and a distinctive toxicologic profile and clinical symptoms."

vapor could be inhaled. Concentrations of ...

side we face from these forms of mercury. ...

Environmental Health Perspectives • volume 110 | supplement 1 | February 2002

11

56

The basic forms of mercury

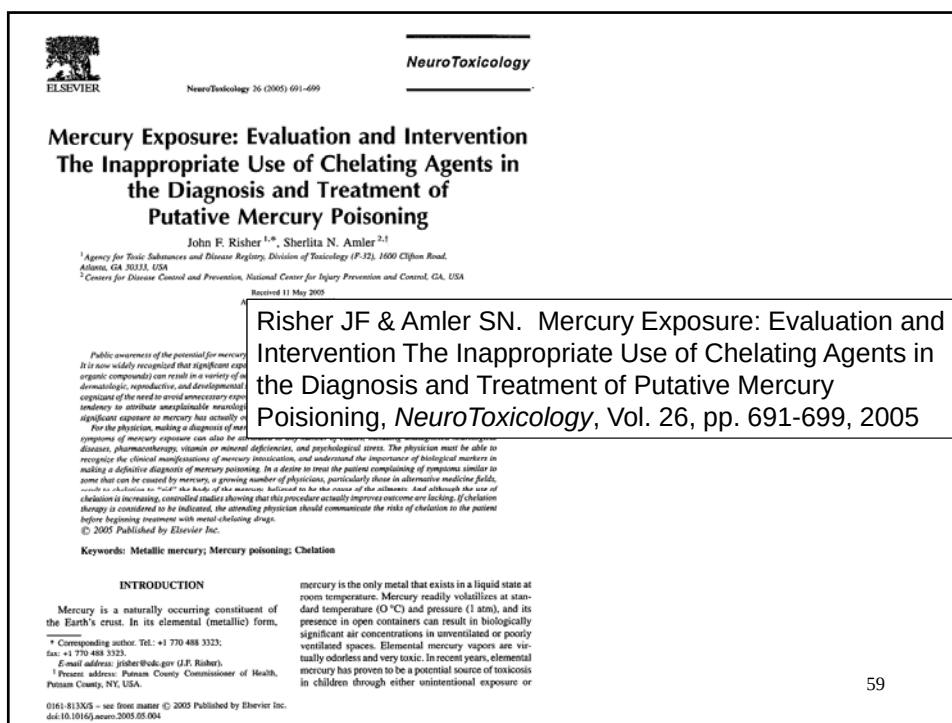
- **“Mercury exists as elemental (metallic) metal, inorganic mercury salts (mercurous or mercuric) and organic mercury compounds (aryl- or alkylmercury).”**

Chang, L.W., *Mercury-related neurological syndromes and disorders*, in *Mineral and Metal Neurotoxicology*, Yasui M et al, Editor. 1997, CRC Press: Boca Raton. p. 169-176.

57

Forms of mercury: Overview and history

58



Inorganic Mercury

- “In the case of metallic (liquid, elemental) mercury only the inhalation route has been proven to be biologically relevant in most instances.”
- “When taken orally, less than 0.01% is typically absorbed through the GI tract.”
- “Skin contact normally results in even less absorption in most instances.”
- “In sharp contrast, however, up to 80% of inhaled mercury vapor can be expected to be absorbed through the lungs into the blood.”

Organic Mercury

- “Unlike inorganic forms of mercury, organic mercurials are readily absorbed through the digestive tract (~95%).”
- “For organomercurials, blood is a good indicator of exposure, and urine is a poor indicator, due to differences in the pharmacokinetics of these compounds.”
- “Hair is also a suitable indicator of a history of organic mercury exposure, since incorporation into the hair follicle of both methylmercury and ethylmercury is a known route of elimination of these organomercurials from the body.”

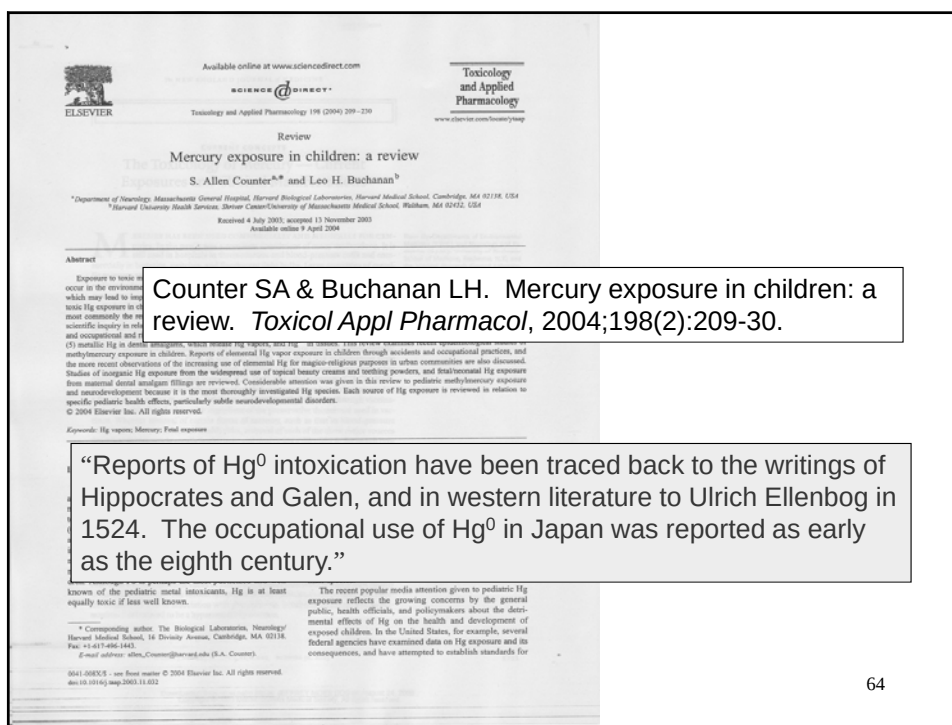
61

- “Perhaps the earliest medical application may have been in ancient Egypt, where mercury compounds in ointments were used to treat infections.”
- “The skin sores from syphilis may have prompted the early application of mercury to combat this disease as it swept across Europe soon after the return of Christopher Columbus.”
- “Treatment included not only the application of mercury compounds but also the exposure of the person’s skin surfaces to mercury vapor.”

62

- “Paracelsus was one of the first advocates for the mercury treatment, which included skin exposure to the vapor.”
- “He soon realized, however, that a little too much mercury might kill the patient, hence his famous dictum ‘Dose makes the poison.’”
- “So it may be argued that mercury played a key role in establishing the basic guiding principle in modern toxicology and risk assessment.”

63



Elemental mercury

65

Elemental mercury

- **“Elemental mercury vapor is absorbed readily by the lungs and transported through the blood to the brain and other tissues. It is oxidized, presumably in the red blood cells, to mercuric ions that combine with sulfhydryl groups on cell membranes and enzymes.”**

Boyd AS et al, *Mercury exposure and cutaneous disease*. J Am Acad Dermatol, 2000. **43**(1 Pt 1): p. 81-90.

66

Elemental mercury

- **“Interestingly, metallic mercury is absorbed negligibly after oral ingestion. Unless regurgitation and aspiration occur, swallowing this element poses no health hazard”**

Boyd AS et al, *Mercury exposure and cutaneous disease*. J Am Acad Dermatol, 2000. **43**(1 Pt 1): p. 81-90.

67

Elemental mercury

- **“When taken orally, metallic mercury is normally not very harmful. In a single case of ingestion of 204 g of metallic mercury, no signs of intoxication were observed.”**

Schafer SG et al, *Metals*, in *Toxicology*, Marquardt H et al, Editor. 1999, Academic Press: San Diego. p. 755-804.

68

Elemental mercury

- **“Occasional intoxication through enteral uptake of metallic mercury cannot be excluded, however. Altered gastrointestinal residence times due to the presence of diverticula or abscesses and the degree of dispersion of the mercury ingested may affect absorption.”**

Schafer SG et al, *Metals*, in *Toxicology*, Marquardt H et al, Editor. 1999, Academic Press: San Diego. p. 755-804.

69

Physiology of elemental mercury

- **“Inhaled mercury vapors have a high affinity for the central nervous system (CNS). After a single exposure to mercury vapor, ten times more mercury is retained in the brain than after intravenous injection of the same dose of mercuric salt. “**

Chang, L.W. and Verity MA, *Mercury neurotoxicity: Effects and mechanisms*, in *Handbook of Neurotoxicology*, L.W. Chang and Dyer RS, Editors. 1995, Marcel Dekker, Inc.: New York. p. 31-59.

70

Physiology of elemental mercury

- “In the brain, most of the mercury is distributed to the gray matter, especially in the occipital and parietal cortical areas of the cerebral cortex, various nuclei in the brain stem, and the cortical area of the cerebellum. The average biological half-time of inhaled vapor in the whole body is about 60 days. The biological half-time for the mercury accumulated in the brain is probably much longer.”

Chang, L.W. and Verity MA

71

Elimination of elemental mercury

- “It is excreted primarily by the kidneys where it accumulates and induces the most damage. Long-term sequelae often include renal failure.”

Boyd AS et al, *Mercury exposure and cutaneous disease*. J Am Acad Dermatol, 2000. 43(1 Pt 1): p. 81-90.

72

Non-amalgam sources of elemental mercury

- “Common sources of metallic mercury exposure include mercury switches, thermostats, barometers, and thermometers. When this heavy metal is spilled onto upholstery and carpeting it may slowly volatilize over time, thereby resulting in toxic air concentrations, a common scenario for pediatric poisoning.”

Boyd AS et al, *Mercury exposure and cutaneous disease*. J Am Acad Dermatol, 2000. **43**(1 Pt 1): p. 81-90.

73

Absorption of elemental mercury from amalgam

- “It is generally believed that the dominant route of uptake of Hg from amalgam fillings is through pulmonary absorption of inhaled Hg vapor. A number of studies show that amalgam fillings continuously emit Hg vapor and that the emission increases as a result of chewing, toothbrushing, or with intake of hot beverages.”

Weiner, J. and Nylander M, *Aspects on health risks of mercury from dental amalgams*, in *Toxicology of metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 469-486.

74

Absorption of elemental mercury from amalgam

- **“Divalent Hg ions that are dissolved in the saliva and swallowed will be partly absorbed in the gastrointestinal tract; such absorption is about 15%.”**

Weiner, J. and Nylander M, *Aspects on health risks of mercury from dental amalgams*, in *Toxicology of metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 469-486.

75

Absorption of elemental mercury from amalgam

- **“Possible routes of uptake of mercury from fillings also include a direct absorption of mercury in the mucosa of the oral cavity and a migration of mercury through the dentin to the dental pulp and the adjacent bones.”**

Weiner, J. and Nylander M, *Aspects on health risks of mercury from dental amalgams*, in *Toxicology of metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 469-486.

76

Absorption of elemental mercury from amalgam

- “In continued Swedish autopsy studies cases with no amalgam fillings showed a mean Hg concentration of 6.7 ng/g (2.4 to 12.2) in the occipital cortex, whereas cases with a moderate amount of amalgam fillings, i.e., an average of 21 tooth surfaces restored with amalgam, showed a mean concentration of 12.3 ng/g (4.8 to 28.7). There was a significant correlation between Hg concentration and number of amalgam surfaces.”

Weiner, J. and Nylander M, *Aspects on health risks of mercury from dental amalgams*, in *Toxicology of metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 469-486.

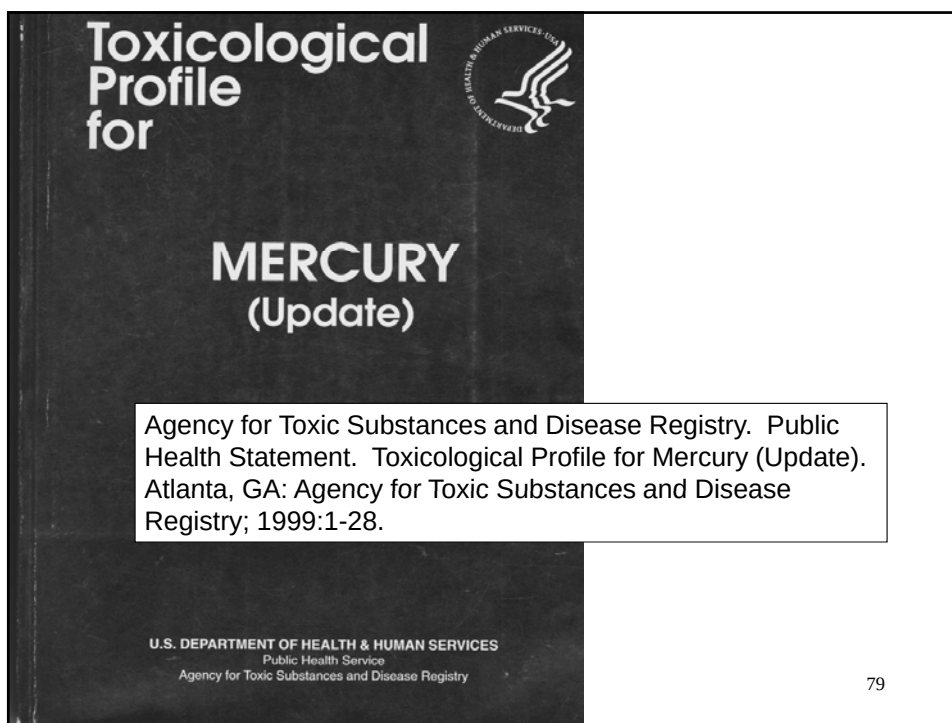
77

Absorption of elemental mercury from amalgam

- “It should be stressed that the individual variation in the release and uptake of Hg from fillings is very large.”

Weiner, J. and Nylander M, *Aspects on health risks of mercury from dental amalgams*, in *Toxicology of metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 469-486.

78



- "The total amount of mercury released from dental amalgam depends upon the total number of fillings and surface areas of each filling, the chewing and eating habits of the person, and other chemical conditions in the mouth."
- "Estimates of the amounts of mercury released from dental amalgams range from 3 to 17 micrograms per day."
- The mercury from dental amalgam may contribute from 0 to more than 75% of your total daily mercury exposure, depending on the number of amalgam fillings you have, the amount of fish consumed, the levels of mercury (mostly as methylmercury) in those fish, and exposure from other less common sources such as mercury spills, religious practices, or herbal medicines that may contain mercury."

80

Inorganic mercury

81

Inorganic mercury salts

- **“Inorganic mercurials include ammoniated mercury, mercuric chloride, mercuric oxide, mercuric sulfide, mercurous chloride, mercuric iodide, and the phenylmercuric salts. These have been previously used as laxatives (mercurous chloride, calomel) and as anthelmintic agents.”**

Boyd AS et al, *Mercury exposure and cutaneous disease*. J Am Acad Dermatol, 2000. **43**(1 Pt 1): p. 81-90.

82

Inorganic mercury salts

- **“Toxicity from laxative abuse is uncommon but may still occur. Most exposure today occurs with pesticides, antiseptics, and germicides. Cutaneous compounds for skin lightening, infected eczema or impetigo, psoriasis, and secondary syphilis may contain inorganic mercury compounds and are still available, particularly in developing countries.”**

Boyd AS et al, *Mercury exposure and cutaneous disease*. J Am Acad Dermatol, 2000. **43**(1 Pt 1): p. 81-90.

83

Inorganic mercury salts

- **“Unlike elemental mercury, the inorganic salts are readily absorbed by the gut and are excreted through the kidneys and gastrointestinal system. Only about 10% of an ingested dose is absorbed, but the half-life is approximately 40 days. Mercury salts interfere with sulfhydryl-containing enzyme systems.”**

Boyd AS et al, *Mercury exposure and cutaneous disease*. J Am Acad Dermatol, 2000. **43**(1 Pt 1): p. 81-90.

84

Inorganic mercury salts

- **“Chronic exposure to mercuric mercury is usually a consequence of occupational exposure where mercury, e.g., mercuric nitrate or oxide, enters the body either via inhalation (dusts of mercuric salt) or via dermal contact.”**

Chang, L.W., *Mercury-related neurological syndromes and disorders*, in *Mineral and Metal Neurotoxicology*, Yasui M et al, Editor. 1997, CRC Press: Boca Raton. p. 169-176.

85

Inorganic mercury salts

- **The best-known example in this situation is the “Mad Hatter” syndrome, with characteristic neurological disturbances similar to those seen in mercury vapor poisoning; micromercurialism, erethism, tremor, personality and neuropsychological changes, and incoordination.”**

Chang, L.W., *Mercury-related neurological syndromes and disorders*, in *Mineral and Metal Neurotoxicology*, Yasui M et al, Editor. 1997, CRC Press: Boca Raton. p. 169-176.

86

Inorganic mercury salts

- **“The primary target organ for mercuric salts is the kidney. Neurotoxicity for mercuric salts is not prominent.”**

Chang, L.W. and Verity MA, *Mercury neurotoxicity: Effects and mechanisms*, in *Handbook of Neurotoxicology*, L.W. Chang and Dyer RS, Editors. 1995, Marcel Dekker, Inc.: New York. p. 31-59.

87

Inorganic mercury salts

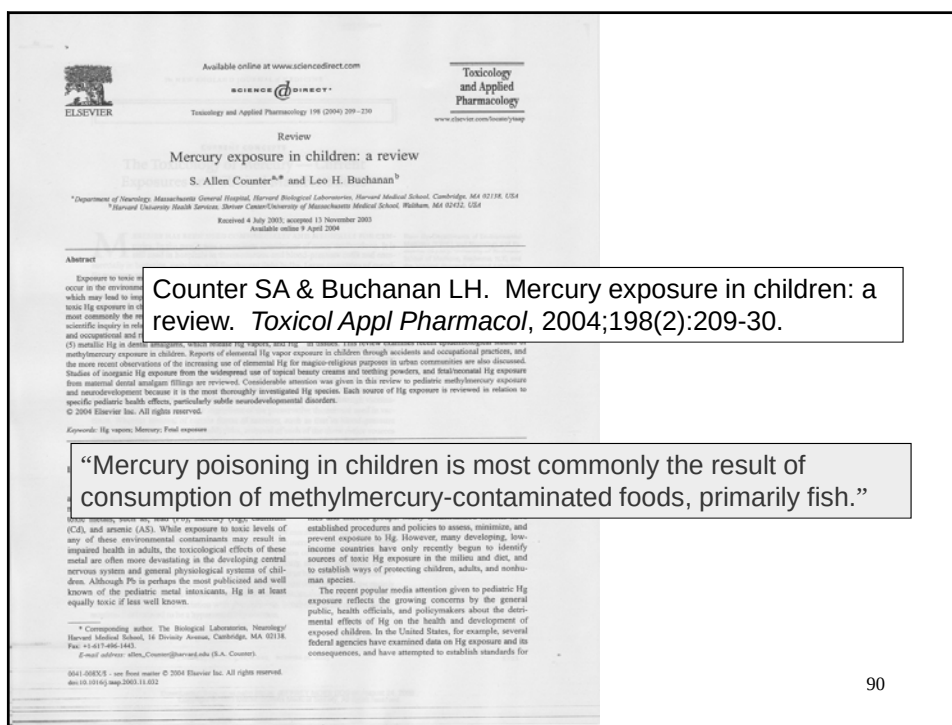
- **“Uptake of Hg in the form of Hg^{2+} is less likely to explain accumulation in the brain, as Hg^{2+} has a limited penetration of the blood-brain barrier.”**

Weiner, J. and Nylander M, *Aspects on health risks of mercury from dental amalgams*, in *Toxicology of metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 469-486.

