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Mercury Induced Alzheimer's Disease: Accelerating Incidence?

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Micromercurialism (MM) is a term coined by the German chemist Professor A. Stock in the 1920's and widely used to denote chronic intoxication from long term exposure to low levels of Hg vapor. He also demonstrated (in himself) that MM can be caused by dental amalgams. Stock stimulated a wave of scientific interest in MM in Germany and Russia. These two countries adopted the lowest tolerable work place Hg vapor levels in the world, 1 and 10 $\mu g/m^3$, respectively (Patterson et al. 1985; Gerstner and Huff 1977). MM differs in many respects from the generally recognized acute form of Hg intoxication. These differences which were recently elucidated in the Bulletin (Ely et al. 1999) are responsible for almost universal failure of physicians to diagnose MM. As explained there, in order to make this diagnosis, urine Hg must be measured in μg/day instead of μg/L because of a highly variable polyuria common in MM. More importantly, "retention toxicity" must be understood. This latter effect, first reported by Public Health Service investigators (Neal and Jones 1938) is an inverse relationship in MM between degree of intoxication and urine Hg content; i.e., the most intoxicated subjects excrete the least Hg. This, of course, is the reason their intoxication continues to worsen until the exposure is terminated. Because of Hg's extreme toxicity as an enzyme inactivator (Webb 1963), it appears plausible that in subjects with long-term chronic exposure, Hg has disabled the enzymes involved in Hg excretion. This not only results in undetectable or extremely low (<5 μg/day) urine Hg, but also causes blood levels to rise resulting in diffusion of Hg to bone storage.

It has long been known from x-ray fluorescence studies that persons with chronic exposure such as dentists, have elevated skeletal Hg stores (Bloch and Shapiro 1981), and low urine Hg (Neal and Jones 1938). This is mistakenly interpreted today almost universally as evidence of low intoxication attributed to adequacy of dental clinic precautionary measures. Also, in old age, osteoporosis may accelerate Hg release to a rate much above that corresponding to the 20 year excretion half-time

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estimated by Sugita (1978). As a result of these complexities, there is almost no awareness of the degree of Hg intoxication in the US today or its possible impact on the incidence of Alzheimer's disease (AD).

Two different types of radiation techniques, neutron activation analysis and photolabelling, were used by two different groups of investigators to compare Hg in brains of AD and control cadavers (Thompson et al. 1988; Pendergrass and Haley 1997). Olivieri et al. (2000) used an in vitro model system (neuroblastoma cells) to investigate the effects of inorganic mercury ($HgCl_2$) on several central nervous system variables including tubulin phosphorylation.

This paper seeks to focus attention on widely ignored features of micromercurialism from amalgam. These features already make Hg one of the two leading causes of Alzheimer's disease incidence and threaten to greatly increase this tragic toll.

MATERIALS AND METHODS

Measurements of Hg^0 release from amalgams were made with a portable battery powered Jerome Model 411 Mercury Vapor Analyzer (Arizona Instrument Co., Phoenix, Arizona, USA). The subjects were people attending meetings related to mental illness who requested the test, and signed an informed consent. Readings were made both before and after chewing stimulation (30 sec vigorous gum chewing). Each subject was supplied with tissues and instructed to dry the surfaces of the teeth immediately before each measurement because Hg^0 will not penetrate the saliva layer. An intake tube terminated in a 10 cm piece of plastic drinking "straw" (discarded after each subject) is held motionless at the edge of an amalgam dental filling while the subject interrupts breathing for 10 seconds. During that collection interval, 125 ml of air are drawn into the instrument via the intake tube. That air has swept across the amalgam surface in the boundary layer region of the tooth and contains all of the Hg vapor emitted by the filling during the 10 sec interval. In the instrument, the air is drawn over a thin gold film that amalgamates the Hg, changing the electrical resistance of the film. Immediately at the end of the 10 sec intake time, a digital readout provides the Hg vapor content of the air sample. Some details of this technique are noteworthy. Gum chewing (which must be vigorous) is done on each side for only 30 sec just before the stimulated measurements on that side's amalgams. This saves much time and produces more consistent results than the often reported 10 min of chewing (Vimy and Lorscheider 1985; Krone et al. 2001). Most importantly, with the motionless technique, a quantity of interest is conserved; all of the Hg^0 from that amalgam entering its boundary layer will be collected and measured with repeatability better than 10%.

