FDA Panel Submission Mercury and Neurotoxicology

Introduction:

Mercury has been known as a powerful neurotoxin since the time of Caesar. In old Rome it was common that if you ran for office and lost, you opponent could banish you to the mercury mines in Almadén Spain. After a 4-year stint in the cinnabar mines no one would trust your judgment any more. Miners were goofy and forgot what they were doing or saying. Anyone speaking with them could tell that they were neurologically impaired.

The Romans knew much about mercury. They knew it was attracted by sulfur for one thing. That is why they named sulfur mercaptan for mercury capture. They also made waterbeds out of mercury and certainly many suffered the symptoms of mercury toxicity from the inevitable leaks that would result.

Lewis Carroll immortalized the neurological diseases of the New England hatters near the end of the last century in his fairy tail "Alice in Wonderland". The rabbit who at times made sense and at other times seemed to be speaking in random disconnected thoughts was typical of the mercury poisoned Irish immigrants who toiled in toxic factories making hats, hence the term "Mad as a Hatter". This is classic mercury poisoning with a healthy dose of alcohol to mitigate the damage.

Discussion:

Research has confirmed that alcohol plays a significant roll in inhibiting the transport of mercury across both the lungs and blood brain barrier[1]. The experiments were simple. First the lethal dose of mercury was obtained. Next the animals were given a non-lethal dose of alcohol and followed with a lethal injection of mercury LD100. Interestingly only 10% of the animals died LD10. Sections of the survivors brains revealed 90% less mercury had been transported across the blood brain barrier. They repeated the experiment only this time they gave the mercury first and followed with the alcohol. 1000% of the animals died leading to the conclusion that the alcohol must be in the blood stream at the time of exposure to prevent the transport across the blood brain barrier. Perhaps this explains the high alcoholism rate in dentists.

The Swedish Dental Amalgam Removal Protection Protocol used at the Uppsala Clinic utilized both alcohol in the form of schnapps and activated carbon by capsule form to assist clients during amalgam removal and prevent further exposure from mercury mobilized during the dental procedures[2].

Only about 1% of the body burden of mercury is retained in the central nervous system and its components and yet 90% of the symptoms of mercury poisoning are neurological[3]. For example depression is a frequent finding in a mercury toxic patient. Confusion, memory loss and delayed reaction times and nerve conduction rates have also been documented. The majority of the body burden of mercury, approximately 80% is retained in the kidneys. The kidney is vulnerable to mercury. It was used as a diuretic in medicine for many years and prized for its ability to increase urinary output for conditions such as congestive heart failure. It was able to perform this effect by poking holes in the tubules. Eventually the kidney succumbed to the effects of mercury and the disease progressed. Fortunately safer diuretics are available to day. Mercury has been removed from all over the counter medications and most pharmaceutical preparations with the notable exception of some vaccines such as the flu vaccine and RhoGam.

And so the question arises as to exactly why mercury is so profoundly neurotoxic and the answer is simple. Mercury loves sulfur[4]. Brains and nerves are high in sulfur so if mercury comes in contact with nerves it attaches itself to the sulfur molecules in the brain tissue. But getting to the brain is not always that easy. The brain is surrounded by a blood brain barrier that is high in lipid content. This barrier selectively admits only uncharged molecules. Once mercury enters the body in an uncharged form the enzyme catalase strips an electron or two to make the molecule positively charged as Hg+ or Hg++. The major pathway for mercury to get out of the body involves glutathione. Glutathione attaches to the mercury and sends it through the liver and into the bowel[5]. 80% of mercury is excreted through the bowel by this mechanism. The body tries to spare and recycle glutathione so that molecule is reabsorbed from the digestive tract. Unfortunately this also allows the mercury to be reabsorbed and the cycle continues. Glutathione must have an electron to be reactivated. An abundant supply of Vitamin C is crucial to this process. In autistic children the glutathione is both reduced in charge and amount indicating that the children either do not have enough glutathione to detox their mercury burden or their reserves have been exhausted.

The mechanism by which mercury causes so much neurological harm has been investigated and is now better understood and appears to be its ability to depolymerize tubulin[6].