88

Methylmercury

89



Organic mercury (Methylmercury)

- **“Mercury is dissipated in the environment largely by transport through the atmosphere, where it exists almost exclusively in the elemental form (Hg^0), as a gas or adsorbed to the surface of small particles. This elemental mercury may then be oxidized to the more water-soluble divalent form (Hg^{2+}) dissolved in raindrops, and deposited from the atmosphere.”**

Flaten, T.A., *Neurotoxic metals in the environment: Some general aspects*, in *Mineral and Metal Neurotoxicology*, Yasui M et al, Editor. 1997, CRC Press: Boca Raton. p. 17-25.

91

Organic mercury (Methylmercury)

- **“In soil and water, Hg^{2+} can be (1) reduced to gaseous Hg^0 , thereby returning mercury to the atmosphere, or (2) methylated by microorganisms. The resultant methylmercury unit CH_3Hg^+ is kinetically remarkably inert towards decomposition, so it may persist in the environment or in an organism even though thermodynamic conditions strongly favor demethylation.”**

Flaten, T.A., *Neurotoxic metals in the environment: Some general aspects*, in *Mineral and Metal Neurotoxicology*, Yasui M et al, Editor. 1997, CRC Press: Boca Raton. p. 17-25.

92

Organic mercury (Methylmercury)

- “The electrically neutral methylmercury species, CH_3HgCl , $(\text{CH}_3)_2\text{Hg}$, etc. are quite lipophilic, and can thus readily pass biological membranes and be concentrated along ecological food chains – a process known as bioamplification. Any substance that is more soluble in the tissues of simple organisms than in the surrounding water will be a more concentrated component of the diet of the more complex species which feed on the simpler ones. Methylmercury has a very strong tendency for bioamplification, which is why the fish in Minamata Bay could attain such toxic levels.”

Flaten, T.A., *Neurotoxic metals in the environment: Some general aspects*, in *Mineral and Metal Neurotoxicology*, Yasui M et al, Editor. 1997, CRC Press: Boca Raton. p. 17-25.

93

Source of mercury for methylation

- “Mercury is also released into the environment by oil burning, from its use as a fungicide (often applied to seeds), from outdoor paint (mercury was banned in indoor paint in 1990), and from processes involving chlorine manufacture and use. Waste mercury is released into the atmosphere by cremations (with estimates that a single crematorium releases more than 5,400 kg of mercury per year).”

Crinnion, W.J., *Environmental medicine, part three: Long-term effects of chronic low-dose mercury exposure*. *Alt Med Rev*, 2000. 5(3): p. 209-233.

94

Source of mercury for methylation

- **“A significant amount of elemental mercury is also released into the environment from wastewater from dental offices. In King County, Washington, mercury contaminates the sludge from wastewater treatment sites, which is often sold as fertilizer. Gold mining in the Amazon Basin utilizes mercury to capture gold particles as amalgam, resulting in widespread mercury pollution in the Amazon River and its human and animal inhabitants.”**

Crinnion, W.J., *Environmental medicine, part three: Long-term effects of chronic low-dose mercury exposure*. *Alt Med Rev*, 2000. 5(3): p. 209-233.

95

Human methylmercury metabolism

- **“After peroral intake, methylmercury is readily absorbed from the gastrointestinal tract. It is transported in the blood and evenly distributed to all tissues within 4 days. In blood, the major part is bound to hemoglobin in the red cells, and the remainder in the plasma proteins. The ratio between the levels in erythrocytes and in plasma is usually about 20:1. Species differences exist.”**

Gerhardsson, L. and Skerfving S, *Concepts and biological markers and biomonitoring for metal toxicity*, in *Toxicology of Metals*, Chang LW et al, Editor. 1996, CRC Press: Boca Raton. p. 81-107.

96

Human methylmercury metabolism

- **“Methylmercury penetrates the blood-brain and placental barriers and accumulates in the brain and in the fetus. In the brain methylmercury is demethylated to inorganic mercury. The ratio between methylmercury and inorganic mercury depends on exposure time, and the time since the cessation of exposure.”**

Gerhardsson, L. and Skerfving S, *Concepts and biological markers and biomonitoring for metal toxicity*, in *Toxicology of Metals*, Chang LW et al, Editor. 1996, CRC Press: Boca Raton. p. 81-107.

97

Absorption of methylmercury

- **“Methylmercury is efficiently absorbed into the body (more than 95-percent absorption from food...)”**

Crinnion, W.J., *Environmental medicine, part three: Long-term effects of chronic low-dose mercury exposure*. Alt Med Rev, 2000. 5(3): p. 209-233.

98

Methylmercury and the blood brain barrier

- **“Methylmercury crosses the blood brain barrier readily, and brain tissues have a high affinity towards methylmercury. Although methylmercury accumulates in the brain at a slower rate than in other organs (e.g., liver and kidney), methylmercury in the brain tissues is relatively stable and resists degradation to inorganic form.”**

Chang, L.W., *Mercury-related neurological syndromes and disorders*, in *Mineral and Metal Neurotoxicology*, Yasui M et al, Editor. 1997, CRC Press: Boca Raton. p. 169-176.

99

Methylmercury and the blood brain barrier

- **“With time, the level of alkylmercury in the brain would eventually accumulate at least 3 to 6 times higher than that in blood to reach the threshold intoxication several weeks after exposure. Data from the Minamata episode suggest that overt neurological signs and symptoms of alkylmercury poisoning correlate with the brain mercury level of 10 ppm or more.”**

Chang, L.W., *Mercury-related neurological syndromes and disorders*, in *Mineral and Metal Neurotoxicology*, Yasui M et al, Editor. 1997, CRC Press: Boca Raton. p. 169-176.

100

Methylmercury elimination

- **“Methylmercury is secreted into the bile and has an enterohepatic circulation. In the gut, a fraction of the methylmercury is demethylated by the intestinal microflora, and most of this inorganic mercury is excreted in the feces. Excretion of urine is limited.”**

Gerhardsson, L. and Skerfving S, *Concepts and biological markers and biomonitoring for metal toxicity*, in *Toxicology of Metals*, Chang LW et al, Editor. 1996, CRC Press: Boca Raton. p. 81-107.

101

Methylmercury elimination

- **“The daily elimination is about 1% of the body burden. The estimated biological half-time in blood and the whole body, described by a single compartment model, is about 40 to 70 days.”**

Gerhardsson, L. and Skerfving S, *Concepts and biological markers and biomonitoring for metal toxicity*, in *Toxicology of Metals*, Chang LW et al, Editor. 1996, CRC Press: Boca Raton. p. 81-107.

102

Other methylmercury storage compartments

- **“Methylmercury is present in the breast milk of lactating mothers who consume mainly a seafood diet.”**

Crinnion, W.J., *Environmental medicine, part three: Long-term effects of chronic low-dose mercury exposure*. Alt Med Rev, 2000. 5(3): p. 209-233.

103

Other methylmercury storage compartments

- **“Methylmercury also has a high affinity for growing hair. At time of hair formation, the concentration ratio of mercury in hair to that in the blood is about 250:1. Thus, when analyzed with appropriate methodology, the hair mercury may serve as a good index for the assessment of mercury exposure.”**

Chang, L.W. and Verity MA, *Mercury neurotoxicity: Effects and mechanisms*, in *Handbook of Neurotoxicology*, L.W. Chang and Dyer RS, Editors. 1995, Marcel Dekker, Inc.: New York. p. 31-59.

104

Key symptom of methylmercury toxicity

- **“Primary sensory neuropathy is probably one of the most sensitive indicators in methylmercury poisoning.”**

Chang, L.W. and Verity MA, *Mercury neurotoxicity: Effects and mechanisms*, in *Handbook of Neurotoxicology*, L.W. Chang and Dyer RS, Editors. 1995, Marcel Dekker, Inc.: New York. p. 31-59.

105

Key factor in methylmercury deposition

- **“The biological disposition of and effects of, inorganic and organic forms of mercury are largely determined by their high affinity for sulfhydryl groups, in particular glutathione (GSH)...”**

Zalups R.K. and Lash L.H., *Interactions between glutathione and mercury in the kidney, liver, and blood*, in *Toxicology of Metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 145-163.

106

How much fish do Americans eat?

- **“EPA estimates that about 85% of people in the US eat fish or shellfish over the course of a month, with about 60% consuming fish four or more times a month or, on average, at least once a week.”**

Mahaffey, K.R., Methylmercury: A new look at the risks. Public Health Reports, 1999. 114(5): p. 397-415

107

How much methylmercury is in fish?

- **“Fortunately, the most commonly consumed fish species in the United States are comparatively low in methylmercury – shrimp, Alaskan pollock, most tuna, and salmon. In its *Report to Congress*, EPA estimated based on dietary surveys that the average concentration of methylmercury in fish and shellfish in the US was 0.12 ppm to 0.14 ppm mercury. In fact, the 10 most commonly consumed species usually contained less than 0.2 ppm mercury.”**

Mahaffey, K.R., Methylmercury: A new look at the risks. Public Health Reports, 1999. 114(5): p. 397-415

108

Which fish are high in methylmercury?

- “Although the most popular species of fish are comparatively low in methylmercury, it is important to recognize that there are also fish species with considerably higher average concentrations. Shark and swordfish average approximately 1 ppm or higher.”

Mahaffey, K.R., Methylmercury: A new look at the risks. Public Health Reports, 1999. 114(5): p. 397-415

109

Which fish are high in methylmercury?

- Other species often in the range of 0.5 ppm and higher include various bass, king mackerel, orange roughy, pike, and porgy. Typically, large, predatory fish at the upper end of the aquatic food chain are high in mercury.”

Mahaffey, K.R., Methylmercury: A new look at the risks. Public Health Reports, 1999. 114(5): p. 397-415

110

Is farm-raised better?

- **“Usually farm-raised fish are lower in mercury concentrations than comparable species and sizes of wild-caught fish.”**

Mahaffey, K.R., Methylmercury: A new look at the risks. Public Health Reports, 1999. 114(5): p. 397-415

111

Methylmercury content of fish based on geography

- **“Freshwater fish can be found with concentrations greater than 0.5 ppm if they swim in contaminated waters. Fishing advisories based on mercury contamination have been issued by 40 states, with 10 states advising limitations on fish consumption from all water bodies.”**

Mahaffey, K.R., Methylmercury: A new look at the risks. Public Health Reports, 1999. 114(5): p. 397-415

112

Methylmercury content of fish based on geography

- “Five coastal states have advisories to limit consumption of marine fish. Data from the Northeast states collected in the mid-1990s showed average mercury concentrations > 0.5 ppm in 20% to 100% of fish samples of some species depending on location. In Wisconsin, the most commonly sought-after game species, walleye, averaged approximately 0.5 ppm, with individual values > 3 ppm, in a 1998 study.”

Mahaffey, K.R., Methylmercury: A new look at the risks. Public Health Reports, 1999. 114(5): p. 397-415

113

Clinical management of methylmercury toxicity Treatment-Gut Microflora-Underlying concepts

- “Methylmercury is unusual among toxic heavy metal compounds in that it is rapidly and almost completely absorbed from the mammalian gut.”

Rowland IR et al, Effects of diet on mercury metabolism and excretion in mice given methylmercury: role of gut flora. Arch Environ Health, 1984. 39(6): p. 401-8.

114

*Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Underlying concepts*

- **“...a considerable amount of methylmercury is secreted into the bile...”**

Urano T et al, *Inhibitory effect of selenium on biliary excretion of methyl mercury in rats*. Biochem Biophys Res Commun, 1997. **239**(3): p. 862-7.

115

*Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Underlying concepts*

- **“It has been recognized that enterohepatic circulation of methylmercury plays an important role in its retention and toxicity...”**

Urano T et al, *Absorption of methylmercury compounds from rat intestine*. Toxicol Letters, 1990. **50**(2-3): p. 159-64.

116

*Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Underlying concepts*

- **“Conversion of MeHg to the poorly absorbed mercuric form could interrupt the enterohepatic cycle and hence increase Hg excretion in feces.”**

Rowland IR et al, *Effects of diet on mercury metabolism and excretion in mice given methylmercury: role of gut flora*. Arch Environ Health, 1984. **39**(6): p. 401-8.

117

*Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Underlying concepts*

- **“The main route of excretion is via the faeces in man and laboratory animals. In rats and mice given MeHg, the majority (50-90%) of the mercury in faeces is in the mercuric form. Therefore demethylation of methylmercury would appear to be a rate-determining step in the excretion of the organomercurial from the body.”**

Rowland IR, *The interaction of the gut flora with metal compounds*, in *Role of Gut Bacteria in Human Toxicology and Pharmacology*, Hill MJ, Editor. 1995, Taylor & Francis, Inc.: Bristol, PA. p. 197-211.

118

*Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Underlying concepts*

- “The cumulative body-burden of mercury after methylmercury exposure is determined not only by the quantity taken in, but also, critically, by its rate of elimination.”

Rowland IR, *The interaction of the gut flora with metal compounds*, in *Role of Gut Bacteria in Human Toxicology and Pharmacology*, Hill MJ, Editor. 1995, Taylor & Francis, Inc.: Bristol, PA. p. 197-211.

119

*Clinical management of methylmercury toxicity
Treatment-Gut Microflora*

- “...the observation that antibiotic treatment of mice leads to almost complete retention of a dose of MeHg (half-time of mercury elimination greater than 100 days) would suggest that non-bacterial demethylation does not play a significant role in determining the body-burden of mercury after MeHg exposure.”

Rowland IR, *The interaction of the gut flora with metal compounds*, in *Role of Gut Bacteria in Human Toxicology and Pharmacology*, Hill MJ, Editor. 1995, Taylor & Francis, Inc.: Bristol, PA. p. 197-211.

120

*Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Demethylation*

- **“MeHg-induced behavioral signs of neurotoxicity and the severity of the histopathological lesions in the cerebellum were much greater in antibiotic-treated rats than in their conventional flora counterparts.”**

Rowland IR, *The interaction of the gut flora with metal compounds*, in *Role of Gut Bacteria in Human Toxicology and Pharmacology*, Hill MJ, Editor. 1995, Taylor & Francis, Inc.: Bristol, PA. p. 197-211.

121

*Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Demethylation*

- **“Treatment of the mice with antibiotics decreased both the rate of mercury excretion and the proportion of mercuric mercury found, and at the same time abolished the dietary differences in mercury excretion, demonstrating that the diets *per se* were not directly affecting MeHg metabolism.”**

Rowland IR, *The interaction of the gut flora with metal compounds*, in *Role of Gut Bacteria in Human Toxicology and Pharmacology*, Hill MJ, Editor. 1995, Taylor & Francis, Inc.: Bristol, PA. p. 197-211.

122

*Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Demethylation*

- **“Large variations have been reported in rates of elimination of Hg in human populations exposed to MeHg. It is conceivable that this variation may be related to the wide variation in composition of gut flora among individuals.”**

Rowland IR et al, *Effects of diet on mercury metabolism and excretion in mice given methylmercury: role of gut flora*. Arch Environ Health, 1984. **39**(6): p. 401-8.

123

*Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Demethylation*

- **Furthermore, if the major differences in gut flora that have been observed in populations in different geographic areas are reflected in their MeHg demethylation rates, it is possible that there are interindividual as well as inter-regional differences in susceptibility to MeHg poisoning.”**

Rowland IR et al, *Effects of diet on mercury metabolism and excretion in mice given methylmercury: role of gut flora*. Arch Environ Health, 1984. **39**(6): p. 401-8.

124

Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Methylation

- **“The bacterial methylation of mercuric mercury converts the metal from a form poorly absorbed from the gut to one which is virtually completely absorbed and so, potentially, should increase the uptake of mercury from an oral dose of mercuric mercury.”**

Rowland IR et al, *Effects of diet on mercury metabolism and excretion in mice given methylmercury: role of gut flora*. Arch Environ Health, 1984. **39**(6): p. 401-8.

125

Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Methylation

- **“The highest levels of methylating activity were seen among streptococci, *E. coli*, yeasts, and staphylococci. Only a small proportion of the obligate anaerobes and lactobacilli formed MeHg.”**

Rowland IR et al, *Effects of diet on mercury metabolism and excretion in mice given methylmercury: role of gut flora*. Arch Environ Health, 1984. **39**(6): p. 401-8.

126

Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Methylation

- Rowland also notes that, generally, the amounts of mercuric mercury ingested by most individuals is so small that methylation mediated by gut microflora will probably have no real toxicologic significance. However, if your history reveals that the patient works in a chloralkali plant, for example, where the presence of mercuric mercury is quite high, this type of bacterial activity could be of tremendous importance in creating the symptoms the patient presents.

127

Ethylmercury

128

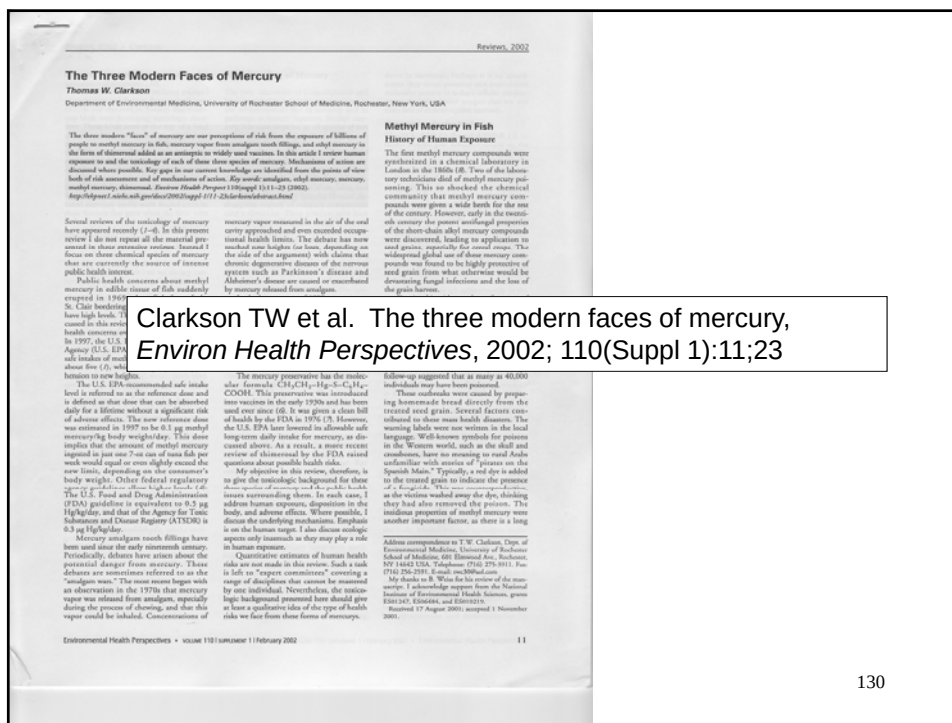
Mercury and vaccines

- How much mercury is in thimerosal?

“[It] is composed of 49.6% mercury by weight in the form of ethylmercury.”

Pless, R. and Resber JF, *Mercury, infant neurodevelopment, and vaccination*. J Pediatr, 2000. **136**(5): p. 571-3.

