

Mercury toxicity: Genetic susceptibility and synergistic effects

Boyd E. Haley, PhD

Professor and Chair
Department of Chemistry
University of Kentucky

Abstract

Mercury toxicity and intoxication (poisoning) are realities that every American needs to face. Both the Environmental Protection Agency and National Academy of Science state that between 8 to 10% of American women have mercury levels that would render any child they gave birth to neurological disorders. One of six children in the USA have a neurodevelopmental disorder according to the Centers for Disease Control and Prevention. Yet our dentistry and medicine continue to expose all patients to mercury. This article discusses the obvious sources of mercury exposures that can be easily prevented. It also points out that genetic susceptibility and exposures to other materials that synergistically enhance mercury and ethylmercury toxicity need to be evaluated, and that by their existence prevent the actual determination of a “safe level” of mercury exposure for all. The mercury sources we consider are from dentistry and from drugs, mainly vaccines, that, in today’s world are not only unnecessary sources, but also sources that are being increasingly recognized as being significantly deleterious to the health of many.
© Copyright 2005, Pearlblossom Private School, Inc.—Publishing Division.

Keywords: mercury toxicity, ethylmercury toxicity, mercury exposure, amalgams, antibiotic susceptibility to neurotoxicity, hormone susceptibility to neurotoxicity

1. Introduction

Mercury toxicity and intoxication (poisoning) are realities that every American needs to face. This article discusses mercury intoxication and several normally appearing factors that increase the susceptibility to mercury toxicity. The sources considered are dentistry and mercury from drugs, mainly vaccines, that, in today’s world are not only unnecessary sources, but also sources that are being increasingly recognized as being significantly deleterious to the health of many who are so exposed.

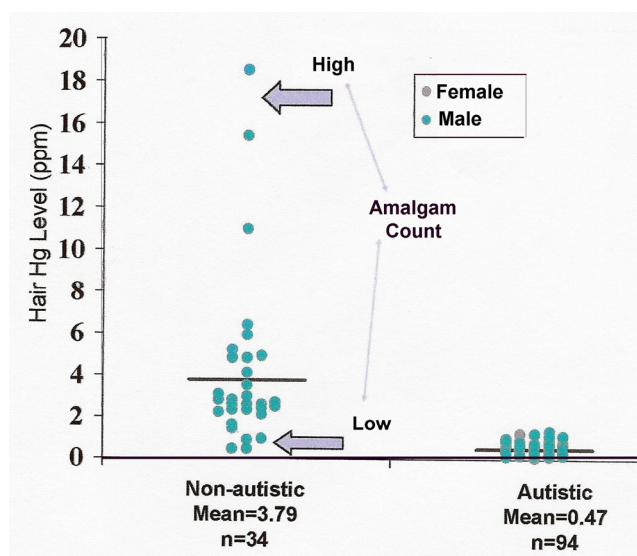
2. Mercury from dentistry

Let us begin by discussing mercury exposure from dental amalgams. Figure 1 is a segment from a movie showing the emission of mercury vapors from a 50 year old amalgam; it is still releasing mercury at the temperature of a cup of coffee. The point of this figure is to provide visual evidence that mercury is indeed released by dental amalgams. It has been reported in a World Health Organization review of mercury that 80% of the mercury vapors inhaled is retained by the human body. This is why dental amalgams have been found to be the major contributor to human body mercury burden. The visualization of mercury emitting from amalgams presents irrefutable evidence that spokespersons for the American Dental Association (ADA) are exceptionally deceptive when they state there is no danger of mercury exposure from dental amalgams.



Figure 1. Visualization of mercury emitting from a dental amalgam. The filling is 50 years old. The tooth was extracted 15 years ago. (Credits: www.uninformedcosent.com)

Figure 2. Birth-hair mercury of autistic vs. control groups. (Data from A. Holmes, M. Blaxill, and B. Haley, *Int. J. Toxicology* v22, p. 1-9, 2003)



This data in Figure 2 show that normal children have birth hair levels of mercury that correlate with the number of amalgam fillings in the birth mother; whereas, in sharp contrast, the autistic children have exceptionally low levels of birth hair mercury, no matter what the number of amalgam fillings are found in the birth mother. This data strongly implies that autistic children represent a subset of the population that does not effectively excrete mercury from their cells.

Mercury vapor, when it enters the body spends a very short time in the blood. Mercury vapor (Hg^0) is a hydrophobic entity and is rapidly absorbed through cell membranes into cells where certain enzymes, such as catalase, rapidly converts it to Hg^{2+} , the reactive and toxic form of mercury called inorganic mercury. It would be nearly impossible for the body to substantially excrete either Hg^0 or Hg^{2+} from the body in their original

form. To rid the body of Hg^{2+} it must first be taken intracellular where it can be complexed with glutathione. It is primarily the mercury-glutathione complex that is excreted from the cells into the blood to be cleared by the biliary transport system in the liver. Therefore, it is primarily the mercury-glutathione complex that is measured in the blood, urine, feces and hair as elevated after mercury exposures. It is not the original Hg^0 as it would prefer partitioning into the more hydrophobic cells of the body.

Therefore, the lack of mercury in the birth hair of autistics strongly implies that they cannot effectively excrete mercury most likely by not being able to effectively couple Hg^{2+} with glutathione. Research by Dr. Jill James of the University of Arkansas has partially explained this phenomenon by demonstrating that autistics are quite low in glutathione, the sequester of mercury that exists intracellular and used by the body in the normal excretion process [1].