Subsets exceptionally vulnerable:

In addition there are subset of individuals in our society who are exceptionally vulnerable to they toxic effects of mercury[7] [8]. This first came to light while investigating Alzheimer's patients. Genetic profiling of AD patients found that early onset AD occurred almost exclusively in the subset who were of the genotype APOe 4/4. Today this genotype is considered a risk factor for early onset AD.

There are three different APOe genes in the human population. They are numbered 2, 3 and 4. The APOe gene makes a transport protein whose function is to removed excess cholesterol from the brain. It is a one-way train out of the brain. Examining the differences between APOe 2 gene which is protective against AD and the 3 and 4 only two amino acids are different. The APOe 2 gene codes two cysteine molecules at the active binding sites for cholesterol. The APOe 3 codes for one cysteine and one arginine for binding cholesterol. The APOe 4 codes for two arginine. Those familiar with the amino acids will quickly recognize the difference between these three copies of genes is the amount of sulfur on this one-way train out of the brain.

APOe 2/2	4
APOe 2/3	3
APOe 2/4	2
APOe 3/3	2
APOe 3/4	1
APOe 4/4	1

Those with APOe 2/2 genes have four binding sites that contain sulfur. The APOe 4 gene has none. Since you get one gene from each parent you can have 6 different combinations of genes. (APOe Table).

Professor Boyd Haley has explained his theory of why APOe 2/2 is protective of AD and 4/4 is predictive or early onset. You are looking at the only known excretion mechanism for removing mercury from inside the blood brain barrier. If all the seats on this one-way train are occupied by the sulfur loving mercury, cholesterol will build up. The body then upregulates the production of the APOe proteins until the cholesterol levels drop to the normal. In the case of APOe 4 there is no interference with mercury since arginine does not contain sulfur or bind mercury but does bind

cholesterol adequately. The cholesterol levels are thus normal but the mercury levels can build up substantially. This is what Marksbury and Ehman determined by examining AD brain[9] [10]. They found 4 fold higher levels of mercury than the normal aged brain.

Research has found very low levels of mercury in fingernail and hair of mercury damaged infants[11]. This explains why hair analysis does not accurately determine the mercury burden. If mercury has lodged in the brain and can't get out then you would not expect to find it in the hair and nails.

Alzheimer's disease (AD) is characterized by 7 hallmark diagnostic signs. The brain is covered with beta amyloid plaque, the nerves have formed neuro-fibrillary tangles and the tubulin that once shielded the nerves has aggregated near the body of the cell. Experiments with 18 other heavy metals have not produced even one of these biochemical and histological diagnostic signs. Early experiments with mercury chloride yielded only minimal results. Upon consultation with the science advisory board of the IAOMT a new experiment where the animals were exposed to elemental mercury vapor[12].

The previous experiments had used mercury chloride with is a charged molecule and thus would be excluded from crossing the blood brain barrier (BBB). Elemental mercury vapor is uncharged and fat soluble so if given the chance it could transport across the BBB[13]. It has been estimated that inhaled mercury vapor may circulate as much as three times before contact with the enzyme catalase places a charge on the molecule and begins the excretion process through the glutathione pathway.

Once inside the BBB mercury will contact catalase and be charged and thus cannot exit the brain. The animals were exposed to mercury 300 μg/M3 vapor for 5 hours a day for a few weeks. They developed all of the 7 hallmark signs of AD. But that has not answered the fundamental question of why mercury is so neurotoxic. For the answer to that we must look at how mercury created those hallmark diagnostic signs. (Neurodegeneration www.iaomt.org Furnished separately to the FDA panel)

A flaw in the animation was pointed out to me by Boyd Haley. In real life the tubulin does not simply float away but instead agglutinates around the cell body. This is due to the fact that the sulfur molecules necessary for the auto polymerization have been occupied by mercury and they no longer can polymerize properly to both provide structural strength and to insulate the neurons. The neuro-fibrillary tangles are due to the fact that the tubulin insulation is missing. If the wires in your house were missing their insulation you'd have more than a momentary memory lapse. You'd have a fire.

The loss of the tubulin coating of the neurons thus causes the tangles but how are the beta amyloid plaques formed. They may be merely another symptom of mercury damage to heme synthesis[14]. A recent paper by Hani illustrates how the heme molecule is essential to removing the normal beta amyloid from brain. If heme production is inhibited numerous functions are also inhibited. Heme is essential for producing hemoglobin the primary oxygen transport molecule. Without adequate oxygen transport the victim would feel lethargic and weak a common finding in the mercury poisoned patients. Over the years that I removed mercury from several hundred individuals I always asked the same question about a year later, did you notice anything different once your mercury fillings were out? The most frequent reply was yes they had more energy.