129



130

- “Mercury in the thiomerosal molecule is in the form of ethyl mercury ($\text{CH}_3\text{CH}_2\text{-Hg}^+$), for which there is limited toxicologic information.”
- “Thus, health risks from thiomerosal vaccines were based on the assumption that ethyl mercury is toxicologically similar to its close chemical relative, methyl mercury ($\text{CH}_3\text{-Hg}^+$), about which much is known. However...there are reasons to believe that this assumption is not necessarily correct for all aspects of the disposition and toxicity of ethyl mercury compounds, including thiomerosal.”

131

- “In the late 1880s, diethyl mercury was first used in the treatment of syphilis, a practice soon abandoned because of the toxic properties of this agent.”
- “...early in the twentieth century, the fungicidal properties of the short-chain alkyl mercury compounds led to commercial application in agriculture.”
- “For example, they are especially effective in plant root disease in wheat caused by *Telletia Triticia*.”
- “In fact, many different organic mercury compounds were being used to prevent seed-borne diseases of cereal by 1914.”

132

- “...two outbreaks occurred in rural Iraq in 1956 and 1960 from the misuse of the fungicide ethyl mercury toluene sulfanilamide.”
“The farmers’ families prepared homemade bread directly from the treated grain instead of planting it.”
- “Hundreds of cases of severe poisoning occurred, many of which had a fatal outcome.”
- “Cases of ethyl mercury poisoning have occurred in China as recently in the 1970s. The exposure pathway was the same as in Iraq: The farmers consumed rice treated with ethyl mercury chloride.”

133

- “Ethyl mercury in the form of thiomerosal has found wide application in medicine as a disinfectant.”

134

- “Thiomerosal contains the ethyl mercury radical attached to the sulfur atom of the thiol group of salicylic acid.”
- “Generally, mercuric ions bind tightly but reversibly to thiol ligands.”
- “It is likely, therefore, that the ethyl mercury cation will dissociate from the ethiosalicylic acid moiety immediately after injection to bind to the surrounding thiol ligands present in great excess in tissue proteins.”

135

- ***Unlike methylmercury, ethylmercury breaks down to inorganic mercury fairly quickly:***
- ***“A significant fraction of the total mercury in both gray and white matter of the brain was in the form of inorganic mercury of the order of 30-40%.”***
- ***“The kidney cortex has the highest percentage. These findings are confirmed by studies on experimental animals.”***

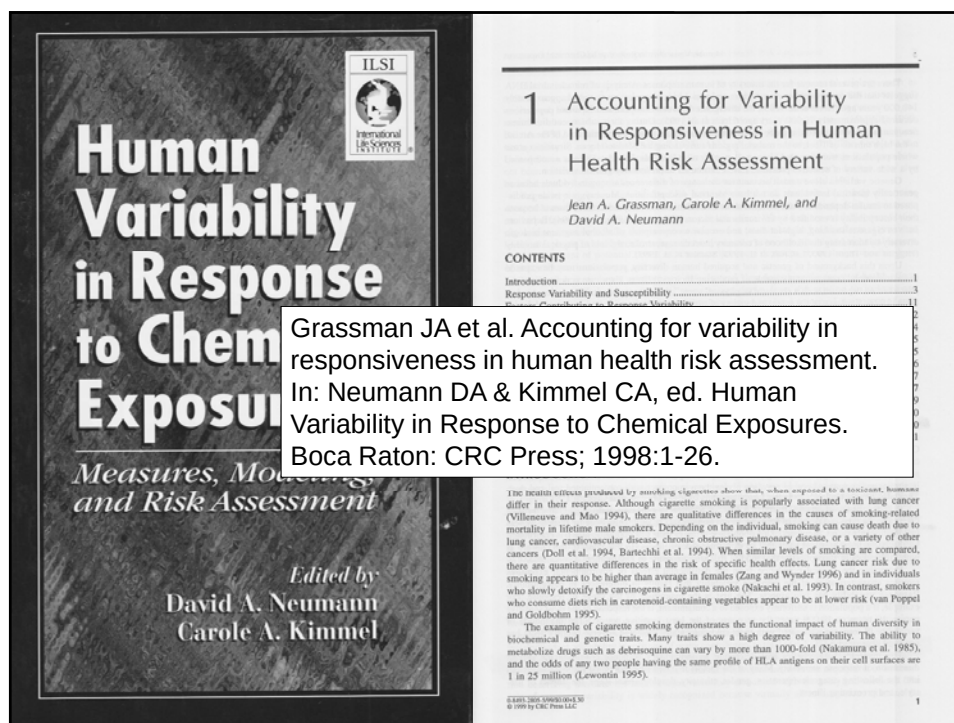
136

- “Blood and tissue levels, including the brain, were higher in animals doses with ethyl mercury compared with an equivalent dose of a methyl mercury compound.”
- “The high tissue levels of inorganic mercury seen in both humans and animals indicate that ethyl mercury breaks down to inorganic mercury more rapidly than methyl mercury.”

137

***Is there a direct relationship
between levels of mercury
in the body and the level of
toxicity experienced by any
individual?***

138



- “Humans are highly diverse and, as a result, variability in response to environmental toxicants should be expected.”
- “Past efforts to address response variability have tended to divide humans into those who are ‘susceptible’ and those who are ‘normal’ in their responses.”
- “A more accurate view of human response to contaminants recognizes a continuum extending from the most resistant to the most susceptible individuals.”

Mechanisms of mercury toxicity and elimination

141

Mechanisms of mercury toxicity and elimination

- **“The biological disposition of and effects of inorganic and organic forms of mercury are largely determined by their high affinity for sulfhydryl groups, in particular glutathione (GSH)...”**

Zalups R.K. and Lash L.H., *Interactions between glutathione and mercury in the kidney, liver, and blood*, in *Toxicology of Metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 145-163.

142

Mechanisms of mercury toxicity and elimination

- **“Once mercury gains access to the circulatory system, the three primary tissues or organ systems that determine the status of mercury are the blood, liver, and kidneys.”**

Zalups R.K. and Lash L.H., *Interactions between glutathione and mercury in the kidney, liver, and blood*, in *Toxicology of Metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 145-163.

143

Mechanisms of mercury toxicity and elimination

- **“In each of these compartments, GSH status appears to be an important determinant in the disposition of mercury.”**

Zalups R.K. and Lash L.H., *Interactions between glutathione and mercury in the kidney, liver, and blood*, in *Toxicology of Metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 145-163.

144

Mechanisms of mercury toxicity and elimination

- **“Due to the presence of the free sulfhydryl group on the cysteinyl residue, GSH has a great propensity for forming complexes with ions of metals that have strong electrophilic characteristics, such as mercury.”**

Zalups R.K. and Lash L.H., *Interactions between glutathione and mercury in the kidney, liver, and blood*, in *Toxicology of Metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 145-163.

145

Mechanisms of mercury toxicity and elimination

- **“Mercury decreases GSH levels in the body, which occurs by several mechanisms. Mercury binds irreversibly to GSH, causing the loss of up to two GSH molecules per molecule of mercury. The GSH-Hg-GSH complex is excreted via the bile into the feces.”**

Crinnion, W.J., *Environmental medicine, part three: Long-term effects of chronic low-dose mercury exposure*. *Alt Med Rev*, 2000. 5(3): p. 209-233.

146

Mechanisms of mercury toxicity and elimination

- **Part of the irreversible loss of GSH is due to the inhibition of GSH reductase by mercury, which is used to 'recycle' oxidized GSH and return GSH to the pool of available antioxidants. At the same time, mercury also inhibits GSH synthetase, so a lesser amount of new GSH is created."**

Crinnion, W.J., Environmental medicine, part three: Long-term effects of chronic low-dose mercury exposure. Alt Med Rev, 2000. 5(3): p. 209-233.

147

Mechanisms of mercury toxicity and elimination

- **"In spite of the focus on handling mercury by the kidneys because of the nephropathy induced by mercury, the liver and intestines are the primary organ involved in the early elimination of mercury, with fecal excretion greatly exceeding urinary excretion. Hence, translocation of mercury, presumably in the form of various mercury complexes, to the liver and intestines is quantitatively the major route of mercury interorgan flux."**

Zalups R.K. and Lash L.H., Interactions between glutathione and mercury in the kidney, liver, and blood, in Toxicology of Metals, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 145-163.

148

Mechanisms of mercury toxicity and elimination

- **“Metals that tend to remain longer in the plasma fraction of blood appear to be more likely to be handled by a greater extent by the kidneys.”**

Zalups R.K. and Lash L.H., *Interactions between glutathione and mercury in the kidney, liver, and blood*, in *Toxicology of Metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 145-163.

149

Mechanisms of mercury toxicity and elimination

- It appears that mercury ends up in the kidneys only after first line protective mechanisms found in the liver, intestine, and erythrocytes have either failed or have been overwhelmed. Therefore, one of our primary clinical goals from a preventive standpoint is to do what we do with virtually every other patient, improve liver and gut function.

150

Mechanisms of mercury toxicity and elimination - The role of erythrocytes

- **“Complexes of GSH with inorganic or organic mercury may be handled by erythrocytes...”**

Zalups R.K. and Lash L.H., *Interactions between glutathione and mercury in the kidney, liver, and blood*, in *Toxicology of Metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 145-163.

151

Mechanisms of mercury toxicity and elimination - The role of erythrocytes

- **“Since mature erythrocytes have the capability to synthesize GSH *de novo* and have significant activity levels of GSH peroxidase and GSH S-transferase, erythrocytes can be viewed as a first line of defense against blood borne oxidants and reactive electrophiles.”**

Zalups R.K. and Lash L.H., *Interactions between glutathione and mercury in the kidney, liver, and blood*, in *Toxicology of Metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 145-163.

152

Mechanisms of mercury toxicity and elimination - The role of erythrocytes

- **“Once GSH in erythrocytes acts on these potential toxicants, the cells transport GSSG or the thioether conjugate into plasma for translocation to other tissues, particularly the liver, kidneys, and intestines, for further metabolism or excretion.”**

Zalups R.K. and Lash L.H., *Interactions between glutathione and mercury in the kidney, liver, and blood*, in *Toxicology of Metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 145-163.

153

Mechanisms of mercury toxicity and elimination - Liver importance

- **“Although the liver is a primary site of the excretion of mercury, little hepatotoxicity is generally observed *in vivo*. This suggests that the mercury that is taken up by hepatocytes for transport across the sinusoidal plasma membrane does not interact significantly with hepatocellular thiols or macromolecules.**

Zalups R.K. and Lash L.H., *Interactions between glutathione and mercury in the kidney, liver, and blood*, in *Toxicology of Metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 145-163.

154

Mechanisms of mercury toxicity and elimination - Liver importance

- **Rather, the mercury that is taken up by the hepatocyte must be efficiently delivered into the bile across the canalicular plasma membrane for excretion into the intestine.”**

Zalups R.K. and Lash L.H., *Interactions between glutathione and mercury in the kidney, liver, and blood*, in *Toxicology of Metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 145-163.

155

Mechanisms of mercury toxicity and elimination - Liver importance

- **“Because of the predominance of GSH in the cell and the existence of specific plasma membrane transport systems, GSH appears to play a central role in the hepatic disposition of both organic and inorganic mercury.”**

Zalups R.K. and Lash L.H., *Interactions between glutathione and mercury in the kidney, liver, and blood*, in *Toxicology of Metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 145-163.

156

Mechanisms of mercury toxicity and elimination - Kidney susceptibility

- **“Of all the organs in the body of a mammal, the kidneys are the primary site for accumulation of mercury after exposure to inorganic or elemental mercury. Organic forms of mercury also accumulate in the kidneys of mammals to a significant degree, but to a lesser extent than inorganic or elemental forms of mercury.”**

Zalups R.K. and Lash L.H., *Interactions between glutathione and mercury in the kidney, liver, and blood*, in *Toxicology of Metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 145-163.

157

Mechanisms of mercury toxicity and elimination - Impact on sulfur metabolism

- **“It has been established that through alterations in intracellular thiol metabolism, mercury can promote oxidative stress, lipid peroxidation, mitochondrial dysfunction, and changes in heme metabolism.”**

Zalups R.K. and Lash L.H., *Interactions between glutathione and mercury in the kidney, liver, and blood*, in *Toxicology of Metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 145-163.

158

***Mechanisms of mercury toxicity and elimination
Kidney and sulfur metabolism***

- **“In all these various renal systems, a threshold effect is generally observed, in that no cellular necrosis (death) is observed up to a certain dose. Above that dose, however, cellular death progresses rapidly, and in some systems an all-or-none response is observed. This does not mean that subtoxic doses of mercury do not have biochemical or physiological effects.”**

Zalups R.K. and Lash L.H., *Interactions between glutathione and mercury in the kidney, liver, and blood*, in *Toxicology of Metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 145-163.

159

***Mechanisms of mercury toxicity and elimination
Kidney and sulfur metabolism***

- **“One possible explanation for the threshold effect and the subsequent steep dose-response curve is that endogenous ligands, such as glutathione, bind mercury and may act as a buffer to prevent functional changes from occurring. Above a certain dose or concentration of mercury, the buffer becomes depleted, and mercuric or mercurous ions can bind more readily to critical nucleophilic groups in the cell, thereby causing functional impairment.”**

Zalups R.K. and Lash L.H., *Interactions between glutathione and mercury in the kidney, liver, and blood*, in *Toxicology of Metals*, Chang L.W. et al, Editor. 1996, CRC Press: Boca Raton. p. 145-163.

160

*Research that suggests a lack
of correlation between
mercury body burden and
toxic responses:
Presence of amalgams*

161

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□ 1: Int J Hyg Environ Health. 2002 Apr;205(3):205-11. Related Articles, Links

Comment in:

- Int J Hyg Environ Health. 2002 Mar;206(2):139-41; author reply 143-5.

Determination of mercury in blood, urine and saliva for the biological monitoring of an exposure from amalgam fillings in a group with self-reported adverse health effects.

Zimmer H et al. Determination of mercury in blood, urine and saliva for the biological monitoring of an exposure from amalgam fillings in a group with self-reported adverse health effects (Abstract). Int J Hyg Environ Health. 2002;205(3):205-11.

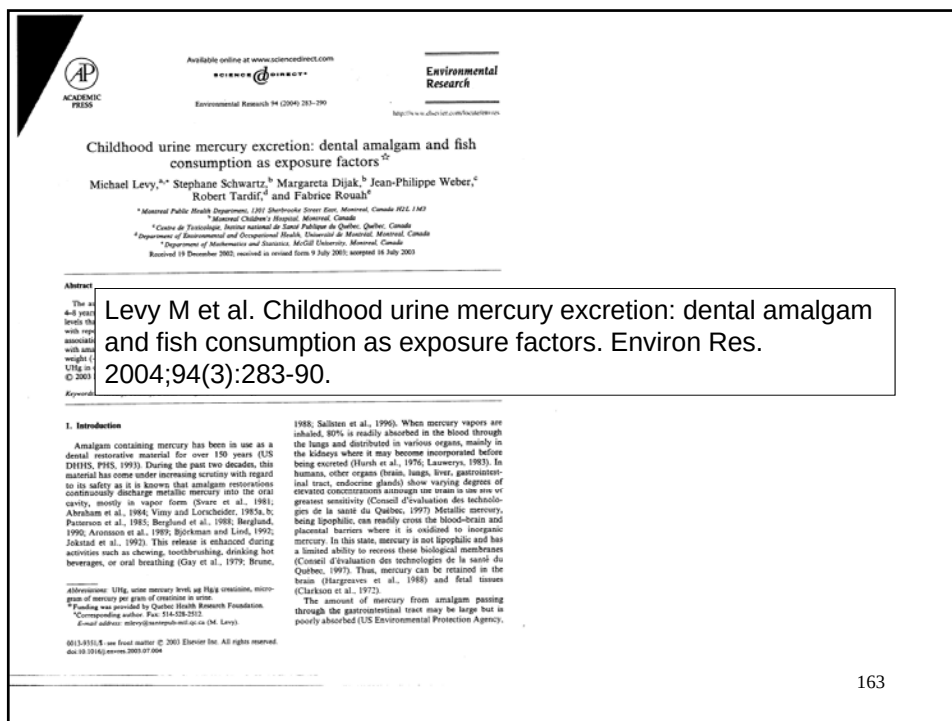
current reference values. Blood, urine and saliva samples were analyzed from 40 female subjects who claimed to suffer from serious health damage due to amalgam fillings ("amalgam sensitive subjects"). 43 female control subjects did not claim any association ("amalgam non-sensitive controls"). Mercury was determined by means of cold vapour atomic absorption spectrometry. Number and surfaces of amalgam fillings were determined by dentists for each subject. Median (range) mercury levels in blood were 2.35 (0.25-13.40) micrograms/l for "amalgam sensitive subjects" and 2.40 (0.25-10.40) micrograms/l for "amalgam non-sensitive controls". In urine, the median

No correlation!!

were within the range of background levels in the general population including persons with amalgam fillings. Stimulated saliva contained 76.4 (6.7-406.0) micrograms mercury/l in "amalgam sensitive subjects" and 57.0 (2.8-559.0) micrograms mercury/l in controls (not significant). Mercury levels in saliva did not correlate with the concentrations in blood and urine, but merely with the number of amalgam fillings or of the filling surfaces. Mercury in saliva is therefore not recommended for a biological monitoring.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uid... 8/24/2005

162



- “The presence of amalgam fillings was the most significant predictor of high urine mercury in children.”
- “Our results support those of previous studies indicating that the concentration of Hg found in urine of adult and children subjects with no occupational exposure is mainly dependent on the presence of amalgam fillings.”

“The evidence presented here confirms previous findings that children with amalgam fillings have an increased exposure to mercury, although no inference can be drawn about possible adverse health effects.”

165

Environmental Medicine | Article

Mercury Derived from Dental Amalgams and Neuropsychologic Function

Pam Factor-Litvak,^{1,2} Gunnar Hasselgren,² Diane Jacobs,⁴ Melissa Bagg,³ Jennie Kline,^{1,4,5} Jennie Geler,¹ Nancy Marvish,¹ Sonia Schoenholz,¹ and Joseph Graziano¹

¹Department of Epidemiology and ²Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, New York, USA; ³School of Dental and Oral Surgery, Columbia University, New York, New York, USA; ⁴Neurology Center, Columbia University, New York, New York, USA; ⁵Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, New York, USA; ⁶Department of Developmental Brain Disorders Department, New York State Psychiatric Institute, New York, New York, USA

There is widespread concern regarding the safety of silver-mercury amalgam dental restorations, yet little evidence to support their harm to safety. We examined whether mercury derived from amalgams is adversely associated with cognitive functioning in a cross-sectional sample of healthy working adults. We studied 550 adults, 30–49 years of age, who were not occupationally exposed to mercury. Participants were representative of employees at a major urban medical center. Each participant underwent a neuropsychologic test battery, a structured questionnaire, a modified dental examination, and collection of blood and urine samples. Mercury exposure was assessed using a mercury exposure questionnaire (UEQ), the total number of amalgam surfaces, and the number of occlusal amalgam surfaces. Linear regression analysis was used to estimate associations between each marker of mercury exposure and each neuropsychologic test, adjusting for potential confounding variables. Exposure levels were relatively low. The mean UEQ was 1.7 ng/g creatinine (range, 0.00–17.50); the mean total number of amalgam surfaces was 19.4 (range, 0–40); and the mean number of occlusal amalgam surfaces was 6.1 (range, 0–19). No marker of exposure was significantly associated with the scores on any neuropsychologic test in analyses that adjusted for the sampling design and other covariates. In a sample of healthy working adults, mercury exposure derived from dental amalgam restorations was not associated with any detectable deficits in cognitive function.

staff. Older employees were not studied because, on average, the total number of amalgam surfaces declines after 50 years of age because of the loss of teeth (National Institute of Dental Research 1987). After excluding 227 noneligible persons, 550 (52%) agreed to participate in a 90-min evaluation that included collection of urine and blood samples, a questionnaire, and a neuropsychologic battery. We excluded personnel no longer employed at the medical center, dental personnel, non-English speakers, and pregnant women.