Figure 3 demonstrates that considering the mercury exposures from dietary fish, vaccines and amalgams versus the predicted birth hair mercury levels that again the normal children have the predicted birth hair mercury levels whereas the autistic children show no significant increase. Considering the data from birth mothers with 8 to 15 amalgams the mercury hair ratio was 12 to 1 in normals versus autistics. There can be little doubt that in this cohort group the autistics do not biochemically excrete mercury in a similar fashion as do normal children

Also, as expected, amalgams are the major contributor to mercury body burden, not the mother's fish diet. In considering different exposures as contributing to mercury body burden one should consider the reactive potential of the mercury. Mercury in fish has already reacted with proteins and other protective molecules or atoms in fish (e.g., glutathione, selenium, and other proteins); this is why the fish does not die of mercury toxicity. This bound mercury, or methylmercury, is not as toxic as an equal amount of the pure equivalent. Therefore, while there may be an equal exposure to mercury from a tuna fish sandwich as from an amalgam or vaccine, the mercury from the amalgam or vaccine has much more toxic potential.

Figure 3. Actual versus predicted birth hair mercury levels. (Data from A. Holmes, M. Blaxill, and B. Haley, Int. J. Toxicology, v22, p. 1-9, 2003)

$$\text{Hair Hg level} = (5.60) + 0.04(\text{amalgam volume}) + 1.15(\text{fish consumption}) + 0.03(\text{vaccine}) \quad [R^2 = 0.79]$$

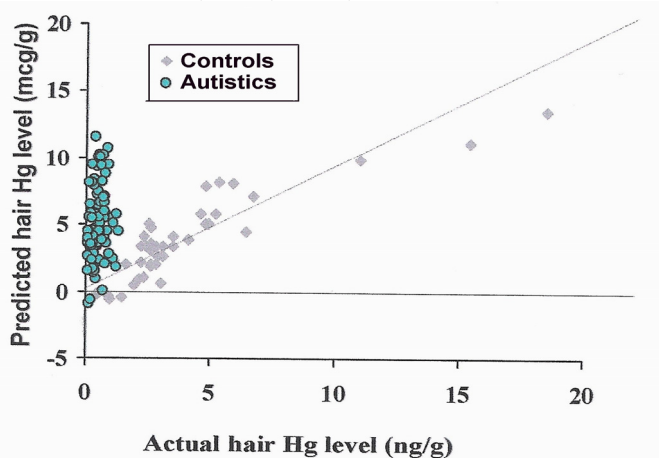


Figure 4. Mercury birth hair levels vs. amalgam in autistics and control groups (Data from A. Holmes, M. Blaxill, and B. Haley, Int. J. Toxicology, v22, p. 1-9, 2003)

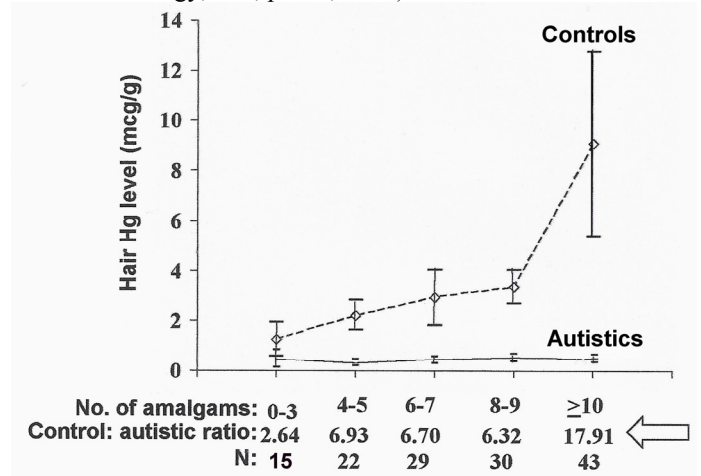
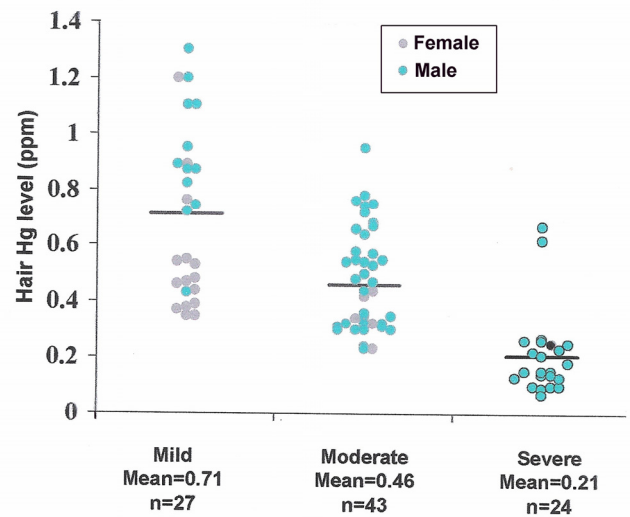


Figure 4 shows that, as expected, the birth hair mercury levels in normal children are determined more by their birth mother's number of amalgams than by any other exposure, such as fish in the mother's diet. In contrast, autistic children born of mothers with greater than 10 amalgam fillings still do not have significant levels of mercury in their birth hair. This confirms that autistic children do not handle mercury biochemically like normal children. The most likely explanation is they are poor excretors. Work from Dr. Jeff Bradstreet [2] and others have shown that autistics do have higher body burdens of mercury than normals. This supports the hypothesis that autistics are in reality poor mercury excretors who retain mercury and are thusly more severely affected by low dose exposures.

