Bull. Environ. Contam. Toxicol. (2001) 67:309–316

DOI: 10.1007/s00128-001-0126-7

Bulletin of Environmental Contamination and Toxicology

Risk Factors for Parenteral Intoxication by Mercury from Dental Amalgam

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Received: 13 February 2001/Accepted: 25 May 2001

The "amalgam wars" continue to take a toll of the affluent nations and no real progress has been made on the issue. Apparently, neither side can convince the other that amalgams are, or are not, a cause of serious disease (Stortebecker 1985; Pleva 1994). A principal obstacle to progress in the past two centuries has been the extreme difficulty of standard wet chemistry for Hg. However, in the past two decades, various types of radiation studies including neutron activation analysis, x-ray fluorescence, photolabeling, etc., have provided a thousand times greater sensitivity and other advantages. Moreover, the present ability to measure the Hg vapor emission rate from each filling in ten seconds is of great value in both research and clinical use. Logical operations on data from the resulting studies yield the simple approach presented here to resolve the amalgam controversy using an easily estimated dimensionless risk factor.

"Micromercurialism" (MM) has been used since about 1930 to denote a condition in which chronic exposure to very low concentrations of Hg vapor (Hg^0) is thought to be etiologic in a number of associated disorders (Gerstner and Huff 1977). Due to variable and nonspecific symptoms, and testing difficulties, MM is one of the most universally missed and least studied diagnoses (Klaassen 1990). As an example, as MM worsens, urine Hg commonly becomes extremely low (a condition now called "retention toxicity") and may be the principal cause of missed diagnoses (Neal and Jones 1938; Ely et al. 1999). An etiological role for Hg in MM is not widely accepted because: (1) essentially no cases of MM are detected and hence no studies are performed or published; (2) amalgam Hg^0 is known to be very poorly absorbed from the gut (PHS 1992) and, hence, the fallacy that it does not contribute to Hg body burden; (3) but, it is not widely realized that conversion of amalgam Hg^0 by oral flora to methyl-Hg with its much higher gastrointestinal absorption and very long (>20 years) excretion half-time can and does greatly increase Hg intoxication (Sugita 1978; Bernard and Purdue 1984; Stortebecker 1985; Friberg and Mottet 1989; Lorscheider et al. 1995); and (4) the vast majority of the U.S.

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population does not appear to suffer serious systemic disease from amalgam.

However, human and animal studies report that Hg from amalgam is deposited in various tissues (Eggleston and Nylander 1987). An accumulation of evidence and arguments in recent years suggest an association with numerous "idiopathic" afflictions including allergies, ALS, Alzheimer's, birth defects, endocrinopathies, psychoses, etc. (Stortebecker 1985; Thompson et al. 1988; Pleva 1994). Certainly, in view of occupational exposure, it was not surprising that Hg was found to be significantly elevated in pituitaries of dentists (Nylander 1986), all of whom are poisoned parenterally by inhalation intoxication, whether breathing through the mouth or nose. However, autopsy studies of nondentists have also been reported to show significant elevation of brain Hg that correlated with the number of amalgams, especially molars (Friberg et al., 1986; Eggleston and Nylander, 1987). And, in Alzheimer's disease cadaver brains, elevation relative to controls was reported by neutron activation analysis to: (1) average 400% in the nucleus basalis of Meynert ($p < .01$); and (2) peak in regions where neurofibrillary tangles (NFT's) also maximized (Thompson et al. 1988; Wenstrup et al. 1990). Dental amalgam sources were among those suggested. The elevation of Hg was reported in about 80% but not all of the Alzheimer brains, which is not surprising in view of the other suspected causes of senile dementias of this type (i.e., vitamin B-12 malabsorption, trauma, vascular disease, Chlamydia pneumoniae (Balin at al. 1998), etc.). In addition to the cadaver studies, photolabelling studies in vitro and in animals have impugned Hg. Of all the elements tested (including Al, Cd, Co, Cr, Pb, etc.), only Hg in human brain tissue culture and in rats in vivo induced the type of tubulin defect that precedes NFT's, a characteristic lesion of Alzheimer's disease (Pendergrass and Haley 1997).

Is it possible then that dental Hg could cause most of 4 million people (about 1.5 %) in the U.S., to suffer a presently incurable disease such as Alzheimer's, if some 200 million others are unscathed by their amalgams? This may be among the most important questions facing medical science today. One first must consider what might be different between the two groups of amalgam wearers. Clearly, if it can be shown that a very small fraction of the population, due to idiosyncratic factors, has a vastly higher-than-average relative risk of parenteral intoxication by amalgam Hg, progress should be made rapidly on this and related problems.