Participants. Compared with nonparticipants, participants were less likely to be professional staff and less likely to be male (Table 1). One hundred nonparticipants agreed to complete a brief questionnaire to obtain

Factor-Litvak P et al. Mercury derived from dental amalgams and neuropsychologic function. Environ Health Perspectives. 2002;111(5):719-723.

50% thought amalgam restorations might have adverse effects (Gelfert et al. 1992). A similar survey of dentists found that although 89% of respondents believed that amalgams posed no risk, 52% reported that they would not use amalgam restorations in a pediatric population (Gelfert et al. 1992). Reviews in both the scientific and lay literature link amalgam restorations to severe psychiatric, neurologic, and immunologic effects (Gunnarsson 1993; Jung and Mohr 1992; Hansen and Plewa 1991; Winer et al. 1990).

Severe chronic occupational exposure to elemental mercury (Hg⁰) vapor has been associated with a constellation of neuropsychologic symptoms, the “Mad Hatter Syndrome.” Amalgam restorations are approximately 50% inorganic mercury (Hg⁰), and systemic absorption of Hg⁰ vapor from amalgams is well documented (Beilin 1960; Berlin et al. 1975; Hanch et al. 1980; Newman and Fry 1978; Takahashi et al. 1979; Watanabe 1960). Occupational exposure to dentists is associated with intentional release of mercury vapor

restoration, occupational exposure, lifestyle behaviors (smoking, alcohol consumption, caffeine consumption, and gum-chewing behavior), location, and health history. Each subject completed a neuropsychologic battery in the clinical research unit. The neuropsychologic tests were administered in a fixed order.

Laboratory assays. UEq was determined by flow-injection cold vapor atomic absorption spectrometry (Gao and Besser 1993) by one technician. The laboratory participated in the quality control program for UEq

Materials and Methods

The Columbia-Presbyterian Institutional Review Board approved the protocol and informed consent documents for this study. Between September 1997 and December 1999, we invited a random sample of 1,066 employees at a university health center to participate in a study titled “Dental Health and General Well-Being.” We used a stratified random sampling of the personnel roster to select a sample with equal numbers in four strata defined by age (20–29 or 40–49 years) and employment status (professional or support

166

- “...it is well known that exposure to high concentrations of organic mercury (notably methyl mercury) via fish and seafood consumption, such as those found in the Minimata Bay episode, is associated with neuropsychologic deficits in children.”
- “Those findings, however, were not confirmed in more recent studies in the Faroe Islands in the lowest exposure groups (which are likely to reflect levels found in U.S. children).”

167

- “The mean urinary mercury concentration was 1.7 µg/g creatinine (range 0.09-17.8); the mean total number of amalgam surfaces was 10.6 (range, 0-46) and the mean number of occlusal amalgam surfaces was 6.1 (range 0-19).”
- “No measure of exposure was significantly associated with the scores on any neuropsychologic test in analyses that adjusted for the sampling design and other covariates.”
- “In a sample of healthy working adults, mercury exposure derived from dental amalgam restorations was not associated with any detectable deficits in cognitive or fine motor functioning.”

168

Research that suggests a lack of correlation between mercury body burden and toxic responses:

Urinary challenge testing

169

Original Article

Dimercaptosuccinic acid loading test for assessing mercury burden in healthy individuals

GP Archbold¹, Rosin M McGuckin¹ and NA Campbell²

Abstract

Background Oral chelation tests have been used to try to define mercury toxicity in individuals with dental amalgams, who are suffering from a variety of non-specific symptoms.

Methods Self-reported healthy individuals volunteered to undergo an oral chelation test using dimercaptosuccinic acid (DMSA) at a dose of 30 mg/kg body weight. Urinary mercury: creatinine ratios were measured pre-dose and 3h post-dose.

Results Urinary mercury: creatinine ratios were similar to levels previously reported in individuals with symptoms that could have been attributed to mercury.

Conclusion DMSA challenge testing is not a reliable test for mercury toxicity.

Archbold GP et al. Dimercaptosuccinic acid loading test for assessing mercury burden in healthy individuals (Abstract). Ann Clin Biochem. 2004;41(Part 3):233-6.

Introduction

Conventional dental amalgam is a mixture of silver and tin (with small amounts of copper and zinc). When this is mixed with mercury a new inter-metallic alloy is formed. Corrosion and wear (e.g. by food chewing or tooth brushing) of amalgam causes the release of small amounts of mercury vapour, which can be inhaled or swallowed, resulting in the absorption of approximately 2 µg/day¹. Individuals suffering from a variety of non-specific symptoms, such as muscle pain, weakness, joint pain, memory disturbance, tiredness, dizziness, headache, sleep disturbance, difficulty in concentration, numbness in the arms or legs, and a burning mouth are sometimes told they have 'amalgam' sickness, which is claimed to be a form of mercury toxicity.

Chelation tests have been used to assess the body burden of mercury in attempts to confirm or refute the possibility that such symptoms could be related to mercury toxicity. These tests include the measurement of urinary mercury before and after a loading dose of the oral chelating agent meso-2,3-dimercaptosuccinic acid (DMSA)². Other chelation tests have also been used, e.g. oral³ or intravenous (IV)⁴ 2,3-dimercaptopropane-1-sulphonate (DMPS).

Individuals and urinary mercury was not corrected for urinary creatinine. The authors showed that the average increase in urinary mercury following DMSA loading at 30 mg/kg was 16.1%. The laboratory that performs this test commercially (which was the source of the paper by Hibbard *et al.*) now uses an upper limit of normal of 150% increase for a urinary mercury: creatinine ratio, but there is no documentary evidence as to how they arrived at this defined limit, and it appears they have simply extrapolated a percentage change in the average uncorrected urinary mercury excretion from their previous work on symptomatic individuals.

Patients who have had this test carried out by other clinicians are sometimes referred for further advice. Usually these patients want chelation therapy on the basis of the test result (some also seek advice about amalgam removal, others have already had amalgam removal). Some of those referred have had mercury toxicity based on our laboratory analysis of urinary mercury, although it has not always been possible to convince the patients that this is the case.

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233

170

- “Self-reported healthy individuals volunteered to undergo an oral chelation test using dimercaptosuccinic acid (DMSA) at a dose of 30 mg/kg by weight. Urinary mercury : creatinine ratios were measured predose and 3 h post-dose.”
- “Urinary mercury : creatinine ratios were similar to levels previously reported in individuals with symptoms that could have been attributed to mercury toxicity. One volunteer suffered a serious reaction to DMSA.”

171

“The oral chelation test using DMSA may lead to misleading diagnostic advice regarding potential mercury toxicity and can be associated with serious side effects.”

172

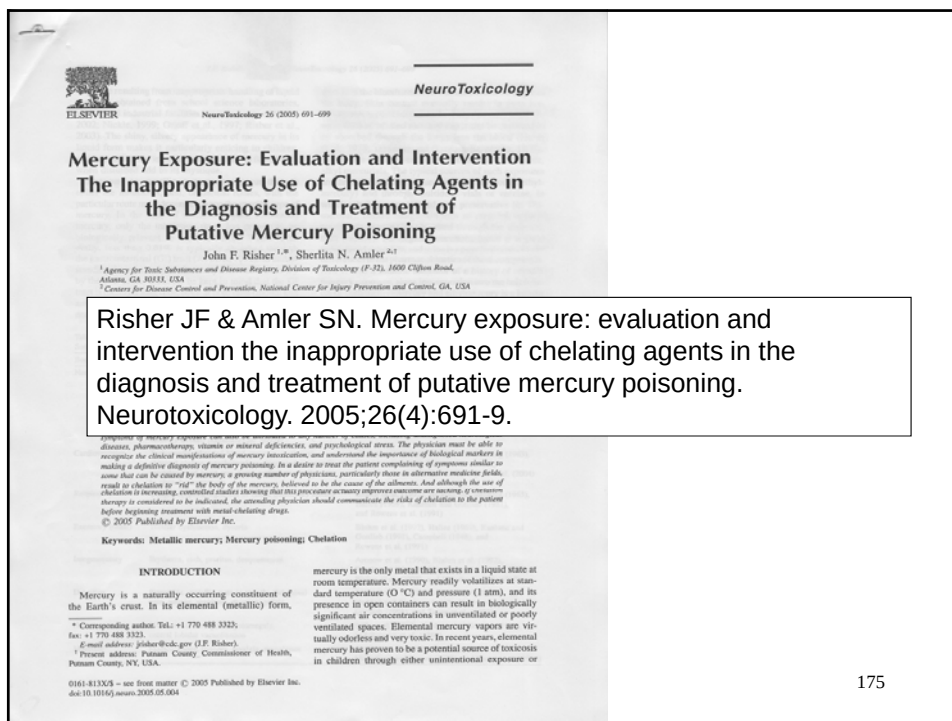
*Research that suggests a lack of
correlation between mercury
body burden and toxic
responses:*

*Mercury removal and elimination
of signs and symptoms*

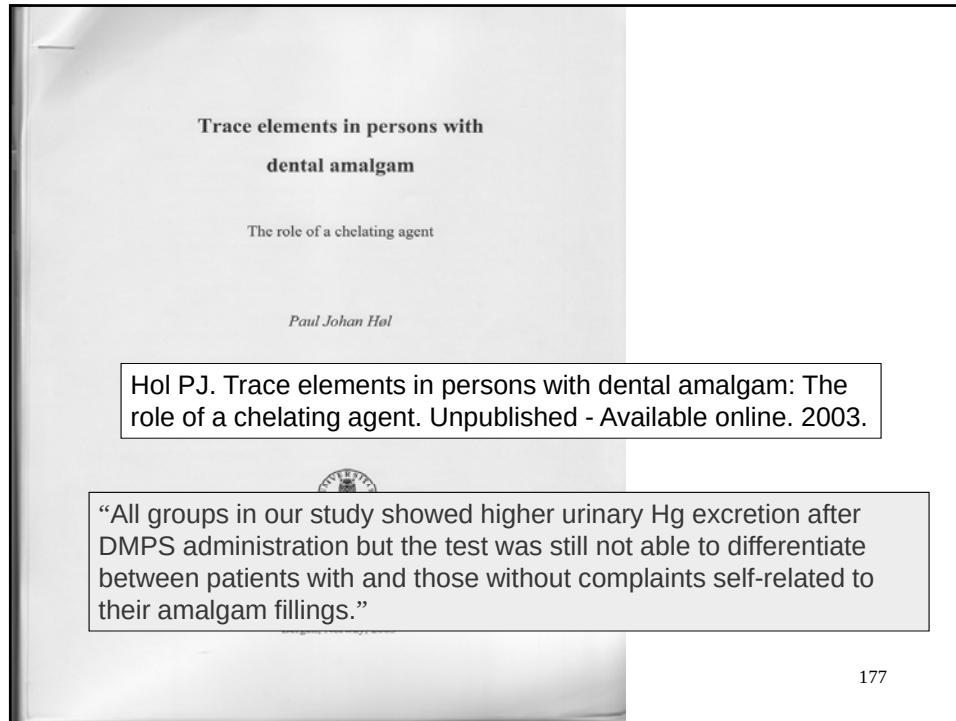
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***As you will see, research on this
relationship is very inconsistent and
conflicting.***

174



- “The efficacy of the chelating agents...to complex mercury and temporarily facilitate the elimination of that metal in the urine is well established. However, while the use of chelation is increasing for known or suspected heavy metal exposure, there is a paucity of controlled studies showing that this procedure actually improves the long-term outcome of the patient.”
- “In fact, a number of studies found no clear clinical benefit from DMSA treatment of humans documented to have been poisoned, or suspected to have been poisoned, by elemental mercury vapor.”
- “The use of chelating agents is even more questionable in cases where symptoms and/or clinical signs of severe mercury intoxication are absent and where urine and/or blood levels are within the normal background range.”

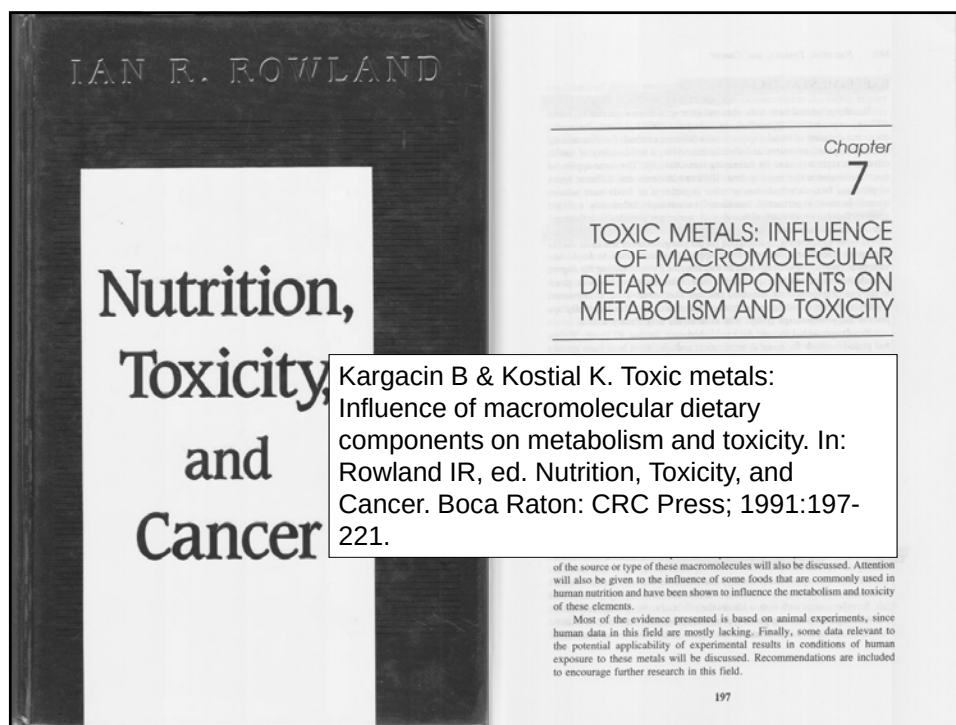


*Why is there a lack of
correlation between body
mercury levels, toxic
responses, and results of
eliminative therapies*

178

Endogenous detoxification!!

179



- **“By increasing the protein content of the diet (from 10% to 20%) or by adding cystine or a combination of cystine and selenium, the toxicity of methylmercury is reduced when methylmercury is added to the diet in an amount of 25 ppm. Not only the level of protein in the diet, but also its source influenced the mercury toxicity, since the survival of rats fed a diet containing 20% protein as fish protein concentrate was higher than the survival of those fed a 20% casein diet.”**

181

- **“A higher protein level (20% vs. 10%) reduced and delayed the onset of toxic signs, and fish protein concentrate was more effective in this respect than was casein. This effect of fish protein concentrate was presumably due to its selenium content, since fish protein concentrate contained about 4 ppm of selenium. It was also shown that 0.4% cystine and 0.6 ppm selenium were about the optimum levels for reducing visible toxic signs produced when diets contained about 25 ppm of mercury from methylmercury chloride.”**

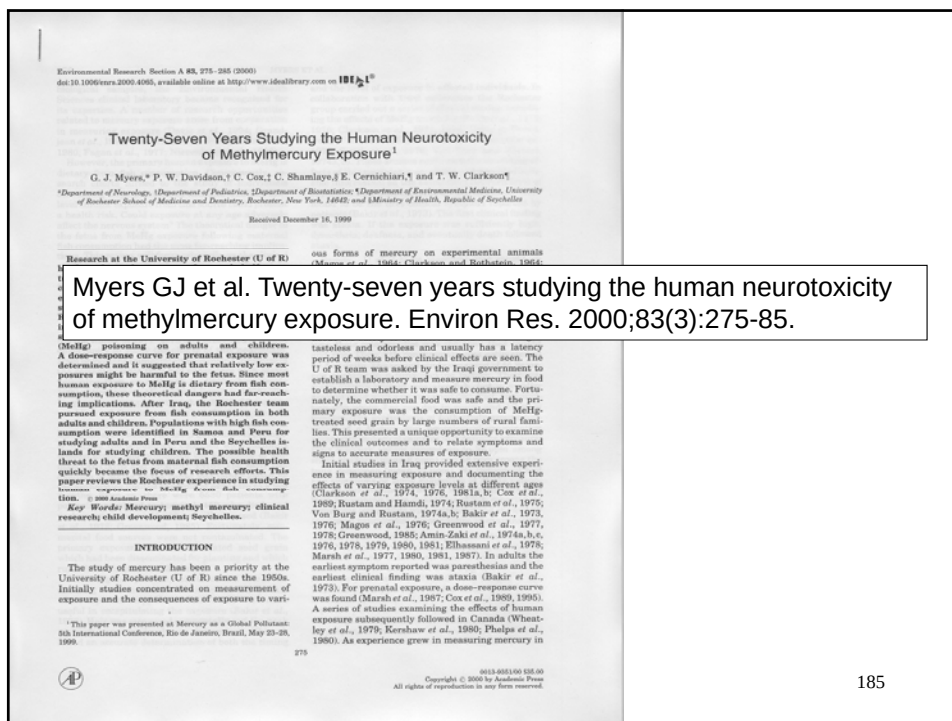
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- **“Mercury concentrations in the kidney were considerably lower when diets contained cystine, selenium, and fish protein concentrate. The protective effect of cystine and selenium may be exerted through a reduction in mercury deposition in the kidney, and hence a delay in the onset of kidney failure caused by continued exposure to high intakes of mercury.”**

183

- **“Another possible explanation is that cystine provides additional sulfur-binding sites in proteins that complex with mercury. At least a partial effect of cystine in these studies may also have been via an increased rate of conversion of methylmercury to inorganic mercury, which is less toxic. Norseth and Clarkson showed that inorganic mercury was released from methylmercury chloride when placed in a buffered solution containing 0.1 M cysteine. No inorganic mercury was released when cysteine was absent.”**

184



- “The small amount of MeHg consumed with each exposure and spreading the exposure over a longer time period may alter the way the human body handles it. Clarkson (1995) has suggested that the liver may excrete or detoxify small amounts, but may be unable to handle larger amounts.”
- “Exposure to MeHg in conjunction with other components of fish such as selenium and amino acids may also influence its potential toxicity in other ways. Selenium may decrease any potentially toxic effects and amino acids may compete with MeHg transport into the brain.”