Figure 5. Birth-hair mercury by severity of autism. (Data from A. Holmes, M. Blaxill, and B. Haley, Int. J. Toxicology v22, p 1-9, 2003)



The major observation of this data is that the lower the birth hair mercury level the more likely the severity of the autism. This fits into the hypothesis as follows: the lower the ability to excrete mercury the more mercury that is retained by the cells

of the body and the more toxic the exposure to the infant (Fig. 5).

Another observation is that of comparing boys to girls. Note that the females mostly fall below the average line in each level of severity and that the “severe category” has only one female (Fig. 5). This indicates that a female must be a much poorer mercury excretor than the males to become autistic at that level. Bottom line, it takes more retention of mercury to make a female autistic than it does for a male. We feel the male/female ratio of about four gives us a hint as to the causal element in autism. We also think that the differential effects of estrogen versus testosterone on mercury toxicity to neurons may explain the increased susceptibility of males to autism.

3. Synergistic effects: Thimerosal, aluminum hydroxide and Neomycin

It is well documented in the literature that mercury toxicity is synergistic with other heavy metals such as cadmium and lead. It is also known that certain antibiotics greatly enhance the toxicity of thimerosal in ocular solutions and that antibiotics prevent test animals from effectively excreting mercury. The major known difference between males and females is their hormones. We therefore investigated the possible involvement of aluminum cation (found in vaccines), antibiotics (neomycin) and male versus female (estrogen versus testosterone) on the toxic effects of 50 nanomolar (nM) thimerosal on neurons in culture. Neurons can be cultured for 24 hours without much death (Fig. 6). Fifty nanomolar thimerosal alone (solid circles [●]) will cause the death of about 70% of the neurons within 24 hours. The synergistic effects of aluminum, neomycin and testosterone are shown (Fig. 6) and are as follows:

Aluminum: Aluminum hydroxide alone (solid triangles [▲]) at 500 nM showed no significant death of cells at 6 hours, and only slight toxicity over the 24-hour period. Thimerosal at 50 nM effected only a slight increase in neuron death at 6 hours.

However, in the presence of 50 nM thimerosal plus 500 nM aluminum hydroxide (open triangles [△]), the neuronal death increases to roughly 60%, an amazing increase and clearly demonstrates the synergistic effects of other metals on mercury toxicity and certainly thimerosal toxicity.

Neomycin: At 1.75 mcg neomycin alone (solid squares [■]) did not cause a significant increase in neuronal death after 12 hours. In the presence of 50 nM thimerosal (open squares [□]) the rate of death at same point increased from about 40% to 60%, a 20% increase in rate of death.

4. Hormonal effects: Testosterone and Estrogen

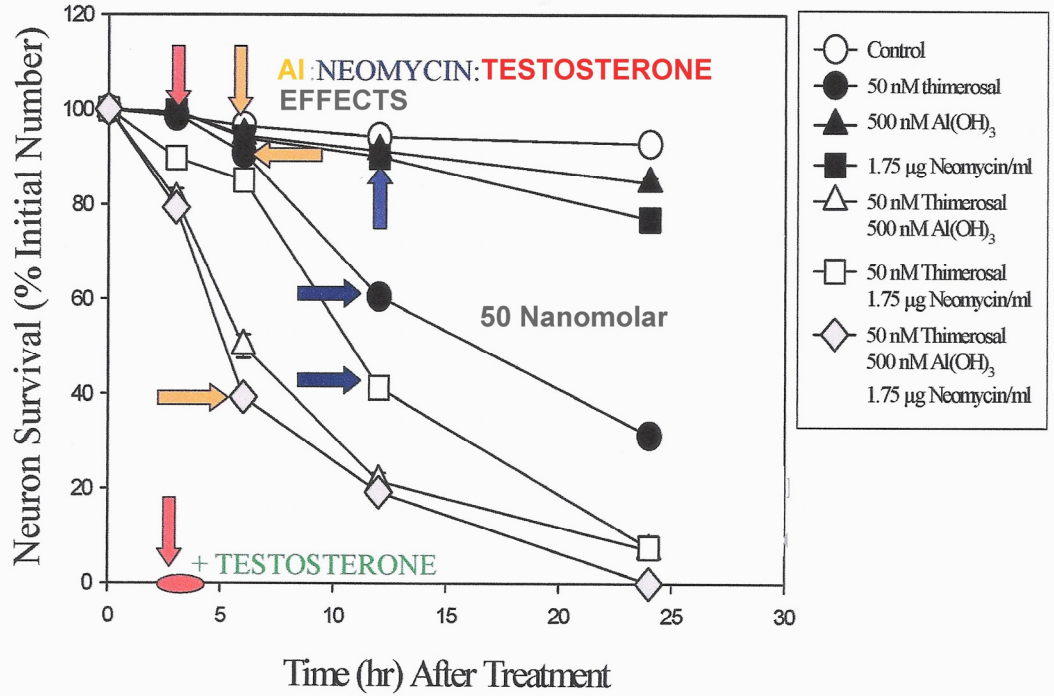
Testosterone and estrogen-like compounds give vastly different results. Using female hormones we found them not toxic to the neurons alone and to be consistently protective against thimerosal toxicity. In fact, at high levels they could afford total protection for 24 hours against neuronal death in this test system (data not plotted). However, testosterone which appeared protective at very low levels (0.01 to 0.1 micromolar), dramatically increased neuron death at higher levels (0.5 to 1.0 micromolar). In fact, 1.0 micromolar levels of testosterone that by itself did not significantly increase neuron death (red flattened oval), within 3 hours when added with 50 nanomolar thimerosal (solid circles) caused 100% neuron death. Fifty nanomolar thimerosal at this time point did not significantly cause any cell death.