Table 1. Mercury release from dental amalgams.

Tooth location & number[1]	Subject 1		Subject 2	
	Before[2]	After[2]	Before[2]	After[2]
Upper right				
2	2	16	-	-
4	0	8	0	8
5	-	-	0	7
Upper left				
12	2	14	-	-
13	-	-	0	11
14	11	43	0	18
16	-	-	1	35
Lower left				
17	4	11	-	-
21	-	-	0	5
Lower right				
27	-	-	0	9
28	-	-	0	8

1. quadrant and tooth number (standard numbering system)

2. concentration measured by Jerome 411 in $\mu g/m^3$ before and after chewing stimulation as described in Materials and Methods. To convert to μg/day, multiply by 1.08.

RESULTS AND DISCUSSION

Table 1 shows representative measurements of Hg release from amalgam restorations using a Jerome 411 in two subjects with multiple dental fillings. Chewing stimulation increased Hg release, frequently by factors of 4 or more. Other workers have measured similar increases in Hg flux after chewing (e.g., Vimy and Lorscheider 1985). Mercury release of a "high copper" amalgam formulation was shown in vivo to increase from a baseline of 5 to 41 $\mu g/m^3$ after chewing stimulation (Ahmad and Stannard 1990). In Table 1, two of the subjects' 13 amalgams released Hg at similar levels, suggesting they could be high copper formulations. In amalgams called "high copper", the usual 3% copper is increased to between 12% and 20%, and silver reduced correspondingly from 18%. The Hg content remains ~52%. At least two reasons suggested for development of these high copper

amalgams were better structural characteristics (smoother finish and longer holding of edges) and the lower cost of copper versus silver.

There are at least four major etiologies of AD. Two of these (Hg and infections) appear well supported and are reported to occur in such large fractions of the AD population that most patients may have both. Infectious etiology for AD (and other CNS lesions) was predicted by Fudenberg (1994) and, in fact, Chlamydia pneumoniae was reported by Balin et al. (1998) in ~85% of AD brains.

Aluminum has been proposed as a cause of AD for over 50 years and is known to be neurotoxic in animals and humans. Exposure is primarily from food and water. It has been reported to have a role in dialysis dementia. The toxicity of aluminum to plants, aquatic life and humans may share common mechanisms, including disruption of the inositol phosphate system and calcium regulation. Facilitation of iron-induced oxidative injury and disruption of basic cell processes may mediate primary molecular mechanisms of aluminum-induced neurotoxicity (Yokel 2000). A relation has been proposed between AD and the influence of aluminum on oxidative and inflammatory processes (Campbell and Bondy 2000). Although aluminum has been reported to be elevated in AD brain, only Hg has been shown to induce formation of neurofibrillary tangles (NFT's), and there is no agreement that aluminum has a significant role in AD. In a recent review, Yokel (2000) considers these many claims and concludes that avoidance of aluminum exposure, when practical, seems prudent. This appears to be the message that should be sent to the public, regardless of whether or not aluminum is also proven to cause AD.

Cadaver studies of the nucleus basalis of Meynert (nbM) from AD brains showed a high incidence of Hg compared to controls in the two methods used, neutron activation analysis and photolabelling. In fact, nbM Hg exhibited the largest trace element imbalance observed in AD brains. Both methods found that approximately 80% of AD brains had very highly significant elevations of nbM Hg (Thompson et al. 1988; Pendergrass and Haley 1997). A probability of $p<<.0001$ was readily obtained using Poisson statistics $[P(x,y) = e^{-y}\, y^x/(x!)]$ on data from Table 3 in Thompson et al. (1988). There, the AD sample nbM avg was x=39 and the control population nbM avg was y=9 (in units of ng/g, i.e., ppb). In essence, it is almost astronomically improbable that the AD and control samples could have come from the same population. NFT's correlate strongly with Hg in the AD nbM. In turn, incidence and worsening of memory defect and other symptoms of AD correlate strongly with nbM NFT's (Thompson et al. 1988).