MATERIALS AND METHODS

Systemic disease and symptoms arise from absorbed dose (i.e., exposure). However, in the method used here, risk is calculated instead of dose because dose is extremely difficult to estimate whereas risk is trivial but provides much valuable information. The relative risk is calculated as the product of estimates of only the three dominant factors (amalgam composition, bruxing and mouth breathing). In addition to these three factors that our method uses to calculate risk, there are many other factors that would have to be determined if we calculated dose. Thus, a great advantage of a method that calculates risk is avoidance of many factors necessary to calculate dose. That list includes oral flora, diet, mastication, hygiene, and total surface area, composition, age and condition of amalgams, etc. Another advantage of our method is that relative risk is dimensionless, being the ratio of the risks of a patient and a hypothetical individual with the same amalgam geometry but defined to be free of the idiosyncratic factors that increase parenteral absorption of Hg from amalgam. Also, the relative risk can be viewed as the relative dose per unit amalgam area, per unit time, per unit weight, etc., i.e., numerous dimensioned factors that would all disappear (i.e., "cancel out") if we actually had to calculate two risks and then form their ratio to obtain relative risk.

During this risk factor study, 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). These were on the amalgams of over 200 people attending meetings related to mental illness. They requested the test, and signed an informed consent. Readings were made both before and after chewing stimulation. Each subject was supplied with tissues and instructed to dry the surfaces of the teeth immediately before each measurement (Hg^0 will not penetrate the saliva layer). Although the Jerome was not intended for this application, the instrument's design permits realization of precision, sensitivity and speed as follows. 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 second interval. In the instrument, the air is drawn over a thin gold film that absorbs (amalgamates) the Hg, changing the electrical resistance of the film. This provides, immediately at the end of the 10 second intake time, the Hg vapor content of the air sample. Two details of technique

are noteworthy. Vigorous gum chewing for only 30 seconds on one side, just before the "stimulated" measurements on that side's amalgams, save considerable time and produce more consistent results than the often recommended 10 minutes of chewing. 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 a repeatability better than 10%.

RESULTS AND DISCUSSION

We have developed a simple method presented here for estimating the relative risk *a priori* that a subject will incur sufficient parenteral intoxication by mercury from dental amalgam to induce MM. It is argued that three factors, two physiological and one physical, dominate this estimate. The amplitudes of these factors, amalgam composition (i.e., Cu content), bruxing (or clenching), and mouth breathing, were approximated from the literature and studied in experimental measurements on over 200 people. One striking theoretical conclusion reached below is that an individual most strongly affected by all three factors (about 1% of amalgam wearers) might receive many thousand times the parenteral dose that is absorbed by another person who has the same amalgam geometry but is not so affected by these factors. If the disease associations mentioned above are real and causal, it seems plausible they must also correlate with the subject risk factors.

As we show, our approximation for relative risk is formed simply as the product of estimates of the three dominant factors described here. The range of relative risk spans many orders of magnitude, running from extremely small to extremely large numbers. If three factors are each much smaller than 1 (i.e., 0.01), their product will be far smaller than 1 even if each has an error of ca 100%; and similarly for products of factors much larger than 1. Thus, estimation of its order of magnitude is all that is required to identify low and high risk individuals. This crude approximation is adequate and is all that we advocate. Although, in principle, it may seem that relative risk could be calculated exactly, it would be extremely difficult, impractical and of no value. What difference would it make to know that a person's relative risk is one very large number (i.e., 50) or another (i.e., 15,000)? If it is large, the person's symptoms should be investigated and amalgams removed if justified. In marginal cases, more refined differential diagnosis and or conservatism on the side of health must be considered along with the immediate costs of dental care.

The literature gives a wide variety of estimates of the net Hg dose rate (i.e., absorption minus excretion) to be expected from amalgam. These depend on route. They range from far below 10 to >100 mcg/d (micrograms per day) depending upon total area, age, composition, and condition of the amalgam, habits of the subject, etc. Note that the 13 milligram figure usually cited for total Hg body burden (Schroeder 1973) would be reached in only 4 years at 10 mcg/d, making this a very significant net dose (n.b., skeletal Hg may prove to be negligible except in MM). For nonintoxicated humans (i.e., good excreters) who are also fortunate with respect to other factors we consider here, the net dose absorbed parenterally may be truly ignorable.

Although a wide range of Cu content (from about 10 to over 30%) has been used in various amalgam formulations frequently called "high-copper" for the last two decades or so, several of the more popular have about 12% Cu (instead of the formerly more common 3%). It has been reported that one of the widely used 12% Cu amalgams releases Hg about 50 times as fast as the 3% Cu (Brune et al. 1983). During our measurements, it was noted that: (1) about 35% of the subjects had one or more amalgams that were releasing Hg^0 at rates much higher than the others (2 to 20 times); and (2) these anomalous high emitters were determined to be high Cu in every case that the dentist was located and could supply the name of the alloy. The order of magnitude estimate for this composition factor is taken as 10. The Jerome 411 readily demonstrates that high Cu amalgams have very high release rates.