These testosterone results, while not conclusive because of the in vitro neuron culture type of testing, clearly demonstrated that male versus female hormones may play a major role in autism risk and may explain the high ratio of boys to girls in autism (4 to 1) and autism related disorders.

5. Thimerosal and ionic mercury: Additive effects

Infants are obviously exposed to mercury from the amalgams of the birth mother and, shortly after birth, from the Hepatitis B vaccines that contained thimerosal. An experiment was done to compare the combined toxicity of thimerosal and inorganic mercury. In this neuron culture system both thimerosal and inorganic mercury were toxic to cells at the low nanomolar levels. Inorganic mercury at 25 nanomolars caused more neuron death at the early exposure times but after 12 hours the toxicity of thimerosal was greater. It probably took some time for the ethylmercurihydroxide, the initial thimerosal metabolite that

Figure 6. Synergistic toxicities. (Dr. Mark Lovell, collaborator)



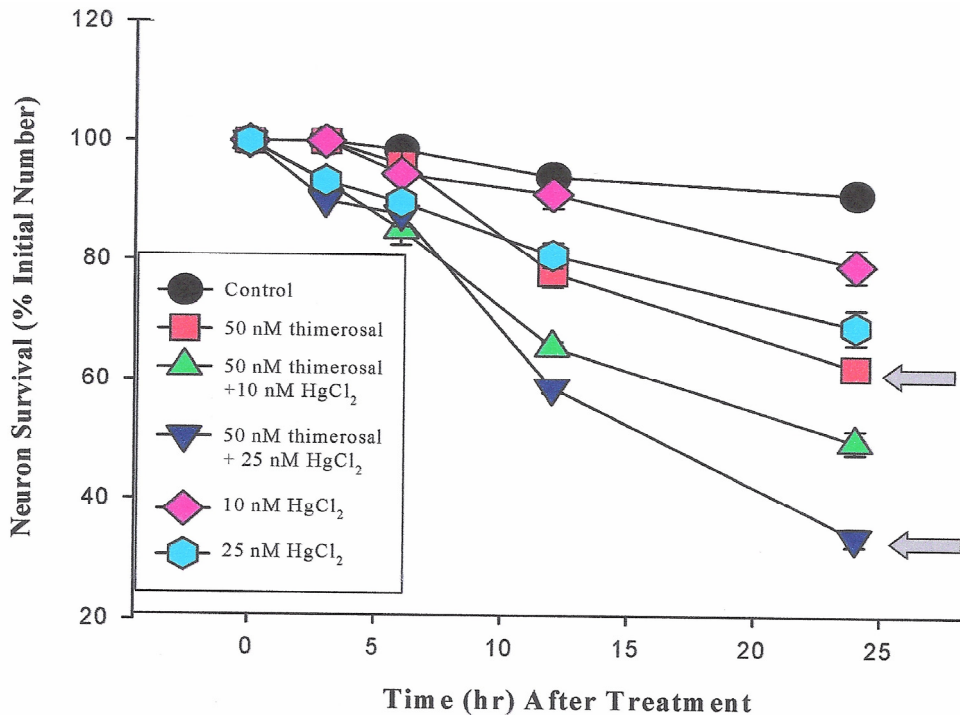
forms rapidly, to be released and it is therefore not as initially as toxic. However, as the thimerosal releases the “ethylmercury” it becomes effectively lethal to the neurons (Fig. 7).

We combined the levels of inorganic mercury and thimerosal at levels which alone gave about 50% neuron death at 24 hours to determine their combined effects (Fig. 7). They appeared to be additive instead of synergistic. This implies that both inorganic mercury(II) ions and the ethylmercurihydroxide from thimerosal cause neuronal death by similar mechanisms.

6. Inorganic mercury poisoning: Acrodynia and Pink Disease

The valid argument against any data obtained using neurons in culture is that the body has protection mechanisms against the toxic exposure that prevents the toxin from getting near the neurons and causing any biochemical abnormalities. However, we have a historical fact that proves a low exposure to mercury can cause a severe neurological disease in infants. Acrodynia, or Pink Disease, was known to affect 1 in 500 children in the late 1800s into the early 1940s. A practicing physician noted that most of the children who suffered from this illness came from the more affluent families, as the disease was much less prevalent in the poorer populations in his area. He also noted that the use of teething powders containing calomel (mercurous chloride, Hg₂Cl₂, 84.98% mercury by weight) was closely associated with the illness and recommended that these teething powders no longer be used. His patients recovered, he reported this and these teething powders were removed from the market and the disease disappeared into history.