Until the article about mercury inhibition of heme I couldn't understand why. Now the reason is obvious. More heme equals better oxygen transport and thus more energy.

One of the classic symptoms of mercury poisoning is tremor[15]. This can be a subtle as an eye twitch. I once had a dentist colleague of mine who I managed to convince his best interest lay in establishing a mercury-free practice and all that that entails. In just three years his eye twitch that had been quite noticeable had resolved. He hadn't realized that they were connected until one day in a big hurry he drilled on a tooth with an old amalgam without the bulky Mine Safety Association Mercury filter Mask. By early afternoon his eye twitch had returned with such a vengeance he canceled patients because he couldn't see properly. He believes that mercury is toxic now but why did it take so many years? The answer is simple. He was taught that it was not toxic.

Few dentists and physicians can even discuss the symptoms of mercury poisoning. I am not talking about the present gathering of experts in mercury toxicology and neurology. But dentists are not allowed to diagnose any medical disorder nor treat them either. I have a letter from the California Dental Board instructing me that as a continuing education provider I may not give any educational credit to dentists, dental hygienists, or dental assistants who attend my class on the health effects of ingested fluoride[16]. They contend that these effects are not within the purview of the dentist who is only licensed to treat structures of the head and neck. Their attitude extends to mercury poisoning since a dentist may not diagnose nor treat mercury poisoning, thus dentists may only poison their patients and after successfully doing that must refer to the local physician, Holistic Health Practitioner, Naturopath, Chiropractor and anyone but the dentist for remediation of the poison from the dentist. Since none of these practitioners know how to remove mercury fillings the patient is left in political limbo looking for solutions. That is why the International Academy of Oral Medicine and Toxicology has pioneered the team approach to rehabilitation of the dental patients. We urge our dentist and physician members to work together for the greater good of the client. This is also why dentists and their associations cannot be reasonably relied upon to establish the safety of implanting time-release mercury fillings.

Lack of Informed Consent:

The advocates for mercury/silver fillings were required by state law to provide informed consent to the citizens of California. In the other 49 states dentists still use the term "silver" to misinform clients as to the exact nature of the materials they intend to implant in the teeth. A recent Zogby poll found that 75% of the public did not realize that their so called "silver" fillings were in fact mainly mercury[17]. The dentists have not willingly given up this deceptive practice either. After 6 years of debate and delay the California Dental Board produced a fact sheet that reads like an advertising brochure for mercury with an almost blanket endorsement for continued use. Below is a partial quote from this travesty.

California Dental Materials Fact Sheet 2001
http://uclasod.dent.ucla.edu/PatientCare/DentalMaterialsFactSheet.pdf

> *Both the public and the dental profession are concerned about the safety of dental treatment and any potential health risks that might be associated with the materials used to restore the teeth. All materials commonly used (and listed in this fact sheet) have been shown -- through laboratory and clinical research, as well as through extensive clinical*

use -- to be safe and effective for the general population. The presence of these materials in the teeth does not cause adverse health problems for the majority of the population. There exist a diversity of various scientific opinions regarding the safety of mercury dental amalgams. The research literature in peer-reviewed scientific journals suggests that otherwise healthy women, children and diabetics are not at increased risk for exposure to mercury from dental amalgams. Although there are various opinions with regard to mercury risk in pregnancy, diabetes, and children, these opinions are not scientifically conclusive and therefore the dentist may want to discuss these opinions with their patients. There is no research evidence that suggests pregnant women, diabetics and children are at increased health risk from dental amalgam fillings in their mouth. A recent study reported in the JADA factors in a reduced tolerance (1/50th of the WHO safe limit) for exposure in calculating the amount of mercury that might be taken in from dental fillings. This level falls below the established safe limits for exposure to a low concentration of mercury or any other released component from a dental restorative material. Thus, while these sub-populations may be perceived to be at increased health risk from exposure to dental restorative materials, the scientific evidence does not support that claim. However, there are individuals who may be susceptible to sensitivity, allergic or adverse reactions to selected materials. As with all dental materials, the risks and benefits should be discussed with the patient, especially with those in susceptible populations.