We suspect that Hg, as possibly its most damaging mechanism,

inactivates enzymes (Webb 1963) simply by attaching in their active sites and thereby slowing manifold some processes necessary for vital functions including repair and metabolism. This can be devastating in the brain (Pendergrass and Haley 1997; Olivieri et al. 2000). It appears plausible to us that two of the hallmarks of Alzheimer's, memory loss and NFT's, may result from Hg inactivating enzymes necessary for: (1) brain cell energy production; and (2) proper assembly of the protein tubulin into microtubules (i.e., without formation of NFT's). The results of much sophisticated research and heated debate on the role of a protein called tau (and numerous other molecules) in the microtubule problem seem attributable to enzyme dysfunctions. These, in turn, appear to be caused by Hg intoxication even at very low Hg levels in certain parts of the brain (Thompson et al. 1988), a thousand (!) times lower than observed in human bone (Bloch and Shapiro 1981; Ely et al. 1999).

It is possible that NFT's result from failure of enzymes that regulate phosphorylation of tubulin. Sections of tubulin are held together by phosphate groups. When tubulin is assembled properly in long cylindrical tubes, it transports molecules (such as neurotransmitters) from sources in the neuronal body long distances down the axon to the synapses. If too few phosphate groups are used the binding is weak and the structures fail. Or, if too many phosphates are attached, the structures repel each other and form NFT's. Proper balance is controlled by two enzymes. In AD, hyperphosphorylation is believed to be the most common of these two failures. We suggest failure of this control is due to the unequaled toxicity of Hg as an enzyme inactivator. Also, it has been demonstrated in an in vitro system that Hg increases phosphorylation of tubulin (Olivieri et al. 2000).

Approximately 90% of the US population (>200 million) have amalgams with 100 million newly installed each year. Since ~1960, the new high copper amalgams (also called "copper-rich") have become increasingly popular and now may be the most commonly used. Two Swedish researchers, Brune et al. (1983) and Pleva (1994), warned that Hg was released 50 times as fast by these formulations. It is trivial to demonstrate with a Jerome 411 Hg Vapor Analyzer that high copper amalgam releases Hg much faster. In studies of hundreds of subjects, it was found that even when > 10 years old these amalgams commonly released Hg ≥ 2 times the rate of the conventional 3% copper (Ely *unpublished*). As mentioned above, a high copper amalgam formulation released 41 $\mu g/m^3$ (Ahmad and Stannard 1990). Krone et al. (2001) found, in 128 amalgams from 46 subjects, over one-third released greater than 50 μg Hg/m^3 after chewing stimulation. This suggests that a significant proportion of amalgams installed in the US population today are high copper. Therefore, many millions alive

today may be at risk for MM and the associated disorders.

Based solely on changes in age distribution (without regard for Hg), it is estimated that AD incidence in the US may increase from the present 4 million to 14 million by 2050 (Helmuth 2000; McQueen 2001). Although alarming, these estimates appear perilously low in view of our findings reported here. If these findings are supported, use of high copper and perhaps all Hg amalgams should be discontinued. In addition, methods of Hg detoxication need to be evaluated. These include sweating, to spare the kidneys (Wedeen 1983), long used by Hg miners in Spain (Sunderman 1988). We combined sweating with high ascorbic acid intake to mobilize intracellular Hg by reducing Hg++ to the mobile neutral Hg^0 (Ely *unpublished*). Uncontrolled preliminary pilot studies with this method: (1) have relieved tremor, ataxia, memory impairment, and diabetes insipidus (all associated with MM); and (2) suggest it may be possible to prevent and even reverse early stages of AD (when the other causes have been eliminated).

There are strong associations between Hg and Alzheimer's disease. The prevalence of high copper (i.e., high Hg release) amalgams suggests that current projections of Alzheimer's disease incidence are greatly underestimated.

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