Figure 7. Hg and Thimerosal display additive toxicities



Calomel is still used today in many diaper rash treatments and other ointments used to treat skin irritations, through the use of organic mercury compounds, like Thimerosal and phenyl mercuric acetate, was banned in 1998 in such products. Calomel is one of the least toxic forms of mercury, yet its use in teething powders caused a major illness with infants. It is not unreasonable to propose that exposure to ethylmercury from thimerosal (exceptionally toxic) could most likely be involved in autism and related disorders.

7. Mercury from Thimerosal in some vaccines

Our government agencies, the FDA, CDC and NIH routinely ignore the possible involvement of mercury in the cause or exacerbation of any disease. It is my opinion this shunning of mercury based toxicity studies is influenced by organized dentistry and medical interests (vaccine manufacturers) who routinely use mercury in the treatment of patients. An outrageous claim one would rationally think.

But look at the facts. In 1999 a report was published in the highly respected *Journal of the American College of Cardiology* that stated that individuals who die of Idiopathic Dilated Cardiomyopathy (IDCM) had 178,400 nanograms of mercury per gram of heart tissue, an amazing amount (Table 1). Measuring mercury is not rocket science, it is easy to accomplish if you have the proper instrument, which most research universities do. This level was 22,000 times higher than the rest of the tissues in the body, and in the heart tissue of subjects who died of other forms of cardiovascular disease (Table 1). IDCM is the named disease that young athletes unexpectedly die of and is one of the major reasons for heart transplants in many adults. Yet, with this data obviously available, neither the NIH nor the FDA has made any requests for grants to study the possible involvement of, or source of, mercury in IDCM. They have essentially ignored this just as they have ignored the obvious emission of mercury vapors from dental amalgams and the elevated mercury levels found in autistic children.

Table 1. Elevated Mercury in idiopathic dilated cardiomyopathy (IDCM). Where does Hg come from?

LEVELS ng/g	Hg	Sb
Controls ^a	8.0	1.5
IDCM ^b	178,400	19,260

^aControls were patients with valvular or ischemic heart disease.
^bAthletic youth who died from IDCM. (Frustaci et al., J. of American College of Cardiology, 33(6):1578, 1999.)

8. Major scientific studies on mercury toxicity

There have been two major studies on mercury toxicity—both involved studying the dietary mercury intake from eating fish and whale. In my opinion, these were likely funded because you cannot sue a fish and it takes the attention away from iatrogenic mercury exposures. In both the Faroe and Seychelles Island studies it was assumed that both blood and hair levels of mercury were indicative of the level of mercury exposure. I don't agree with this assumption because it ignores the fact that a subset of the population studied were possibly poor excretors and did not have a level of mercury in their hair or blood that was indicative of their mercury exposure, as demonstrated for autistic children. In both these studies there were anomalies that indicated that the erroneously assumed exposures were correct.

In the Seychelles study (see comments in M. Bauman and K. Nelson) of more than 700 children, it was implied that boys with the highest hair levels of mercury did better on the Boston Naming test and two tests of visual motor coordination. Spokespersons for the American Dental Association have used this data to claim that a little exposure to mercury is good for your brain. However, in my opinion the boys with the higher hair mercury levels were the boys that effectively excrete mercury and would likely have a lower body burden of mercury.

In the Faroe Island study it was the boys with the lower blood mercury levels (poorer excretors?) that had the blood pressure problems.

I feel it would be important to review the raw data from the Seychelles and Faroe Island studies with the understanding that blood, urine and hair mercury levels do *not* indicate level of exposure. In fact, it is not level of exposure at these low doses obtained in a fish diet that is critical, it is the lack of ability to excrete the mercury these children were exposed to that is critical. Inability to excrete causes the illnesses, not the total exposure.

9. Mercury levels in hair and nails of Alzheimer's diseased patients

I further investigated the theory of low-level mercury toxicity causing problems in just those individuals who were unable to excrete mercury. I was involved in the mercury/autism issue because of my earlier research that showed that exposure of brain tissue to mercury would cause many of the same aberrant biochemical factors found in Alzheimer's disease (AD). Therefore, I did a literature search on any relevant studies regarding mercury retention in tissues of AD versus normal controls. In doing this I found a series of studies that seem to have been forgotten. The references and quotes from the various papers are shown in Table 2.

Table 2. References and quotes regarding mercury retention in tissues

- Ehmann, Markesbery, et al. Neurotoxicology 9(2):197–208. Trace element imbalances in hair and nails of Alzheimer's diseased patients.
- Ehman, Markesbery, et al. Biological Trace Element Research, pp. 461–470. G.N. Schrauzer, ed., 1990 by the Humana Press, Inc.

- “Mercury is decreased in the nail of AD subjects compared to controls.”
- “Mercury tended to decrease in nail with increasing age of patient, and with the duration and severity of the dementia.”
- “This decrease is counter to the elevated levels of Hg observed in AD brain, as compared to age-matched controls.”

It seems as if AD subjects have low mercury levels in their nail tissues when compared to normal age-matched controls. Also, the level of mercury in the nail tissue of AD subjects drops with increasing duration and severity of the dementia. Nail and hair tissue are very similar and it appears as if the subjects suffering from AD may have an impeded ability to excrete mercury similar to autistics.