There are differences between dental materials and the individual elements or components that compose these materials. For example, dental amalgam filling material is composed mainly of mercury (43-54%) and varying percentages of silver, tin, and copper (46-57%). It should be noted that elemental mercury is listed on the Proposition 65 list of known toxins and carcinogens. Like all materials in our environment, each of these elements by themselves is toxic at some level of concentration if they are taken into the body. When they are mixed together, they react chemically to form a crystalline metal alloy. Small amounts of free mercury may be released from amalgam fillings over time and can be detected in bodily fluids and expired air. The important question is whether any free mercury is present in sufficient levels to pose a health risk. Toxicity of any substance is related to dose, and doses of mercury or any other element that may be released from dental amalgam fillings falls far below the established safe levels as stated in the 1999 US Health and Human Service Toxicological Profile for Mercury Update.

All dental restorative materials (as well as all materials that we come in contact with in our daily life) have the potential to elicit allergic reactions in hypersensitive individuals[18]. These must be assessed on a case-by-case basis, and susceptible individuals should avoid contact with allergenic materials. Documented reports of allergic reactions to dental amalgam exist (usually manifested by transient skin rashes in individuals who have come into contact with the material), but they are atypical. Documented reports of toxicity to dental amalgam exist, but they are rare. There have been anecdotal reports of toxicity to dental amalgam and as with all dental material risks and benefits of dental amalgam should be discussed with the patient, especially with those in susceptible populations.

The only reference for this grandiose claim of safety is the much criticized and very biased 1993 USPHS review of dental amalgam. It is important to note that they acknowledged the existence of the ATSDR profile for mercury but did not inform the reader of the actual ATSDR

conclusions. The ATSDR concluded as have other scientific bodies that the predominant source of human exposure to mercury is from in situ mercury/silver fillings. This fact would seem to be germane to any accurate informed consent document. In addition, they again rely upon Mackert's recalculation of mercury amalgam exposure studies to come up with their minimal risk scenario[19]. This same argument was soundly rejected by the World Health Organization expert scientific committee on mercury because it did not satisfy the presently available experimental evidence.

On the other hand, mercury/silver fillings have been associated in the scientific literature with fetal exposure to mercury, periodontal problems, bone loss, allergic reactions, oral lichen planus, immune suppression, multiple sclerosis, fatigue, short-term memory loss, delayed nerve conduction, cardiovascular problems, cardiac arrhythmias, skin rashes, endocrine disorders and eye problems including cataracts according to the literature. (Discussed in *The Scientific Case Against Amalgam* provided separately)

What mercury advocates are often fond of saying is that there is no peer reviewed science linking mercury in an amalgam to any harm. This is the equivalent to saying the bullet in the gun has never harmed anyone. That is a very true statement but only a lawyer could appreciate the nuances of in vs. from. There is a large body of peer reviewed evidence linking in situ mercury/silver fillings to increased body burden, maternal/fetal exposure, neurological impairment, and even autism.

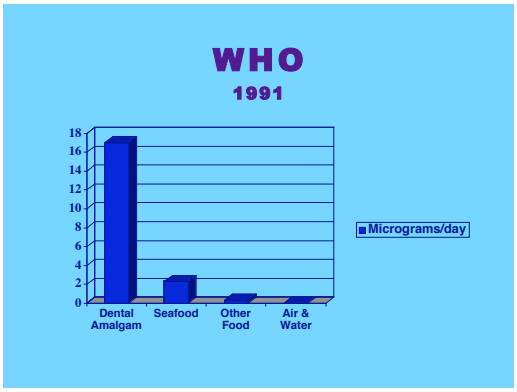
In 1992 Vas Aposhian challenge tested students at the University of Arizona with sodium salt of 2, 3-dimercaptopropane-1-sulfonic acid (DMPS)[20]. He found that two thirds of the recoverable mercury was apparently from their fillings. He also found that those with the greater number of fillings and consequently the greater amount of mercury excreted upon challenge scored significantly lower on a battery of neurological tests than those with fewer fillings and less mercury[21]. Aposhian and Echeverria went on to test dentists and their assistants who used mercury in the practice of dentistry. He recovered a great deal more mercury and found even more neurological impairment that the students with a mouth full of amalgam[22]. They also studied the mercury-free dentists of the IAOMT. The results were not reassuring. He found they too had some degree of neurological impairment that placed their scores between the mercury packing dentists and the mouth full of amalgam students. It is probable that some of this impairment came from their exposure during their schooling and from their clinical practices before they became mercury free but it is also likely that the practice of dentistry carries real risks to the personnel involved even when rigorous safety protocols are followed. Echeverria went on to write a book on the subject of dental personnel neurological injury from mercury[23].