*Is the best way to deal with
mercury body burden always
elimination from the body as
quickly as possible?*

187

*Selenium:
Possibly the most important
“X factor” that explains why
mercury levels do not
correlate with symptomatology*

188

- “Regarding the concern about mercury contamination, the National Oceanic and Atmospheric Administration (NOAA) statement advises: ‘Women will not put their baby at risk if they avoid eating shark, swordfish, tilefish, king mackerel, tuna steaks and whale meat until after they have delivered and stopped breast feeding.’ For good measure, women planning to become pregnant should avoid these fish for six months beforehand.”
- Press release – Reuters, December 21, 2005.

189

- **“The recommendations have a 10-fold safety margin built in for precaution, which some scientists think is scaring people away from seafood. ‘This margin might make people continue depriving their families and their children of the benefits of consuming seafood,’ William E. M. Lands, a retired Professor of Biochemistry at the University of Michigan and the University of Illinois, and an expert in the field of the metabolism of fats, phospholipids, and prostaglandins, told Reuters Health.”**

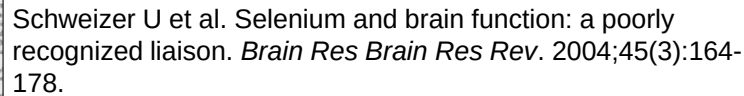
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- Evidence presented at the conference showed that selenium, another element present in ocean fish, neutralizes the effects of mercury acquired from foods. 'This very important, but little analyzed, point helps us understand how people from the Seychelles Islands can eat fish 12 times per week and show no toxic signs,' Lands said. 'The subtle toxic signs seen in places like the Faroe Islands now seem attributable to mercury being ingested in mammalian meats (pilot whale) that have much lower selenium than mercury.'
- "“Not eating seafood is more harmful than eating it,' Lands concluded. 'The benefits of eating seafood far outweighs the risks of the little bit of mercury that are in the seafood.'”

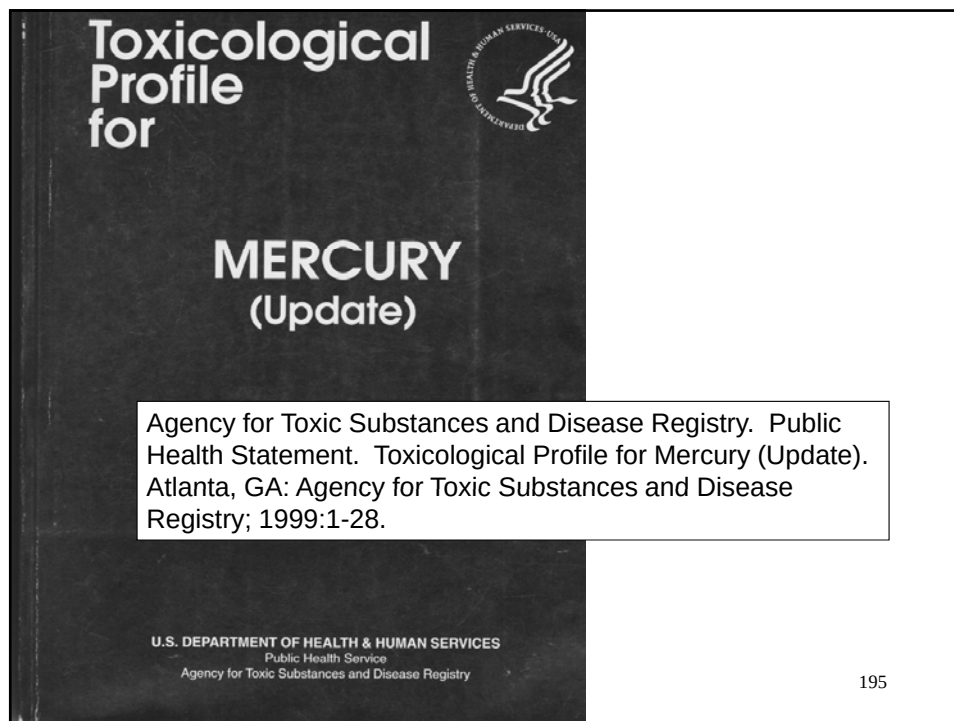
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Selenium and the brain

192

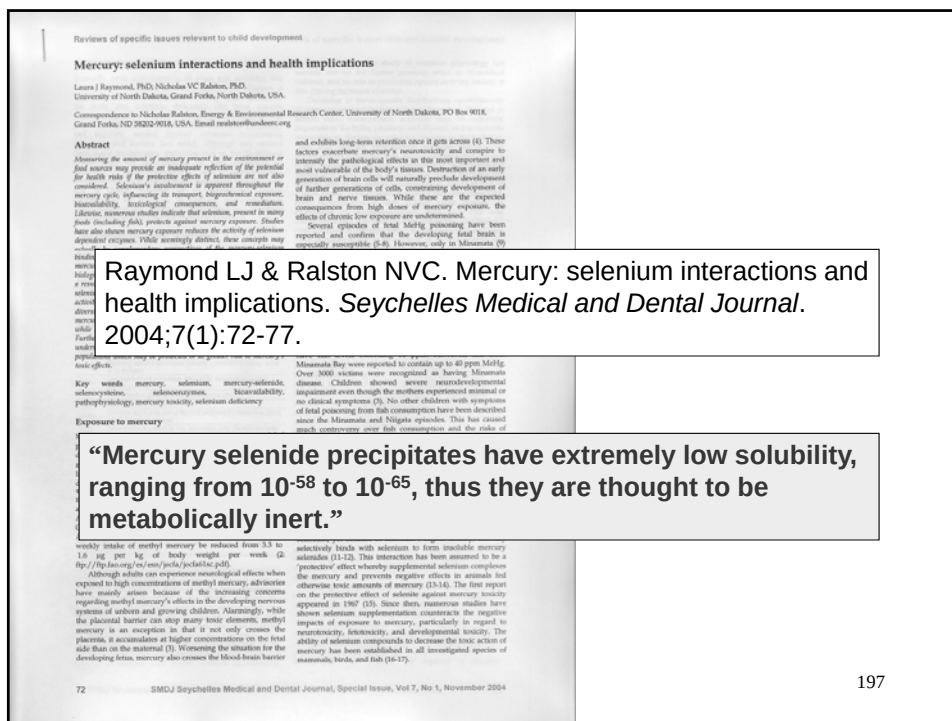


- “It becomes more and more apparent that the essential trace element Se plays a critical role in the maintenance of proper functioning of the nervous system.”
- “Furthermore, insufficient brain Se levels have potentially detrimental effects on brain function and may exacerbate neuronal loss and dysfunction subsequent to endogenous or exogenous stimuli, trauma and other neurodegenerative conditions.”
- “Selenium is a potent protective agent for neurons through the expression of selenoproteins, which are mostly involved in regulation of redox status under physiological conditions and in antioxidant defense.”

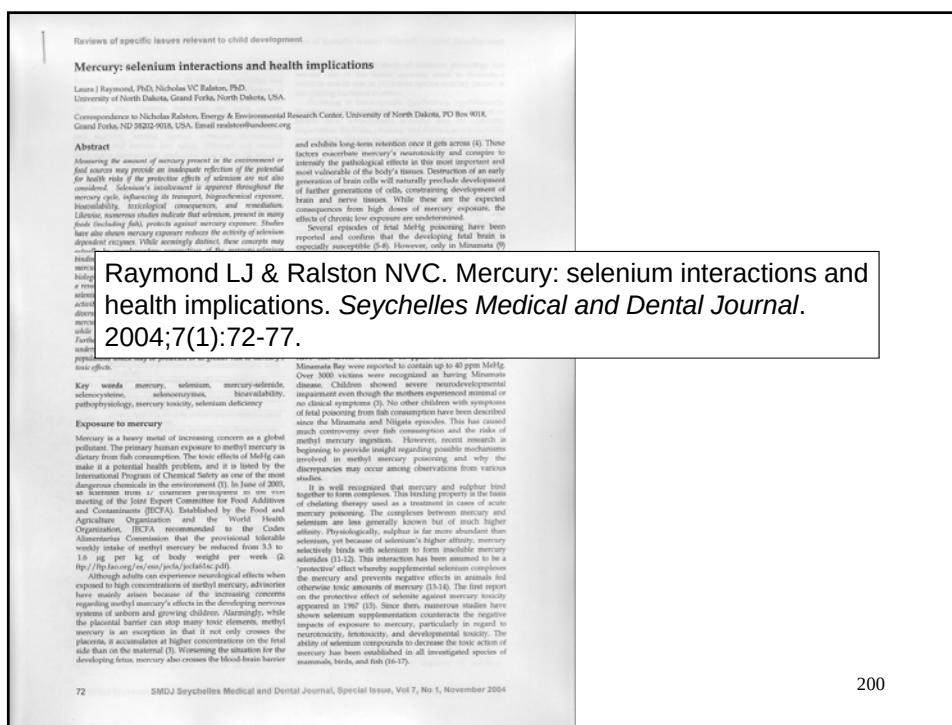
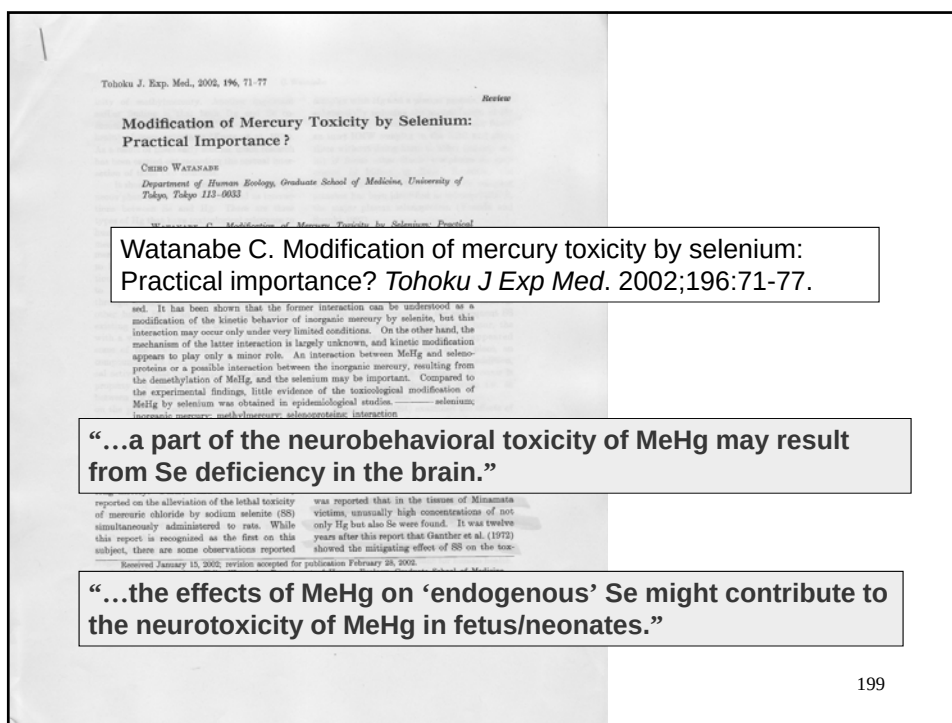


- **“The co-administration of methylmercury and selenium is known to depress methylmercury toxicity. Furthermore, the level of selenium in human hair has been found to negatively correlate with the level of mercury in brain tissue. Methylmercury forms a bismethylmercury selenide complex. Selenium in foods (especially fish) may also complex with methylmercury and, therefore, may potentially reduce the bioavailability of methylmercury.”**

196



“It is reasonable then to assume that not only does selenium have an effect on mercury’s bioavailability, but mercury may also have an effect on selenium bioavailability.”



- **“Their research confirmed the neurological deficits reported from MeHg poisoning incidents in Japan. However, they found no adverse associations from consuming fish containing typical mercury levels. Additionally, their studies of both prenatal and postnatal measures of MeHg exposure from fish consumption in Seychellois children have been associated with beneficial effects.”**

201

- **“Their results, however, contrast with those found in studies being carried out in the Faroe Islands, which reported adverse associations from prenatal MeHg exposure. There are several differences between these studies and the populations in general. However, the most intriguing distinction may be the source of the MeHg exposure.”**

202

- **“The diet consumed by the Faroe Islanders includes whale whereas the Seychelles Islanders diet does not. Whale is known to contain PCBs as well as possibly other toxins not typically found in fish. Additionally, the amount of MeHg in some types of whale meat analyzed has been reported to be exceedingly high. The concentration of mercury present in whale rises continually with age and can exceed the selenium content. This is seen in high-end predator whales such as pilot whales rather than filter feeders such as bowhead whales. Mercury concentrations in samples of pilot whale have been 5000 times greater than the Japanese government’s limit for mercury contamination of 0.4 ppm.”**

203

“In contrast to whales, methyl mercury concentrations in fish rise with age, but as their mercury contents increase, so do their selenium concentrations. To our knowledge, there are no reports of mercury exceeding selenium concentrations in any ocean fish.”

204

- **“Friedman et al studied the protective effect of freeze-dried swordfish on methylmercury toxicity in rats. The rats that were experimentally administered methyl mercury and fed a swordfish diet showed no signs of neurotoxic effects characteristic of mercury poisoning, while rats not fed swordfish did. Analysis of the swordfish showed selenium concentrations were at least twice as high as the mercury levels. The authors suggested that the excess selenium protected the rats from the effects of the administered methyl mercury.”**

205

- **“Several studies suggest an important role of selenium in the bioaccumulation of mercury in fish. Paulsson and Lindbergh reported selenium supplementation to lake waters in Sweden resulted in a 75%-85% reduction in mercury levels of fish when measured over a three-year period.”**

206

- **“Southworth et al reported that the elimination of selenium-rich discharges of fly ash to Rogers Quarry in Tennessee in 1989 caused a steady increase in mercury concentrations. The aqueous selenium concentrations decreased from 25 to <2 µg/L. The mean selenium concentrations in bass declined from 3 to 1 mg/kg over the first 5 years and remained at 1-1.5 mg/kg for the last three years of the study. During this time, the mean mercury concentrations in bass rose from 0.02 to 0.61 mg/kg.”**

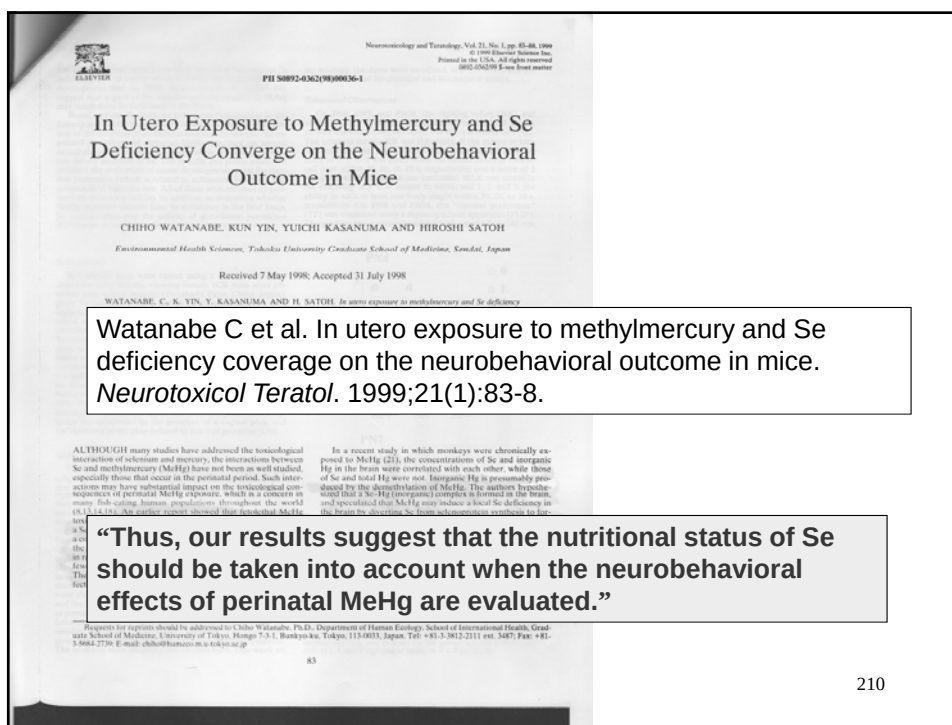
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- **“Although several population studies have suggested an association between high fish intake and reduced coronary heart disease (CHD), *men in eastern Finland who consume large amounts of freshwater fish have an exceptionally high CHD mortality.* Salonen et al studied the relationship between mercury intake from fish and CHD in Finland. The authors hypothesized that the high mercury levels from fish contributed to increased incidence of CHD. Before soil supplementation, Finland had the lowest selenium levels throughout Europe.”**

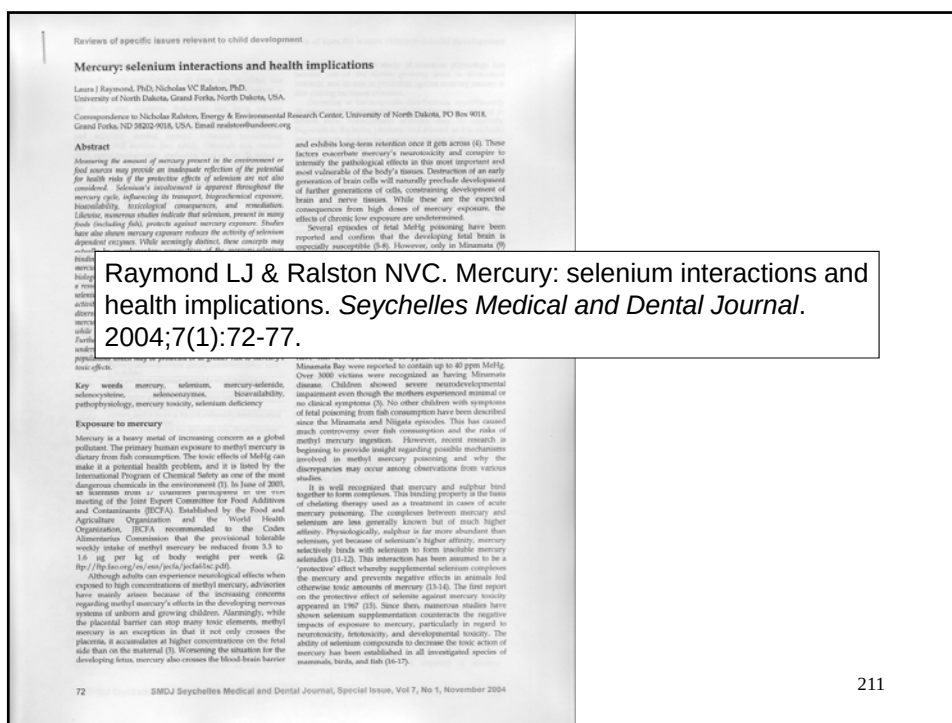
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- **“The authors suggested that mercury might contribute to CHD risk by complexing to selenium and reducing its bioavailability for glutathione peroxidase, thus promoting lipid peroxidation. They further suggest that the lack of a similar correlation between CHD and fish consumption in other population studies was owing to high intakes of selenium.”**

209



210



211

- “In summary, studying the pathology of mercury toxicity may require a more insightful question than simply, ‘How much mercury is consumed?’ The more appropriate question may be, ‘Is a sufficient amount of free selenium available in the cell to create the necessary selenoenzymes or is too much selenium lost by binding to mercury?’”