However, autism and AD are quite different diseases and this needs explanation. First, one has to remember that the mercury exposures in autism and AD would be quite different. First, is the matter of age. In autism the infants are exposed to bolus amounts of the organic mercury compound, ethylmercury. This is while their central nervous system is developing and while they are still on a milk diet (and perhaps antibiotics). Also, their ability to excrete mercury in the biliary transport system is low because the infants are not producing adequate amounts of bile in the first few months. These are factors that prevent excretion of mercury in laboratory animals. Therefore, ethylmercury from early vaccination with thimerosal-containing vaccines likely prevents the development of normal brain neuronal connections. This situation is exacerbated in autistics that appear to be less capable of excreting mercury.

In AD the major mercury exposure is the vapor from dental amalgams and this exposure starts after the individual is mostly mature in regards to mental development and ability to excrete mercury. However, these individuals are exposed to mercury constantly from their amalgams from the time they are placed until they are removed. Mercury vapors enter the brain with a great deal of ease where the Hg⁰ is converted to Hg²⁺, the toxic form. While Hg⁰ enters the brain with ease the Hg²⁺ does not cross the blood brain barrier very well in either direction. Therefore, the Hg²⁺ is trapped in the brain and is not effectively excreted. This would be increased in the elderly who seem unable to excrete mercury as easily as when they were younger, based on the mercury levels in nail tissue. Additionally, these older subjects are on the top of the priority list to obtain flu and other thimerosal-containing vaccines. This subjects them to bolus amounts of ethylmercury throughout their lives and cannot help but add to their mercury body burden and the total toxic effects of mercury.

When does the mercury start affecting the AD subject? Recent data show that individuals with mild cognitive impairment (MCI) have already started a build up of amyloid plaques, possibly before any clinical dementia has set in. An earlier study demonstrated that mercury exposure can increase the production of beta-amyloid, the protein that makes up the bulk of the amyloid plaque [3]. At the same time it disassembles tubulin from the neurofibrils [4]. The preceding publications confirm

the earlier reports of mercury inducing similarities to the AD brain [5].

The bottom line is that exposure to low levels of mercury can cause tubulin to abnormally aggregate and not be found in the supernatant of a brain homogenate, preventing the natural interaction with GTP, all facts that are consistent with observations on AD brain. Since Tau protein binds tubulin protein to neurofibrils the Tau protein is now dislodged from its normal setting and can become abnormally phosphorylated as it is in AD brain. This Tau protein and neurofibrils are major proteins found in neurofibrillary tangles, a major pathological diagnostic hallmark of AD. Beta-amyloid protein is produced by two proteases acting on amyloid precursor protein, a large membrane spanning protein. The increased production of beta-amyloid by Hg^{2+} exposure is quite relevant. The produced beta-amyloid peptide forms the aggregates that are called senile plaques, another pathological diagnostic hallmark of AD.

To dissolve amyloid plaques effectively one needs to use a heavy metal chelator. Therefore, the amyloid peptides are held within this plaque by interacting heavy metal linkages. This increase in heavy metals, or metals like Zn^{2+} and Cu^{2+} in the wrong place, is what would be expected if mercury levels have reached the concentration at which it has been shown to obliterate microtubulin structure and to disrupt normal homeostasis of Cu^{2+} and Zn^{2+} , etc.

Also, the disruption of the microtubulin structure impairs the transport of glutamate containing vacuoles down the axon and it is likely that these vacuoles disintegrate releasing glutamate inducing regional “excitotoxicity” and additional neuronal death. This would explain the exceptionally high levels of glutamine synthetase found in the CSF of AD versus other neurological diseases (ALS being the exception) [6]. Additionally, glutamate synthetase is a very sensitive thiol-enzyme that is rapidly inhibited by mercury.

10. Conclusions regarding mercury in brain tissue

In summary, mercury build up in the brain tissue has the ability to cause the equivalent of a biochemical train wreck. Most importantly, the axon, which contains tubulin, is rapidly and effectively disrupted by Hg^{2+} . Many pathways and many supramolecular structures are injured by mercury similar to the aberrancies observed in AD brain pathology and biochemistry. While it is possible that other environmental factors, yet unidentified, could affect brain changes similar to mercury and as observed in AD brain, it seems unquestionable that exposure to mercury vapors for scores of years and high dose vaccine-delivered thimerosal in the aged would exacerbate the disease in those who are afflicted.

Table 3 shows some data that determined the level of brain mercury and any correspondence with the number of dental amalgams in a group of nuns from the samereligious order. Mercury collection in the brain of certain individuals at a higher rate than others would be expected if the “retention toxicity” of a subset of the population were a fact. A publication on the mercury levels in the brain tissue of Nuns in a study on Alzheimer’s disease gives us some information on this issue. Nuns in a specific, single location were studied as they essentially had the same daily diet and roughly the same exposures to envi-

ronmental mercury. In this study roughly 6% of the nuns had what would be defined as extremely mercury toxic brains of 1 micromolar level or higher and this percentage increased to about 15% when the cut-off point was a 0.5 micromolar level. This strongly indicates that certain individuals among these nuns did not have the ability to clear mercury from their brains and that this is independent of diet or amalgam exposure. According to the authors, the level of mercury in the brain did not correlate with the number of existing amalgam fillings, the major contributor to human mercury body burden. Therefore, it does appear as if the inability to excrete mercury may play a major role in the build up of brain mercury levels over many years.