A fetus is much more vulnerable to mercury for a number of reasons. For one their body size is small. In addition they have no billary excretion route, their brain is growing rapidly and lastly their immune system is immature and not equipped to handle heavy metal exposure. For these and other reasons it has been noted from incidents both in Minamata Japan and Iraq that infants are severely harmed at levels of mercury exposure that cause no readily apparent harm to the mother. Infants born to mothers contaminated by mercury in Japan's Minamata Bay in 1956 had profound neurological disabilities including deafness, blindness, mental retardation, and cerebral palsy.

In adults, mercury poisoning can cause numbness, stumbling, dementia, diabetes and death. Advocates for mercury fillings point out that the form of mercury in Minamata was methyl mercury. While it may be true that methyl mercury was what poisoned the fishermen in Minamata it is important to note that the form of mercury discharged into Minamata Bay was in fact inorganic mercury from a chloralkali plant up stream from the village. Mercury biotransformed in the bay just like it does in the plaque on your teeth and the bacteria in your gut[24] [25] [26].

The reason that methyl mercury is considered so toxic is because of its high absorption rate from the skin and gut. Liquid elemental mercury is so poorly absorbed that those attempting suicide have swallowed liquid mercury and frequently failed to achieve their goal. A chemistry professor at Dartmouth, Karen Wetterhahn, spilled just two drops of dimethyl mercury on her latex gloved hand. She died a few months later of mercury poisoning[27]. Dimethyl mercury penetrates latex and absorbs readily through skin. Elemental mercury vapor is absorbed in high doses about 80% from the lung. In lower doses it is almost 100% absorbed from the lung[28] [29].

Since the toxic nature of mercury is primarily a function of the absorption rate, elemental mercury vapor is one of the most toxic forms of mercury. *"It is a fallacy that mercury is neutralized when it is combined with other components of silver amalgam. The laws of physical chemistry are followed."*[30] The International Academy of Oral Medicine and Toxicology in 1984, after it had been firmly established in the peer reviewed scientific literature that substantial amounts of elemental mercury vapor was coming off set dental amalgam fillings[31], called for a ban on all future placements of the so called "silver" fillings until such time as the alleged evidence of safety was produced by the advocates and manufacturers. As of this date no safe level of exposure to mercury has been established. In 1973 William Ruckelshaus, head of the new EPA stated, "We've been asked to do the impossible. There is no safe level of exposure to mercury." The World Health Organization concurs with this opinion. They have also established that dental amalgam produces the largest exposure of humans to mercury[32]. The EPA now estimates the annual number of births in the US that exceed the EPA exposure limit to be 630,000[33].



Conclusions:

It is our sincere belief that the only logical conclusion of this panel is that the continued implanting of time-release mercury/silver fillings should cease. Since by the most recent survey more than 25% of the practicing dentists no longer use any mercury in their practices and many dental schools worldwide no longer teach its use, the argument that this kind of filling is essential to the productivity of dentists and continued dental care is illogical[34]. What those dentists need who have not learned to place alternative filling materials is better training and furthermore, all dentists should be required to protect their staff and patients from the bolus dose of mercury received during dental procedures[35] [36] [37]. As a preliminary step due to the present crisis in fetal mercury exposure, we urge this panel to call for an immediate halt to state and federal government funding for new mercury filling treatment in pregnant and potentially fertile

women and that mercury/silver amalgam fillings be classified as the FDA rules require as a Class III implant material for which there is definitive evidence of safety[38].

Selected References: Additional references in the Scientific Case Against Amalgam and Toxics in Dentistry FDA submitted electronically

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[38] FDA definition of an implant is any substance implanted into a natural or manmade body cavity. This material must be classified as Class III.