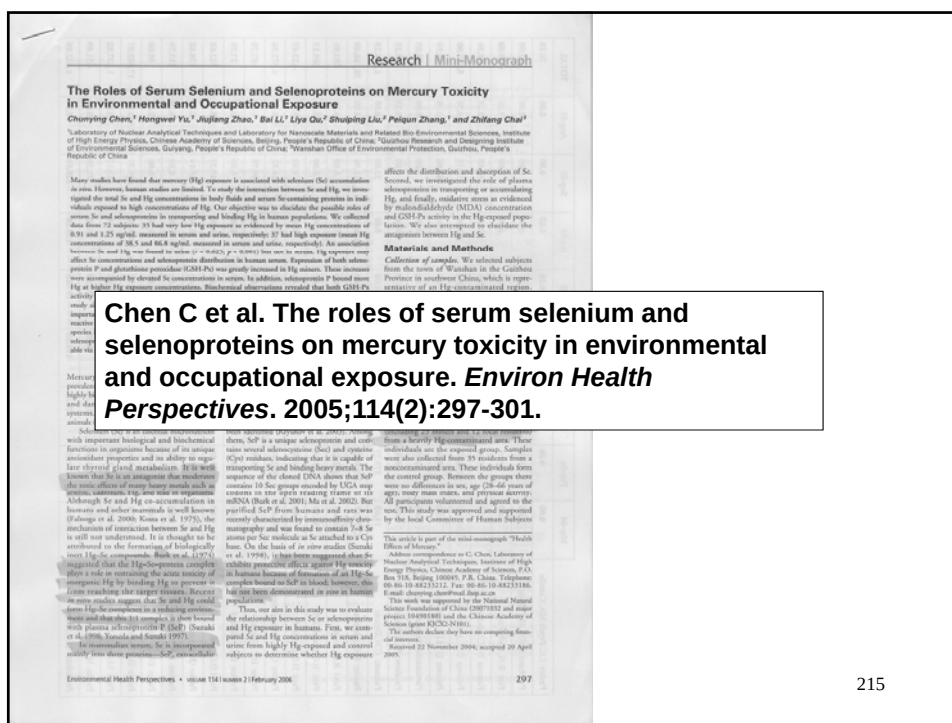
212

“In this regard, the sensitivity to mercury-induced neurotoxicity may be due to the balance of mercury and selenium.”

213

- **“Selenium’s involvement is apparent throughout the mercury cycle, influencing its transport, biogeochemical exposure, bioavailability, toxicological consequences, and remediation. Therefore, measuring the amount of mercury present in the environment or food sources may provide an inadequate reflection of the potential for health risks if the protective effects of selenium are not also considered.”**

214



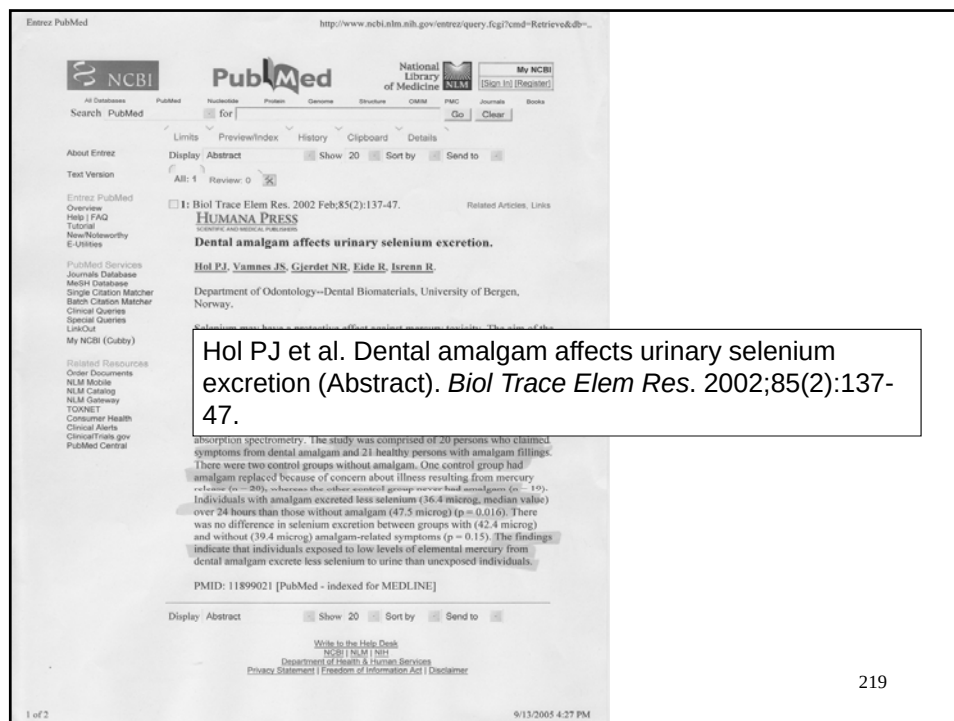
- “It is well known that Se is an antagonist that moderates the toxic effects of many heavy metals such as arsenic, cadmium, Hg, and lead in organisms.”
- “Burk et al. suggested that the Hg-Se-protein complex plays a role in restraining the acute toxicity of inorganic Hg by binding Hg to prevent it from reaching the target tissues. Recent *in vitro* studies suggest that Se and Hg could form Hg-Se complexes in a reducing environment and that this 1:1 complex is then bound with plasma selenoprotein P (SeP).”

“Thus, we propose that selenoproteins may have two important roles in protecting against mercury toxicity. First, they may bind more Hg through their highly reactive selenol group, and second, their antioxidative properties help compromise the reactive oxygen species induced by Hg in vivo.”

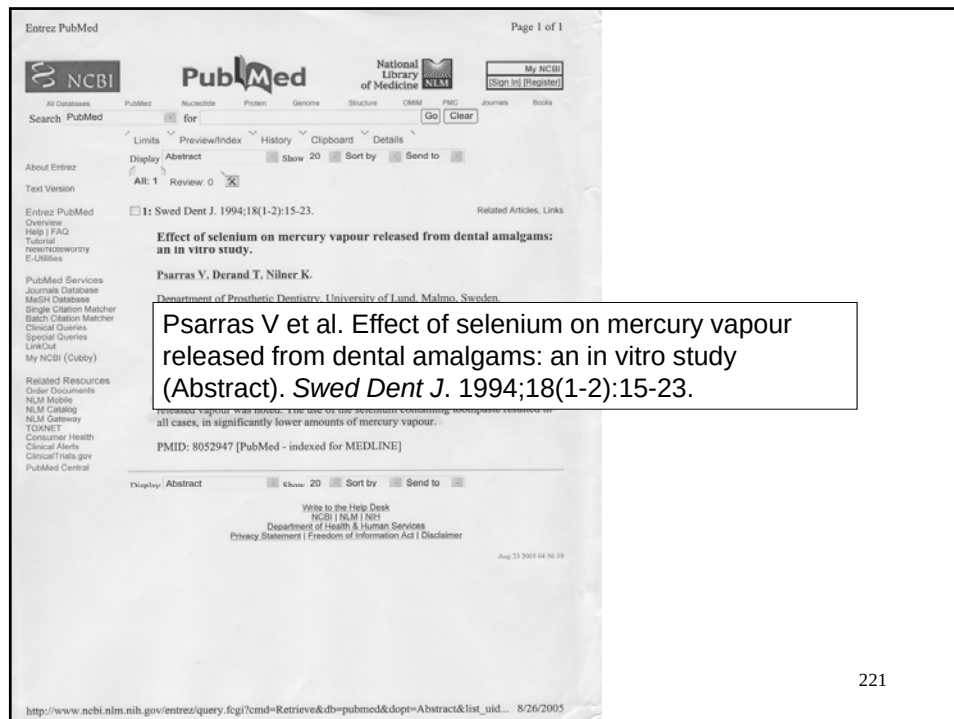
217

Selenium and amalgams

218



- “Individuals with amalgam excreted less selenium (36.4 microg, median value) over 24 hours than those without amalgam (45.5 microg).”
- “The blood selenium concentrations were statistically significantly lower in subjects who claimed symptoms of mercury amalgam illness, than in healthy subjects with amalgam. This difference was more evident between the individuals with more than 35 amalgam surfaces.”



221

- **“The use of the selenium containing toothpaste resulted in all cases, in significantly lower amounts of mercury vapour.”**
- **“When the amalgam surfaces were brushed with the conventional toothpaste, an increase of the released vapour was noted.”**

222

Mercury, selenium, and other nutrients

223

INTERACTIONS OF VITAMIN E AND SELENIUM WITH MERCURY AND SILVER

Howard E. Ganther

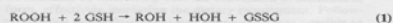
Department of Nutritional Sciences
University of Wisconsin
Madison, Wisconsin 53706

INTRODUCTION

The theme of this conference is fully reflected in the subject of this paper, which discusses some well-established interactions between a vitamin, an essential trace element, and two hazardous metals. With metals, interactions are the rule rather than the exception, and since selenium is a close relative of sulfur, interactions of selenium with metals are also to be expected. It is more difficult to see how a fat-soluble substance like vitamin E can interact with metals, from the purely chemical standpoint. Perhaps the most interesting aspect of this problem is the way in which

levels of selenium are reduced by substantial amounts by the presence of these metals. This is a problem of great importance to the biological sciences, and the metals do to a better understanding of how the toxic metals actually exert their toxic effects.

The functions of vitamin E and selenium in the control of peroxidative damage have been generally accepted. Vitamin E can give up a hydrogen atom to a free radical and thereby inhibit propagation of radical chain reactions.¹ Vitamin E may also play a role in membrane structure beyond that of an antioxidant.² The discovery by Rotruck and Hoekstra that glutathione peroxidase was a selenoprotein, catalyzing hydroperoxide decomposition (Equation 1), greatly clarified the biochemical



basis for the nutritional interactions of vitamin E, selenium, and sulfur amino acids.³ This topic was reviewed by Hoekstra and is discussed elsewhere at this conference by Tappel.^{4*}

There may well be other functions in animals for selenium and for vitamin E, but for the present, we may ask whether the interactions of silver and mercury with these micronutrients can be explained in terms of radical-induced peroxidative damage. It is known that metals that undergo univalent redox reactions can initiate peroxidative destruction. Historically, it was the idea that silver could have a prooxidant effect that led to the work by Shaver and Mason 30 years ago that first demonstrated the strong protective effect exerted by vitamin E against silver toxicity.

VITAMIN E AND SILVER

In 1951, Shaver and Mason reported in an abstract that weanling rats fed a

* See page 18 for Tappel's paper.

212

0077-8923/80/0355-0212 \$01.75/0 © 1980, NYAS

Ganther HE. Interactions of vitamin E and selenium with mercury and silver. *Annals NYAS*. 1980;355:212-226.

224

- **“The susceptibility of a tissue to damage would be a function of the methylmercury concentration, the rate at which hemolytic breakdown occurred, and the capacity of the tissue to defend against peroxidative damage, as determined by levels of glutathione peroxidase, vitamin E, and other substances.”**

225

*The best way to remove
mercury
Boyd Haley, Ph.D.*

226

- “The following is my opinion on the use of natural materials and compounds that may be safely used to remove mercury from the body. It is totally based on the science known about how the mammalian body removes toxic mercury.”
- “I do not present any opinion on EDTA, DMSA, DMPS, or BAL or other manufactured chelators. It is my opinion they should be used only after the use of natural compounds has failed.”

227

- ***“Using the adage “First, do no harm” I think that supplementing the body’s metabolic system that is active and needed for natural removal of mercury is the best approach. This is not as much “chelation therapy” as “anti-oxidative stress therapy” and is based on the supplementation that enhances the production of materials normally used to remove heavy metals.”***

228

Boyd Haley's protocol

- Vitamin C
- Lipoic acid
- IV glutathione
- Melatonin
- Vitamin B12
- Selenium
- Sulfurized amino acids

229

Boyd Haley's thoughts on selenium

- "Se²⁺ forms a very tight bond with Hg²⁺ and forming HgSe (similar to HgS, mercury sulfide or cinnabar the ore where mercury is mined from) would greatly reduce the toxicity of mercury."
- "However, it may also interfere with the removal of mercury from the body as HgSe would not be removed by GSH or lipoic acid."
- "One should also consider that any patient who is mercury toxic should also be selenium deficient as the mercury would remove the selenium from bioavailability."

230

Boyd Haley's thoughts on chelation

- “After the patient is showing improvement it may be advantageous to use DMPS or DMSA to enhance the removal of mercury. I am not totally against their use but I do not think they will represent the best or safest way to approach removal of mercury from a very sick patient due to their own toxicity as British Anti-Lewisite agents.”

231

Boyd Haley's thoughts on chelation

- “Also, they do not effectively enter cells nor cross the blood brain barrier as do natural compounds. However, in the hands of a good physician they may prove very helpful. It is when the pills of DMPS and DMSA are given to the lay-person for them to decide how to use on a daily basis that I feel they can become dangerous.”

232

“...especially in chronic toxicity, the presence of vitamin E and selenium might allow for a sustained decomposition of alkylmetals by stabilizing microsomal cytochrome P450 systems involved in alkylmetal metabolism.”

233

DMSA/DMPS

234

Is DMSA/DMPS a valid tool for
diagnosis
of *mercury body burden*?

235

Maybe

236

237

96



Is DMSA/DMPS a valid tool for
diagnosis
of mercury related symptoms?

According to much research,
No!!

241



NeuroToxicology 28 (2007) 691–699

Mercury Exposure: Evaluation and Intervention The Inappropriate Use of Chelating Agents in the Diagnosis and Treatment of Putative Mercury Poisoning

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Received 11 May 2007
Available online 11 July 2007

Abstract

Public awareness of the potential for mercury to cause health problems has increased dramatically in the last 15 years. It is now widely recognized that significant exposure to all forms of mercury (elemental, inorganic, and organic) compounds can result in a variety of adverse health effects, including neurological, renal, respiratory, immune, dermatologic, reproductive, and developmental sequelae. And while the various media have made the general population cognizant of the need to avoid unnecessary exposure to the naturally occurring element, there has also evolved a growing tendency to embrace unwarrantable neurology, as well as other, vague and complex, hypotheses to mercury, whether or not significant exposure to mercury has actually occurred.

For the physician, making a diagnosis of mercury intoxication can be difficult because many of the clinical signs and symptoms of mercury exposure can also be attributed to any number of causes, including undiagnosed neurological diseases, pharmacotherapy, vitamin or mineral deficiencies, and psychological stress. The physician must be able to recognize the clinical manifestations of mercury intoxication, and understand the importance of biological markers in making a definitive diagnosis of mercury poisoning. It is a desire to treat the patient complaining of symptoms similar to those that can be caused by mercury, a growing number of physicians, particularly those in alternative medicine fields, reach a conclusion to “treat” the body of the mercury, believed to be the cause of the symptoms. And although the use of chelation is increasing, controlled studies showing that this procedure actually improves outcome are lacking. If chelation therapy is considered to be indicated, the attending physician should communicate the risks of chelation to the patient before beginning treatment with metal-chelating drugs.

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Keywords: Metallic mercury; Mercury poisoning; Chelation

INTRODUCTION

Mercury is a naturally occurring constituent of the Earth's crust. In its elemental (metallic) form, mercury is the only metal that exists in a liquid state at room temperature. Mercury readily volatilizes at standard temperature (0 °C) and pressure (1 atm), and its presence in open containers can result in biologically significant air concentrations in unventilated or poorly ventilated spaces. Elemental mercury vapors are virtually odorless and very toxic. In recent years, elemental mercury has proven to be a potential source of toxicosis in children through either unintentional exposure or

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1: J Dent Res. 2000 Mar;79(3):668-74.

Printed Articles, Links

Diagnostic value of a chelating agent in patients with symptoms allegedly caused by amalgam fillings.

Yamnes JS, Eide R, Jorann B, Hol PJ, Gjerdet NR.

University of Bergen, Department of Odontology-Dental Biomaterials, Norway. jan.yamnes@odont.uib.no

The chelating agent 2,3-dimercaptopropionate-1-sulfonate (DMPS) has been used in a mercury mobilization test for diagnosis of illnesses allegedly associated with the presence of amalgam restorations. DMPS is an accepted antidote to heavy metal poisoning. The aim of the present study was to evaluate the diagnostic value of DMPS in patients with symptoms self-related to their amalgam fillings. The subjects consisted of four groups: 19 healthy controls without amalgam experience; 21 healthy controls with amalgam fillings; 20 patients who claimed symptoms of “mercury poisoning” from dental amalgam; and 20 patients who had amalgam fillings removed because of such symptoms. DMPS (2 mg/kg body weight) was injected intravenously, and urine was collected prior to the injection, 30 and 120 min after the injection, and throughout the next 22 hrs. The samples were analyzed for total mercury by cold vapor atomic absorption spectrophotometry. The total median amounts of mercury excreted over 24 hrs for those with complaints allegedly associated with amalgam and for the healthy controls with amalgam fillings were similar. Persons with amalgam fillings excreted about three times more mercury than those without. The controls, who had never had amalgam fillings, and the subjects who had had their fillings removed excreted median amounts of 8.5 microg and 7.2 microg mercury, respectively. The present DMPS challenge test did not differentiate between patients with or those without complaints self-related to their amalgam fillings but did confirm the higher mercury values in patients with dental amalgam.

Publication Types:
• Clinical Trial
• Controlled Clinical Trial

PMID: 10765962 [PubMed - indexed for MEDLINE]

Is DMSA/DMPS a valid tool for
treatment
of mercury body burden?

243

Yes!!

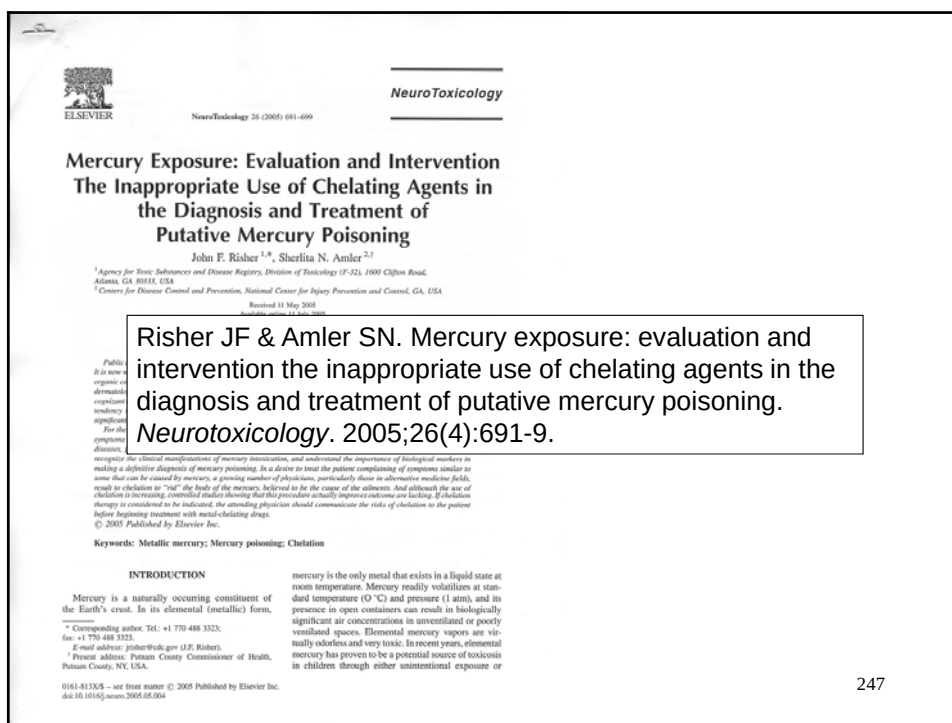
244

Is DMSA/DMPS a valid tool for
treatment
of mercury related symptoms?