Table 3. Mercury levels in the human brain

- Saxe et al., with Ehmann and Markesbery in Alzheimer’s Disease, Dental Amalgam and Mercury, JADA v130, p. 191–199, 1999, determined Hg levels in the brains of 101 human subjects, mostly Nuns, both AD and normals.
- The histogram in this paper showed 6 of 101 subjects with brain Hg levels about 200 ng/g [wet weight; (ppb)] (C=236, 248, 319; AD=394, 622, 698). This represents between 1.2 and 3.5 micromolar, highly toxic levels of Hg in 6% of these subjects. At 100 ng Hg/g of sample, this increases to about 15% of subjects with highly toxic levels of brain mercury.
- This indicates that certain adult individuals do not effectively excrete mercury from their brain tissue.

Figure 8 shows that addition of Hg^{2+} in the presence of excess of the chelator ethylenediamine tetraacetic acid (EDTA) still could mimic the effects seen on the brain protein tubulin in AD. This is shown where increasing Hg^{2+} decreased the binding of a GTP analog to the tubulin of normal brain; whereas, the tubulin of AD brain did not bind even in the absence of added Hg^{2+} (see band at red arrow). This is direct confirmation that Hg^{2+} exposure, if not causal, exacerbates a major biochemical flaw found in AD brain.

In earlier studies, publications from my laboratory demonstrated that the major brain protein tubulin, which polymerizes to form microtubules, was aberrant in AD brain with an average of about 80% not being viable. This lack of viability was demonstrated in two ways. First, the tubulin has to bind the natural compound GTP (guanosine-triphosphate) to be viable and polymerize. AD tubulin could not bind the GTP analog (8-azido-GTP), a proven marker for beta-tubulin. This showed the GTP binding sites on tubulin was not available or blocked. Second, normal brain tubulin is a soluble protein at 0°C and remains in the supernatant of a centrifuged homogenate. However, in AD brain the tubulin is over 80% found in the pellet indicating that it is abnormally polymerized, something effectively done by heavy metals.

Since tubulin is well known to be sensitive to heavy metals we tested all possible metals for their ability to mimic the effect seen in AD brain. One has to consider that there are considerable metal “chelation” molecules in the brain, such as citrate

and other organic acids. We observed that many metals, Hg^{2+} , Pb^{2+} , Cd^{2+} , Zn^{2+} , etc. could mimic the effects we observed in AD brain regarding tubulin. However, only one metal could do this in the presence of huge excesses of organic acid chelators (e.g., EDTA, citrate) and that was Hg^{2+} . Chelation, or binding, of heavy metals by biological organic acids is one way to decrease their toxic effects. This worked for all metals tested except Hg^{2+} .

A major question relative to autism would be the difference in the neurotoxic mechanism of organic mercury toxicity (e.g., ethylmercury) versus inorganic mercury (Hg^{2+}). To investigate this we treated normal human brain homogenates with thimerosal just as we had treated brain in Figure 8 with Hg^{2+} . The results were dramatic, with thimerosal totally inhibiting tubulin viability at very low concentrations and very rapidly (Fig. 9). Further, exposing thimerosal to light (causes a more rapid release of ethylmercury) made the thimerosal mixture more toxic or at least more rapid in its toxic effects on tubulin.

A major difference between thimerosal and Hg^{2+} was on the protein migrating just below tubulin, which was not adversely affected by Hg^{2+} levels (see Fig. 8). Thimerosal effectively prevented this protein from interacting with the GTP analog. The major protein in this band is actin, another cytoskeletal nucleotide binding protein of high abundance in brain axons. Therefore, thimerosal had a major inhibitory effect on a protein that, at the concentrations used, was not significantly affected by Hg^{2+} .

Also, these experiments were exposed to thimerosal at 0°C for only a few minutes. This is too short of a time for the ethylmercury to be converted to Hg^{2+} . Therefore, it appears as if ethylmercury is more toxic to many proteins than is Hg^{2+} and that it does not have to break down to Hg^{2+} to cause extensive enzyme or protein toxicity (Fig. 9).

11. Conclusions

In summary, it appears as if autistics represent a subset of the population that are more susceptible to the toxic effects of mercury and thimerosal because they are not efficient excretors of these toxic materials. Further, it appears as if the sex hormones play a major role in susceptibility with the male hormones increasing susceptibility to the neurotoxicity of ethylmercury and the female hormones affording a good degree of protection. Common sense tells us that a lead toxic person would be more susceptible to mercury toxicity than a healthy, non-toxic person. Research confirms this and we routinely observe that many heavy metals increase the apparent toxicity of low levels of mercury. It is well known that a milk diet will

cause the retention of mercury as does the exposure of mammals to certain antibiotics. This would make infants with ear infections prime candidates for mercury retention toxicity. Certainly, the findings of aberrant biochemistries in the autistic child that appear to correlate with mercury sensitive enzymes increases the possibility of mercury involvement in autism causation.

If certain infants are more susceptible to mercury toxicity due to their inability to excrete mercury then it seems plausible that, since this is a genetic susceptibility, older individuals may suffer from the inability to excrete mercury also. Based on the ability of mercury to mimic many of the biochemical aberrancies found in AD brain and to produce aspects of the pathological diagnostic hallmarks of AD it seems plausible that AD is a disease related to mercury toxicity. The published decrease of mercury in the nail tissue of AD versus normal age-matched individuals seems to support this possibility.