The habits of grinding teeth or clenching jaws (usually in sleep): (1) are reported in about 10% (with some evidence of episodes in 30 %) of the population (Duckro et al. 1990); (2) are readily shown to increase the release rate of Hg^0 from amalgams (and the relative risk) by about a factor of 10; and (3) are also suggested to result from MM (Ziff 1992) in addition to other causes. Episodes of clenching or bruxing are reported to occur frequently during the night and usually last less than 10 minutes. However, the elevated Hg^0 release may last an hour after each episode, adding to the Hg^0 that can be inhaled parenterally by mouth breathers (see below). However, if the mouth is shut, the Hg is swallowed.

The third factor, mouth breathing, becomes important when saliva dries, Hg^0 enters intra-oral air and is inhaled. In contrast to the gut, the lungs absorb about 80% of inhaled Hg^0, 8000 times more than the .01% if swallowed (Nielsen-Kudsk 1965). If a mouth-breathing sleeper exhales half of the Hg^0 released from amalgams and inhales the other half, "only" 40% is absorbed (4000 times more than if swallowed). Clearly, the fraction of the day (the subject mouth breathes) strongly affects the degree this factor would play in a precise calculation of

relative risk. Even with this factor, the absolute dose may not be excessive if the amalgams are neither large, numerous, nor high-copper (see below). If the mouth is open when chewing gum, or running, etc., obvious combinations of the factors occur.

Naturally, various amplitudes of these factors exist. Clearly, the worst case is the existence of a strong effect by all three in the same individual. When we multiply that person's dose rate by the product of the three factors (10, 10, and 4000), we get 400,000 times the dose rate (and relative risk) of a hypothetical person who has the same amalgam geometry but does not brux, mouth breathe, convert Hg^0 to other forms, or have high-copper amalgams. Of course, this enormous number is simply a useful artifact of our method. Although clenching and bruxing may occur in only 10% of the U.S. population, both mouth breathing and high-copper amalgams are estimated to occur in over 20%. If we assume the factors are independent, a simplistic estimate (.1x.2x.2) yields 1/250 or about 1,000,000 people in the U.S. with this model's maximum relative risk factor. And, naturally, larger numbers of people who mouth breathe fewer hours per day, or etc. (if we needlessly calculated all of the variables) would be found to have smaller (but still extremely large) relative risk factors. As discussed above, to estimate absolute dose, amalgam surface area, etc., would be needed, but that is not the purpose of this work. In fact, the potentially quantifiable nature of absolute risk factor is not of practical value. On the other hand, great benefit for society may result if use of the *relative* risk estimate resolves the centuries long amalgam debates. Also, clinicians individually will find it useful simply for the realization that, in most cases, a subject's relative risk is readily determined (i.e., between very low and very high) from two history statements (re bruxing and mouth breathing) and a few minutes of intraoral measurement with a Hg vapor analyzer such as the Jerome model 411, if amalgams are already in place.

In conclusion, we developed the estimated relative risk factor because the great variations in susceptibility reported to correlate with serious disease need to be examined. Widespread use of this method (even in its present form) in persons with established or suspected neurological, psychiatric and other diseases as well as in the general population can, with very minimal effort and cost, quickly divide these groups with respect to susceptibility and permit systematic inquiry to focus on the questions related to MM and amalgams. Other more complex diagnostic procedures including x-ray fluorescence of bone, DMPS challenge, fecal Hg, etc., can then be used to estimate body burden and distribution, and whether amalgam removal and Hg detoxification appear justified. Although there are extremely few modern references to Hg in bone, it was shown by animal studies ca 1930 that bone was

the major reservoir for Hg in MM, and over 90% of the absorbed dose was in the skeleton (Young et al. 1930). It should be noted that x-ray fluorescence measurements showed skeletal Hg in 20% of 300 working dentists ranged from 20 to 200 ppm (Bloch and Shapiro 1981); multiplying by 7 kg suggests their skeletal Hg ranged to over 1 g (!). In MM patients much more incapacitated by inhalation intoxication, the body burden may be correspondingly higher. If skeletal stores exceed even 100 mg in MM, development of detoxification protocols via sweat (Sunderman 1988) and feces (Stone 1974; ascorbate as the principal electron donor in the liver enhances fecal excretion of toxic metals) may be necessary to avoid endstage renal disease that would result from chelation of Hg and excretion through the kidneys (Wedeen 1983).

Acknowledgments. Support of Wallace Genetic Foundation, Northwest Oncology Foundation, and Applied Research Institute are gratefully acknowledged. For helpful editorial comments, I thank Dr. C.A. Krone, Toxic Metals Group Leader (Emeritus), NOAA.

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