245

According to much research,
No!!

246



- “...while the use of chelation is increasing for known or suspected heavy metal exposure, there is a paucity of controlled studies showing that this procedure actually improves the long-term outcome of the patient. In fact, a number of studies found no clear clinical benefit from DMSA treatment of humans documented to have been poisoned, or suspected to have been poisoned, by elemental mercury vapor.”

- “The use of chelating agents is even more questionable in cases where symptoms and/or clinical signs of severe mercury intoxication are absent and where urine and/or blood levels are within the normal background range. In addition to being unnecessary and financially burdensome, inappropriate use of chelators may present untoward danger to the patient and may also bind other divalent mineral cations essential for normal physiologic function.”

249

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1: J Dent Res. 1994 Mar;73(3):620-6.

DMSA administration to patients with alleged mercury poisoning from dental amalgams: a placebo-controlled study.

Sandborgh Englund G, Dahleqvist R, Lindelef B, Soderman E, Jonzon S, Vesterberg O, Larsson KS.

Department of Odontological Toxicology, Karolinska Institute, Huddinge, Sweden.

The present investigation was performed to determine the effect of 14-day oral administration of meso-2,3-dimercaptosuccinic acid (DMSA) on the urinary mercury excretion and the potential reduction of blood and plasma mercury concentrations, and also to relate these effects to possible decrease of symptoms, allegedly associated with amalgam fillings. Twenty subjects, relating their symptoms to mercury from amalgam fillings, received 20 mg/kg DMSA or placebo for 14 days. Their symptoms and mood states were recorded during the study and at a check-up 3 months later. Interpretation was based on intra-individual differences. DMSA-treatment resulted in an average increase in urinary mercury excretion by 65% and a decrease in blood mercury levels of 0.04 microgram/L/day. At the check-up after 3 months, urinary mercury excretion had returned to the pre-treatment level. No treatment effect of DMSA was apparent on subjective symptoms and mood state. One statistically significant treatment effect was noted: a decrease in fatigue-inertia in the DMSA-group, but there was no demonstrable correlation with increased urinary excretion or decreased blood concentration of mercury. Three subjects showed hypersensitive reactions, probably DMSA-specific, at the end of the treatment period. This placebo-controlled study provides no scientific support for diagnostic or therapeutic administration of DMSA for symptoms allegedly associated with chronic mercury exposure from dental amalgam fillings.

PMID: 8163732 [PubMed - indexed for MEDLINE]

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AR: 1 Review: 0

4: Eur J Oral Sci. 2000 Dec;108(6):511-22.

Biological mercury measurements before and after administration of a chelator (DMSA) and subjective symptoms allegedly due to amalgam.

Schou A, Exterkale R, ten Cate JM.

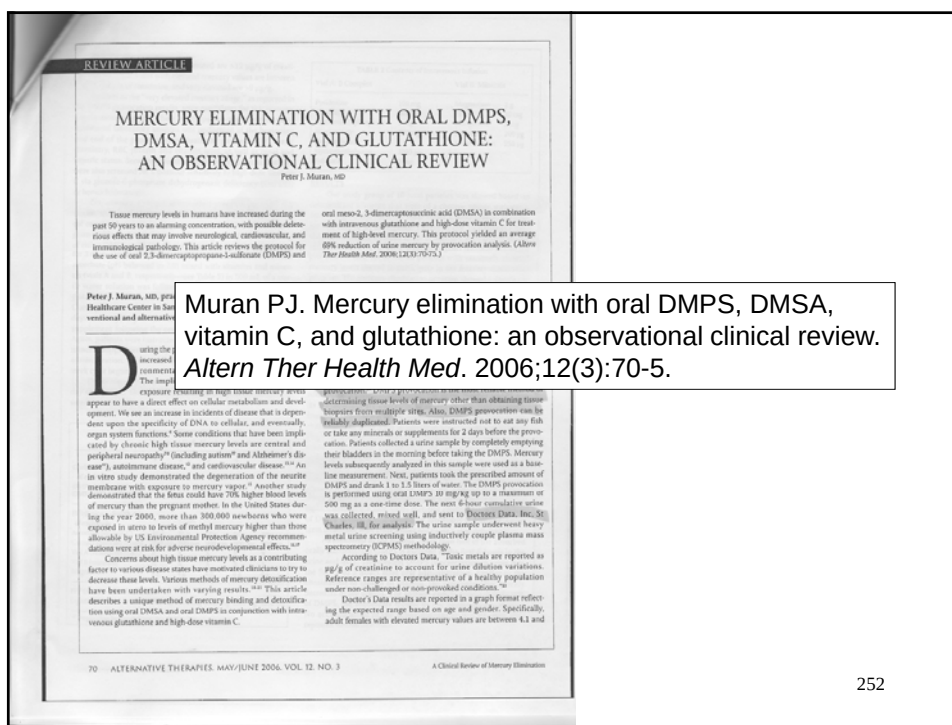
Department of Cariology Endodontology Pedodontiology, Academic Centre of Dentistry, Amsterdam, The Netherlands. A.Schou@acta.nl

The aim of the study was to explore multivariately the relationship between subjective symptoms allegedly due to amalgam and mercury measurements before and after administration of a chelator. Of 120 participants, the mercury concentrations in urine (U-Hg) and plasma (P-Hg) before and after a chelating agent or placebo were determined as were the numbers of fillings and symptoms allegedly due to subjective symptoms. The dental status was charted. Blood was analysed on 13 parameters. The analysis revealed neither the parameters in blood nor the subjective symptoms to be associated with a dimension determined by "mercury indicators". The final analysis was therefore performed with "number of subjective symptoms" and enabled to distinguish two subgroups. One subgroup was characterised by > 2 subjective "symptoms", highest scores for U-Hg, P-Hg and filled surfaces, and chewing gum for > 1 h a day. The other subgroup comprised the subjects with few filled surfaces and low U-Hg and P-Hg, but was not characterised by "no subjective symptoms". The chelator was considered neither to invalidate nor to improve these findings and was concluded not to be helpful in diagnosing "symptoms". The chelator caused side effects in 42% of the subjects and the placebo in 27%. A relationship between amalgam fillings and subjective symptoms could not be shown. Therefore, the mere fact of knowing to have amalgam fillings was assumed to be the reason why subjective symptoms were attributed to amalgam and side effects were ascribed to the treatment.

PMID: 11157926 [PubMed - indexed for MEDLINE]

However, what happens when DMSA/DMPS is combined with nutritional therapies?

251



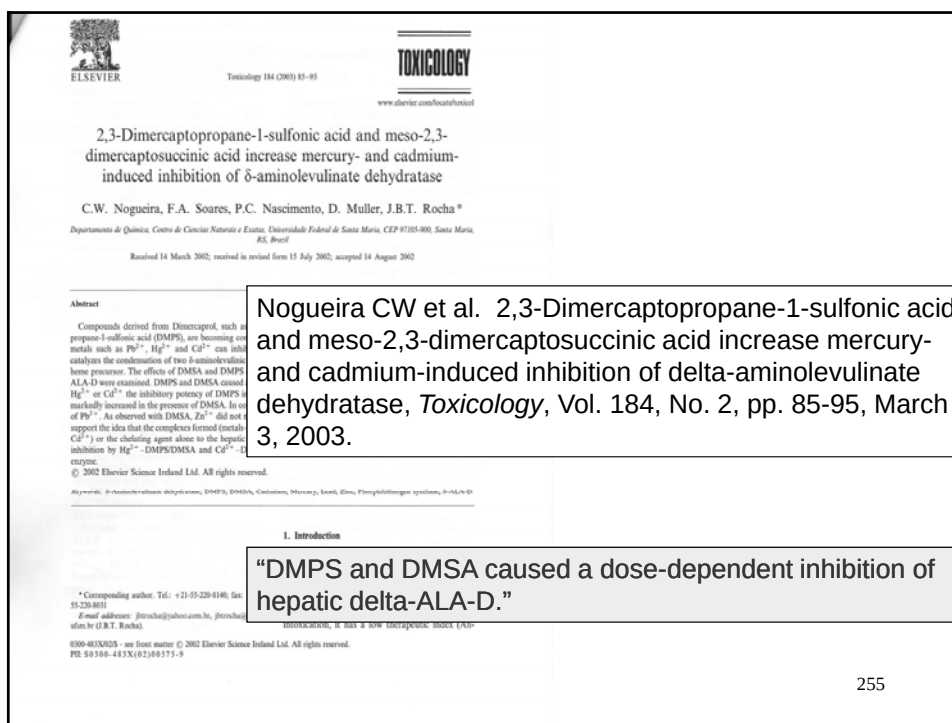
252

- **“All patients who experienced a reduction in mercury levels reported improved overall health, increased energy, and decreased symptoms. Chronic candidiasis...resolved as a possible result of the mercury extraction and other appropriate treatment protocols. Symptoms of depression and allergies were markedly reduced.”**

253

Could adverse effects be the reason for all of the conflicting findings?

254



- "Delta-aminolevulinate dehydratase (delta-ALA-D) is a sulfhydryl-containing enzyme that catalyzes the asymmetric condensation of two delta-aminolevulinic acids molecules yielding porphobilinogen, a heme precursor."
- "Consequently, delta-ALA-D inhibition can impair heme biosynthesis and can result in accumulation of delta-ALA, which may disturb aerobic metabolism and also have some pro-oxidant activity."

Which parts of the body does DMSA/DMPS favor concerning mercury removal?

257

Chem. Res. Toxicol. 2004, 17, 999–1006 999

Articles

Mercury Binding to the Chelation Therapy Agents DMSA and DMPS and the Rational Design of Custom Chelators for Mercury

Graham N. George,^{*,1} Roger C. Prince,¹ Jürgen Gailer,³ Gavin A. Buttigieg,² M. Donner Denton,² Hugh H. Harris,⁴ and Ingrid J. Pickering¹

¹Department of Geological Sciences, University of Saskatchewan, Saskatoon, Saskatchewan S7N 3J2, Canada, ²ExpoMetal Research and Engineering Company, Annapolis, New Jersey 08801, ³Bodringier Ingelheim Austria GmbH, Dr. Bodringier Gasse 5-11, 1120 Vienna, Austria, ⁴Department of Chemistry, The University of Arizona, Tucson, Arizona 85721, and ⁵School of Chemistry, University of Sydney, Sydney, NSW 2006, Australia

Received March 26, 2004

Clinical chelation therapy of mercury poisoning generally uses one or both of two drugs—meso-dimercaptosuccinic acid (DMSA) and dimercaptopropanesulfonic acid (DMPS), commercially sold as Chemet and Dimaval, respectively. We have used a combination of mercury

George GN et al. Mercury binding to the chelation therapy agents DMSA and DMPS and the rational design of custom chelators for mercury. *Chem Res Toxicol.* 2004;17(8):999-1006.

lems (i.e., myocardial infarction (8), and a possible involvement in the development of some kinds of autism (5, 6). The treatment of mercury poisoning in humans generally involves the use of chelation therapy (7, 8). A chelator is a molecule that binds a metal or metalloid ion by at least two functional groups to form a stable ring complex known as a chelate. Chelation therapy is the clinical treatment by which heavy metals are removed from the body through binding to a chelation therapeutic drug to form a chelate, which is in turn excreted, typically excreted in urine. Dimercaptosuccinic acid (DMSA) and dimercaptopropanesulfonic acid (DMPS) are commercially sold as Chemet and Dimaval, respectively, and have both been widely used in the chelation therapy of mercury and heavy metals (7–13). These chelation agents are vicinally disubstituted on the same methylene (in the case of DMSA) or 2,3-dimercaptopropionate (Figure 1b) which was developed as an antidote for the arsenical war gas Lewisite (dimercaptopropionate (14)). (14b-DMSA) suffers from the disadvantages of low water

Figure 1. Structures of (a) BAL, (b) DMPS, (c) meso-DMSA, (d) rac-DMSA, (e) BAL⁺ chelate with BAL, and (f) the structure previously proposed for DMSA chelate with Hg²⁺.

solubility and a racemic isomer, and so, it was modified to produce DMPS (Figure 1b), which is water soluble and nearly odorless. DMSA (Figure 1c) is racemized later and has similar properties (i.e., excellent water solubility, and no odor) with lower toxicity (20–24). The clinical use of DMSA differs from DMPS (and BAL) in that it is usually administered by mouth, whereas the others are generally given intravenously.

Essential amino acids such as L-cysteine bind by interacting with essential thiols, and in particular the distal thiol acid in enzymes such as pyruvate dehydrogenase (15). DMPS and DMSA are ideally suited for chelation therapy

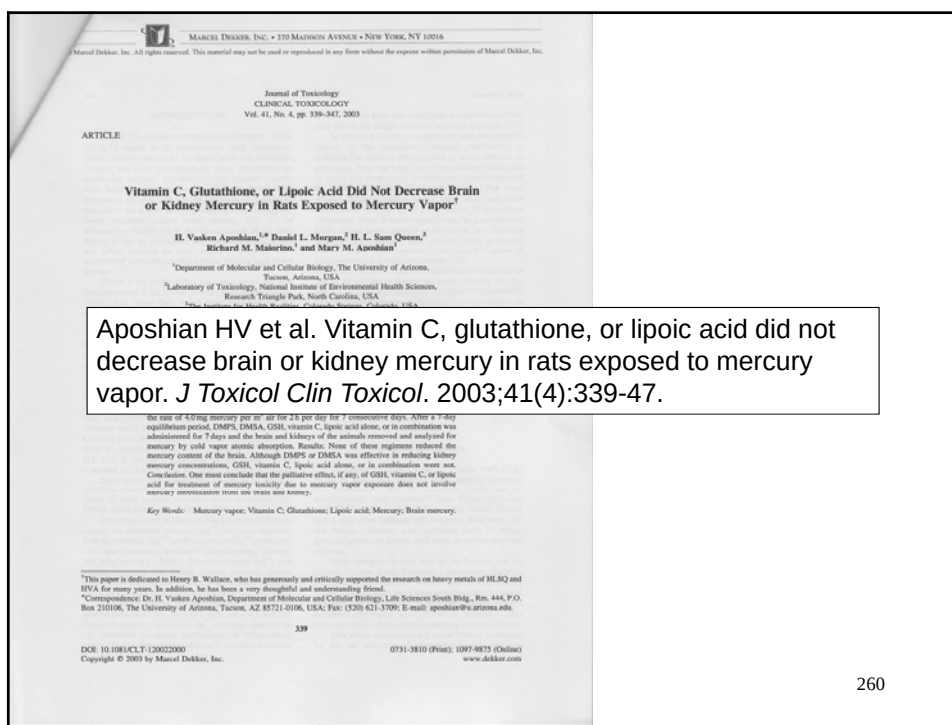
To whom correspondence should be addressed. Tel.: 306-966-8722. Fax: 306-966-8039. E-mail: g.greene@usask.ca.
¹University of Saskatchewan
²ExpoMetal Research and Engineering Company
³Bodringier Ingelheim Austria GmbH
⁴The University of Arizona
⁵University of Sydney

10.1021/t040004a CCC: \$27.50 © 2004 American Chemical Society
Published on Web 07/22/2004

258

- “...mercury in certain tissues (e.g., the brain) is known to be essentially impossible to remove using DMSA and DMPS [although this may be due to a lack of access to the brain, rather than the effectiveness (or lack of it) of DMSA and DMPS].”

259



260

- **“The purpose of this study was to test the hypothesis that DMPS, DMSA, glutathione, vitamin C, or lipoic acid, alone or in combination, would decrease brain mercury in rats exposed to elemental mercury vapor. Our results clearly indicated that none of these agents did so.”**

261

*Fact or Fallacy:
Before chelating with DMSA
or DMPS all amalgams should
be removed. If this is not
done, these compounds will
leach mercury from
amalgams, which will, in turn,
be reabsorbed.*

262

- **“Ideally intravenous DMPS should never be used in patients who still have amalgam fillings in place...DMPS appears in the saliva and may mobilize significant amounts of mercury from the surface of the fillings and precipitate seizures, cardiac arrhythmias, or severe fatigue.”**

Mercola J & Klinghardt D. Mercury toxicity and systemic elimination agents. *J Nutr Environ Med.* 2001;11(1):53-62

- **“...investigators have done this diagnostically, as a one-time dose, without complications.”**

263

- **“However, orally administered chelating agents forming hydrophilic metal complexes may efficiently reduce intestinal metal uptake and local toxicity at early times after oral intoxication.”**

Andersen O & Aaseth J. Molecular mechanisms of in vivo metal chelation: Implications for clinical treatment of metal intoxications. *Environ Health Perspectives.* 2002;110(Suppl 5):887-890.

264

- “Also orally administered dimercaptosuccinic acid (DMSA) reduced the intestinal uptake and toxicity of oral Cd^{2+} . Chelation of Ni^{2+} with EDTA and Hg^{2+} with DMSA or dimercaptopropionic sulfonate (DMPS) reduced intestinal uptake. Accordingly, oral administration of chelating agents may in some cases offer both reduction of local toxicity and prevention of intestinal metal uptake.” (Andersen & Aaseth)

265

*Fact or Fallacy:
DMPS and DMSA cause
increased mercury uptake into
the brain*

266

- **“DMPS and DMSA do not mobilize heavy metals to the brain.”**

Nogueira CW et al. 2,3-dimercaptopropane-1-sulfonic acid and meso-2,3-dimercaptosuccinic acid increase mercury- and cadmium-induced inhibition of delta-aminolevulinate dehydratase. *Toxicology*. 2003;184(2-3):85-95.