Finally, the synergistic effects of other heavy metals, diet, antibiotics, etc. on mercury toxicity make it impossible to define a “safe level of mercury exposure.” Therefore it is imperative that we try to eliminate all exposure to mercury; and removal from dentistry and medicines is most important and critical for human health.

References

- [1] James SJ, Cutler P, Melnyk S, Jernigan S, Janak L, Gaylor DW, Neubrandner JA. Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. *Am J Clin Nutr*, 2004 Dec; 80:1611–7.
- [2] Bradstreet J. A case-control study of mercury burden in children with autistic disorders and measles virus genome RNA in cerebrospinal fluid in children with regressive autism. *Immunization safety review: Vaccines and autism*. Institute of Medicine, Feb. 9, 2004.
- [3] Olivieri G, Brack C, Muller-Spahn F, Stahelin HB, Herrmann M, Renard P, Brockhaus M, Hock C. Mercury induces cell cytotoxicity and oxidative stress and increases beta-amyloid secretion and tau phosphorylation in SHSY5Y neuroblastoma cells. *J. Neurochem*, 2000 Jan; 74(1):231–6.
- [4] Leong, CCW, Syed NI, Lorscheider FL. Retrograde degeneration of neurite membrane structural integrity and formation of neurofibrillary tangles at nerve growth cones following in vitro exposure to mercury. *NeuroReports*, 2001;12(4):733–7.
- [5] Pendergrass JC, Haley BE. Inhibition of brain tubulin-guanosine 5'-triphosphate interactions by mercury: Similarity to observations in Alzheimer's diseased brain. In: *Metal Ions in Biological Systems*; 34:461–78. *Mercury and Its Effects on Environment and Biology*, Chapter 16. Sigel H and Sigel A, eds., 1996. Marcel Dekker, Inc. 270 Madison Ave., N.Y., N.Y. 10016.
- [6] Gunnarsen D, Haley B. Detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer diseased patients: a potential diagnostic biochemical marker. *Proc. Natl. Acad. Sci. USA*, 1992 Dec 15;89(24):11949–53.

Figure 8. HgEDTA induces aberrant [³²P]8N₃GTP-β-Tubulin interactions indicative of AD

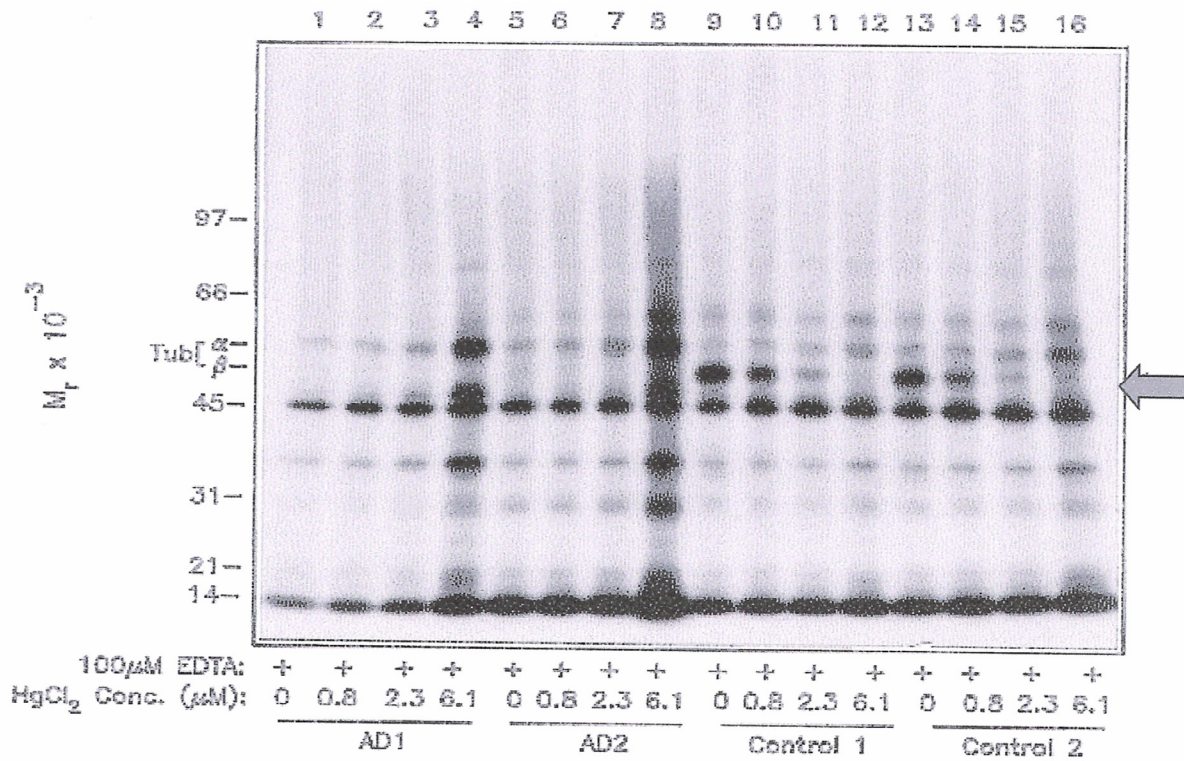


Figure 9. Autoradiogram showing Thimerosal inhibition of [³²P]8N₃GTP photolabeling of brain β-Tubulin