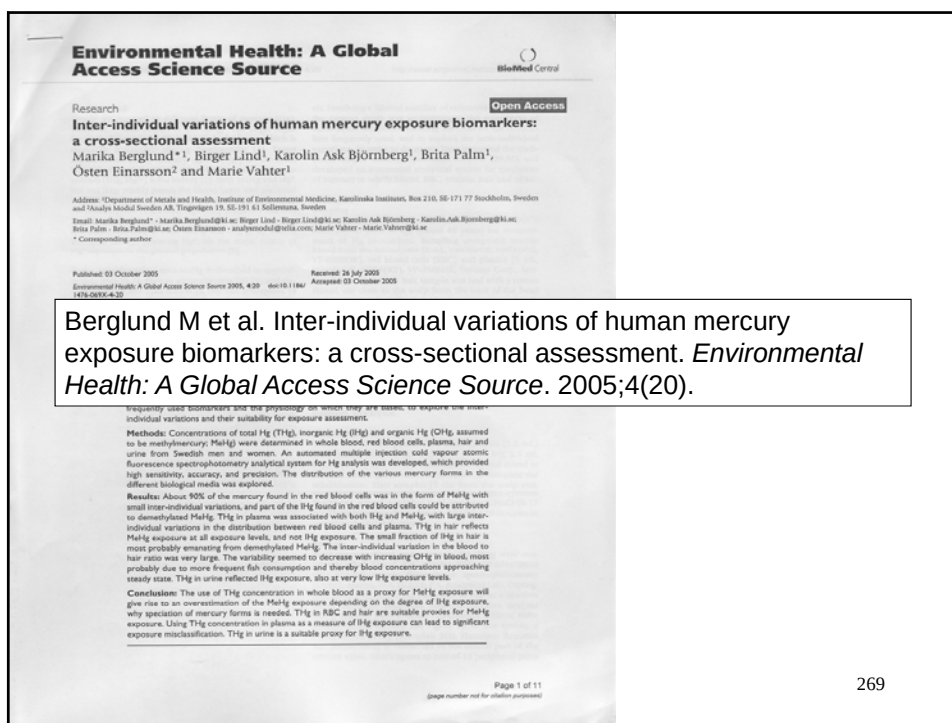
- **“DMPS does not redistribute arsenic, lead, or inorganic mercury to the brain...”**
(Anderson & Aaseth)

- **“...DMSA chelation decreases the brain deposition of lead and methylmercury.”**
(Anderson & Aaseth)

267

*Other diagnostic modalities:
RBCs, Plasma, Hair, Urine*

268



Whole Blood

- “In the blood, more than 90% of MeHg is bound to haemoglobin in the red blood cells (RBC), while IHg is more evenly distributed between RBC and plasma. Therefore, total Hg in RBC is also sometimes used as a proxy measure of MeHg exposure and total Hg in plasma is used as a proxy measure of IHg exposure (Hg²⁺ and Hg⁰).”

Plasma

- **“Using total mercury concentrations in plasma as a measure of inorganic mercury exposure can lead to significant exposure misclassifications.”**

271

RBCs

- **“It can be concluded that IHg in RBC is partly emanating from inorganic Hg exposure, mainly Hg⁰ via amalgam, and partly from MeHg exposure via fish, which has demethylated to IHg in the body...”**
- **“”Most of the Hg found in RBC is in the form of MeHg with small inter-individual variations.”**

272

Hair

- **“Our data strongly indicates that the small fraction of IHg in hair (about 9%), with relatively small inter-individual variations (CV about 15%) is a result of MeHg exposure and demethylation of MeHg in blood or hair follicles (and in the analysis), rather than a result of IHg exposure.”**

273

Hair

- **“IHg in hair was positively correlated with fish intake, but not with dental amalgam fillings. It was also highly correlated with Hg⁰ in blood, RBC, and plasma.”**
- **“...it should be borne in mind that artificial waving and other hair treatments may reduce Hg concentrations within the hair strand.”**

274

Hair

- **“The concentrations of total Hg in hair (H-THg) is often used as a measure of MeHg exposure, assuming that > 80% of Hg in hair is in the form of MeHg. Mercury is incorporated in hair during formation in the hair follicle, and mercury in hair is associated with the concentration of MeHg in blood.”**

275

Mercury vapor - Use of hair for diagnosis

“Elemental mercury (from amalgams) does not show up well in the hair. In fact, other hair mercury studies have shown hair mercury levels are 79-94 percent methylmercury, leaving only 6-21 percent as elemental mercury. With such a low affinity of elemental mercury for the hair, one may have a significant amount of elemental mercury and exhibit no presence of such on hair test.”

Crinnion, W.J., *Environmental medicine, part three: Long-term effects of chronic low-dose mercury exposure*. Alt Med Rev, 2000. 5(3): p. 209-233.

276

Mercury vapor - Use of hair for diagnosis

- Individual cases have been published showing urinary mercury excretion to be 23-60 µg/Hg/day (25-54 µg/g creatinine) indicating a daily intake as high as 100 µg. In these individuals, bruxism and gum chewing were noted as probable causes of the high mercury output, which fell back to normal levels with amalgam removal. Higher levels of mercury release from dental amalgams have also been found with toothbrushing and after consuming hot drinks.”

Crinnion, W.J.

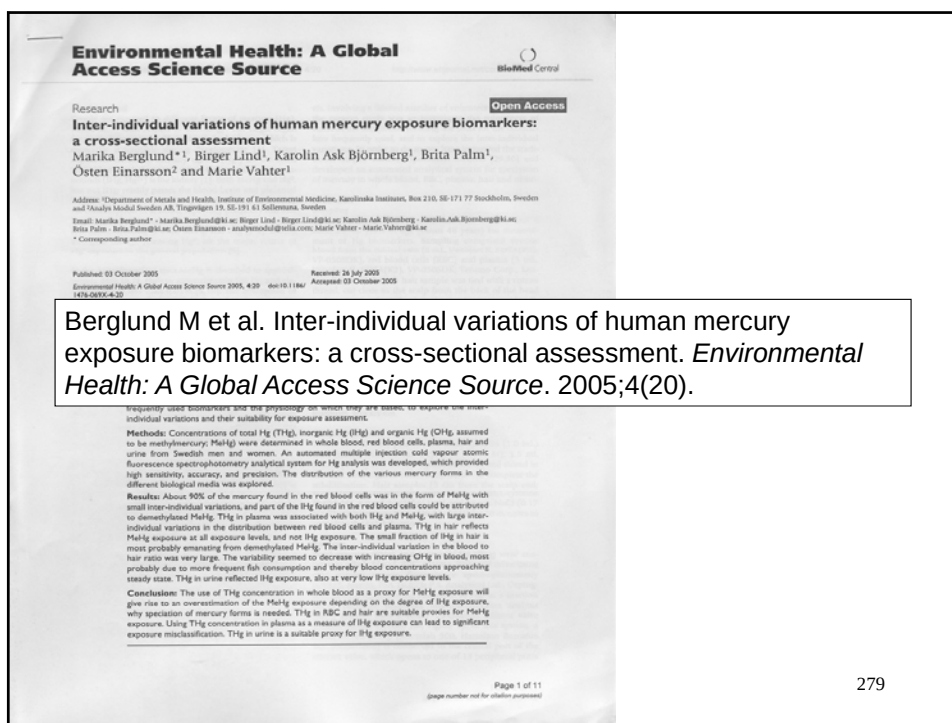
277

Mercury vapor from amalgams

- “Elemental mercury from amalgams shows up best in the plasma and urine.”

Crinnion, W.J., *Environmental medicine, part three: Long-term effects of chronic low-dose mercury exposure*. Alt Med Rev, 2000. 5(3): p. 209-233.

278



Urine

- “The total Hg concentration in urine is used as a measure of IHg exposure as MeHg is excreted primarily via the bile (as glutathione complex) and faeces (about 90%: as IHg) and only to a limited extent (about 10%) in urine (as IHg).”

Urine

- **“Our data shows that IHg in urine reflects the IHg exposure as nearly all Hg in urine (>98%) was IHg and as IHg in urine did not reflect fish consumption or the OHg concentration in various media.”**

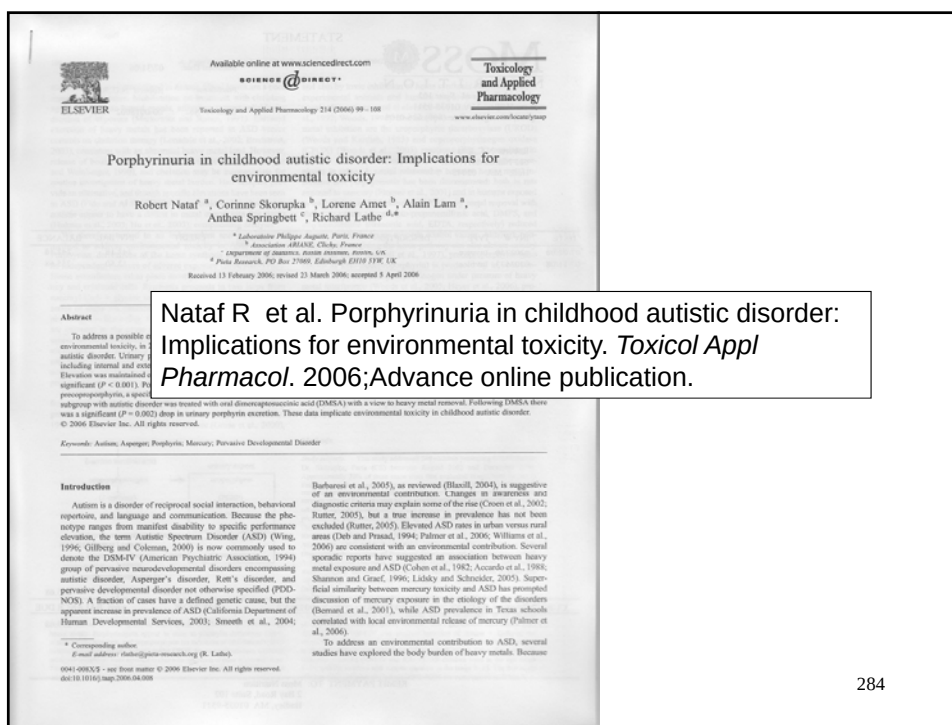
281

Porphyrin testing

282

Porphyrin testing is the best way via laboratory testing to determine if the mercury body burden is contributing to my patient's chief complaint

283



284

- **“Porphyrins, derivatives of the heme synthesis pathway, afford an independent measure of adverse exposure. Heme manufacture takes place most prominently in the liver, kidney and erythroid cells.”**
- **“Synthesis proceeds in two steps from succinyl-CoA + glycine to uroporphyrinogen and in a further series of steps via pentacarboxyporphyrinogen and coproporphyrinogen to heme.”**

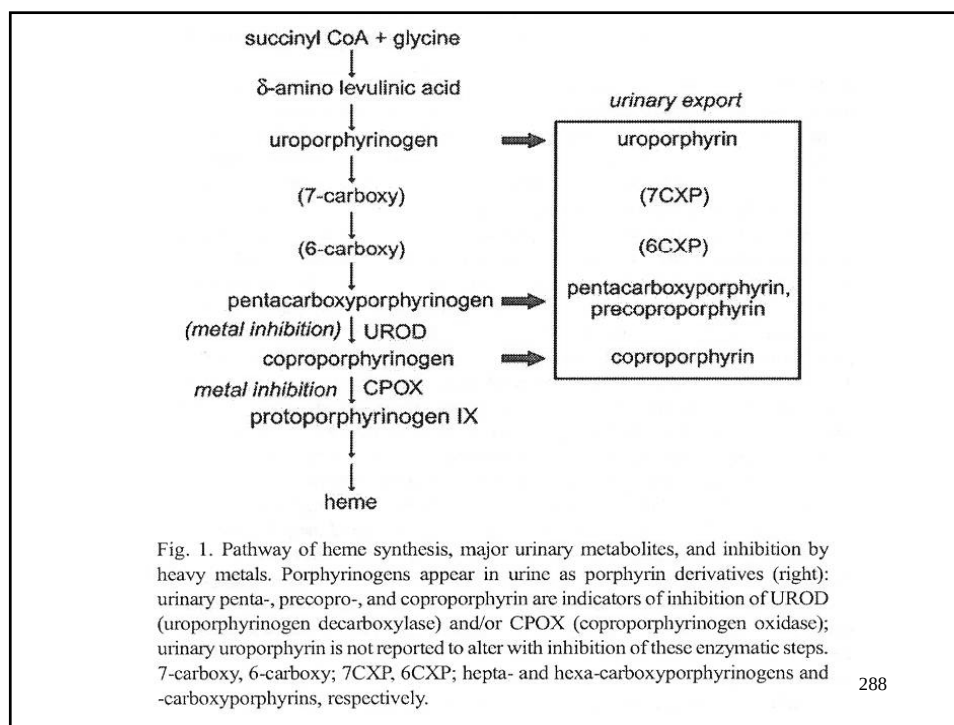
285

- **“Excess porphyrinogen metabolites are excreted in the urine as oxidized porphyrins, particularly uroporphyrin and corprotoporphyrin, reflecting the most abundant molecules in the rat kidney cortex.”**
- **“Excess urinary porphyrin excretion or porphyrinuria results from blockade of key enzymatic steps in conditions including genetic deficiencies in heme manufacture enzymes, hepatic, renal and erythroid disease and also by toxic inhibition of heme synthesis enzymes.”**

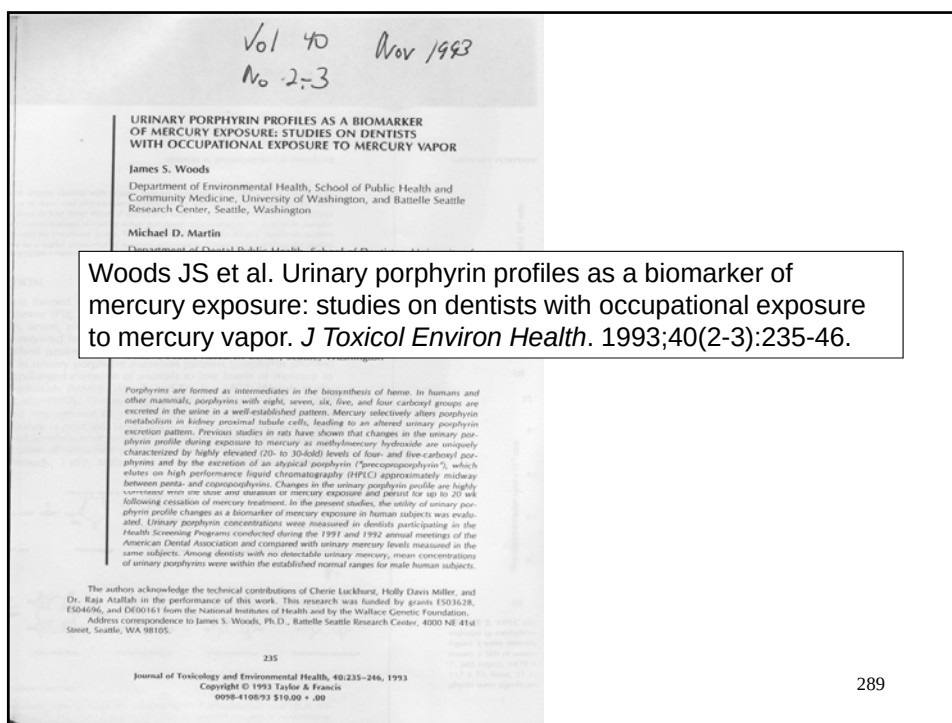
286

“In both experimental animals and humans exposed to heavy metals, porphyrins are exported at elevated levels into urine.”

287



288



- **“In terms of specificity, the unique change in the porphyrin excretion pattern, characterized by elevated levels of five- and four-carboxyl porphyrins, as well as by the expression of the atypical porphyrin, precoproporphyrin, is, to our knowledge, unique to mercury exposure. This pattern is different from that which characterizes any of the known forms of inherited porphyria, and also differs distinctly from those elicited by exposure to other metals.”**

- **“The biochemical etiology of changes in five- and four-carboxyl porphyrins observed during mercury exposure has previously been shown to occur as a result of mercuric ion (Hg^{2+}) (or $\text{CH}_3\text{Hg}^{+-}$) directed impairment of the specific heme pathway enzymes, uroporphyrinogen decarboxylase and coproporphyrinogen oxidase...”**

291

“Changes in urinary porphyrin concentrations...vary directly in proportion to the dose of mercury administered.”

292

- **“Since the change in the urinary porphyrin excretion pattern is unique to mercury exposure and occurs in subtoxic, as well as potentially toxic mercury levels, *the urinary porphyrin profile method could be employed in the clinical setting to indicate whether a biological response to mercury has occurred, or to monitor the effectiveness of treatment regimens for facilitating mercury clearance.*”**

293

*Porphyrin testing as a marker
for DMSA chelation*

294

The screenshot shows a PubMed search result for the article "Disappearance of heme metabolites following chelation therapy with meso 2,3-dimercaptosuccinic acid (DMSA)." by Tutunji MF, al-Mahasneh QM. The article is from the *J Toxicol Clin Toxicol.* 1994;32(3):267-76. The abstract mentions a lead poisoned adult with a blood lead level of 384 micrograms/dL. The page number 295 is visible in the bottom right corner of the screenshot.

Case report:
***Lead toxicity with elevations of coproporphyrin
& pentacarboxyporphyrin***

- **“Both compounds were restored to normal levels following two courses of meso 2,3-dimercaptosuccinic acid...”**
- **“Blood lead decreased from 384 to 24 micrograms/dL, urine lead from 1286 to 188 micrograms/L and urine coproporphyrin III from 5712 to 25 micrograms/L.”**

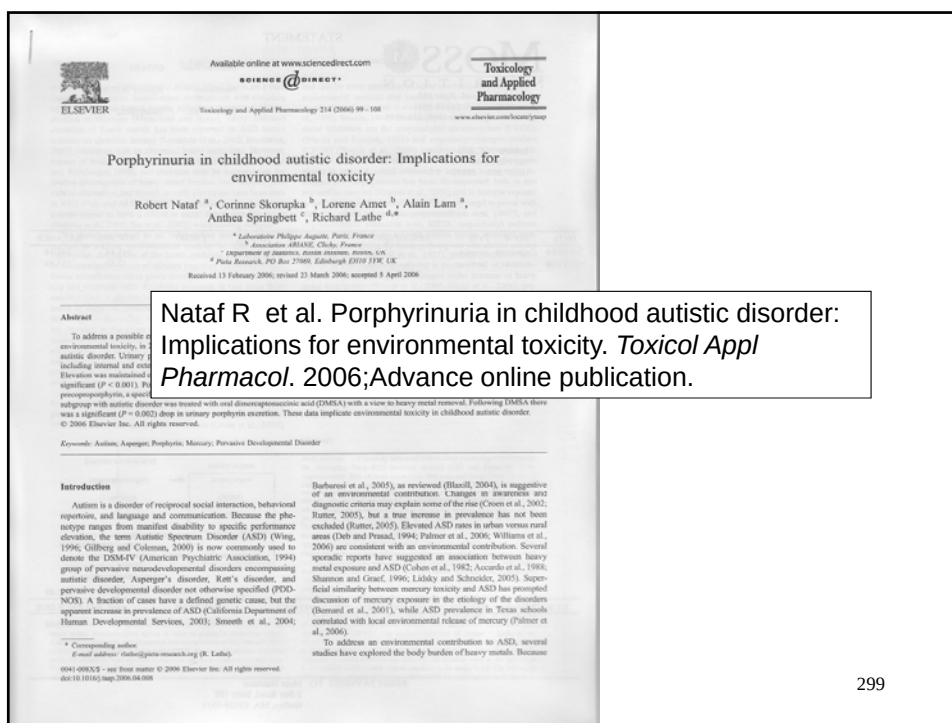
Brady chelation protocol

- DMSA: 500 mg M-W-F x 3 weeks, 1 wk wash-out, repeat 3-5 cycles.
- Wait one month and repeat entire cycle as needed and conduct serial laboratory analysis for follow-up assessment.

297

Porphyrin testing and autism

298



- **“Excess urinary porphyrin, in addition to being a marker of toxicity, could play a contributory role in the behavioral manifestation of autistic disorder. Porphyria is accompanied by elevated blood levels both of porphyrins and the precursor molecule 5-aminolevulinic acid (δ ALA).”**

- **“These metabolites target benzodiazepine receptors in the brain and have been associated with neurologic disturbances, epilepsy and autism. Excess of these metabolites could contribute to the brain and behavior disturbances in some subjects with autism.”**

301

Some parting thoughts

302

