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Urine Mercury in Micromercurialism: Bimodal Distribution and Diagnostic Implications

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The term Micromercurialism (MM) has long been used to denote those disease conditions in which chronic exposure to very low concentrations of mercury (Hg) is thought to be etiologic (Gerstner and Huff 1977; Nylander 1986; Eggleston and Nylander 1987; Sunderman 1988; Klaassen 1990; Ziff 1992). It is believed to occur in several percent of the population and is reported to be a probable cause of serious disorders including psychoses (Pleva 1994) and Alzheimer's disease (Thompson *et al.* 1988). Yet MM is almost never diagnosed because of nonspecific symptoms, and certain complexities in urine excretion of Hg (Klaassen 1990; Gerstner and Huff 1977). We explain a model of MM that predicts two states and, therefore, two populations. Population One, a first stage, is predicted to be accumulating Hg into both soft tissue and bone storage due to extremely impaired excretion (a condition called "retention toxicity"). Population Two, a second stage in which exposure has been lessened or terminated, is predicted to excrete normally, but still have bone storage. In a group of subjects containing both populations, a distribution of total daily urine Hg excretion with two peaks should result. Urine Hg from all 18 subjects reported here (some in each of the two states) did fall in this bimodal distribution, strongly supporting the model. Awareness of the model prevents diagnostic failure for MM and will enable study of this condition and reported associations with serious idiopathic disorders.

The distribution and kinetics of the Hg body pool differ greatly between acute and chronic intoxications. Soft tissue levels (e.g., blood, lung, kidney, heart) are high following acute exposure to mercury vapor (Casarett and Doull 1975). Human and animal research has shown that Hg accumulates in various tissues following chronic exposure (Klaassen 1990). In Alzheimer's disease cadaver brains, Hg elevation relative to controls was reported to: (1) average 400% in the nucleus basalis of Meynert ($p < 0.01$), a region heavily lesioned with

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neurofibrillary tangles; and (2) peak wherever the neurofibrillary tangles also maximized. Dental amalgam sources of Hg were among those suggested in this study (Thompson et al. 1988). No other metal displayed such a high elevation in the Alzheimer brains (compared to control brains), and only Hg was found to stimulate neurofibrillary tangle formation in brain tissue culture (Thompson *et al.* 1988).Among the several etiologies accepted for Alzheimer's, two (Hg and infections) appear to occur in such large fractions (~80%) that most patients may have both (Fudenberg 1994). Very little has been published on skeletal storage of mercury. However, as shown below, bone has been found (Bloch and Shapiro 1981) to contain a very large fraction of body burden only in chronic intoxication (MM). This is similar to the case of Pb intoxication (Casarett and Doull 1975). The long Hg excretion half time, ca 20 years, that has been reported in chronically intoxicated individuals (Sugita 1978), can be calculated from our MM model using a dimensional argument based on the perfusion of bone compared to soft tissue.

The "Mercury Wars" have continued for over 150 years because of the continued failure of mainstream medicine to understand MM and two of its principal characteristics: retention toxicity and bone storage of Hg, both of which are clarified by this paper. Diagnosis of MM hinges frequently on a test for urine Hg with reference (0-20 μg/L) and "toxicity" (>150 µg/L) ranges intended to detect acute intoxication. A 1938 study of MM in hatters, showed that the most intoxicated had the lowest urine Hg (Neal and Jones 1938), a condition now called "retention toxicity". According to our model, most MM subjects initially exhibit retention toxicity and very low urine Hg (i.e., 0-5 µg/d), and are storing Hg in bone, primarily due to inhalation intoxication. If the source of exposure is eliminated (environmental or amalgams), subjects recover from retention toxicity and exhibit elevated Hg excretion, sometimes for many years from bone storage (in agreement with both our measurements and model).

We describe enough of our model of MM to make clear how and why any person might enter MM without any idiosyncratic predisposition. Initially every human has some chronic exposure to ambient environmental Hg that does not exceed the person's excretory ability. If the chronic exposure rises due to any cause (workplace, dental amalgams, etc), a level of intake can be reached that exceeds the subject's excretory ability. Then, according to the model, the accumulation of Hg is not simply the difference between intake and the original excretory ability, but rapidly becomes much worse, approaching the total intake. The theoretical reason is that the rising soft tissue Hg burden inactivates the enzymes involved in excretory processes (presumably by bonding as Hg++ to SH groups). It is well

known that Hg strongly inhibits enzymes (Webb 1963), which can lead to diminished excretion, retention toxicity, and the associated diagnostic difficulties (i.e., low urine Hg concentrations). The decreased excretion and rise in blood levels are also associated with diffusion of Hg into the skeleton where large body burdens can accumulate in bone (Bloch and Shapiro 1981).

MATERIALS AND METHODS

The study group consisted of 18 subjects whose urine porphyrin patterns (MetPath Test 340, MetPath Labs, NJ) were highly abnormal (e.g., unusually high uroporphyrins). For initial enrollment in the study, it was required that the subjects have had a minimum of 5 occlusal amalgams and currently suffer signs and symptoms associated with MM. Their disorders included allergies, Alzheimer's, severe depression, diabetes insipidus, eating disorder, memory defect, multiple sclerosis (blind and paralyzed), premenstrual syndrome, schizophrenia, ataxia, and tremor. The purposes and procedures of the study were fully explained to each subject and informed consent was obtained from each.

Measurements of total daily urine Hg excretion determined Population identity of all 18 subjects at the start of the study to have been as follows (before any changes were made in initial amalgam status). The four subjects with all occlusal amalgams in place were in Population One. Population Two contained the other 14 subjects who had three categories of amalgam status described as follows: seven had had all amalgams replaced by other materials from 3 months to 10 years prior; three had only non-occlusal amalgams (having had all occlusal amalgams replaced with composite prior to the study); four possessed only aged amalgams installed 30 to 60 years earlier. Very old amalgams are largely depleted of Hg near the surface and a strong gradient in Hg concentration can be seen using PIXE (particle induced x-ray emission) if such amalgams are removed and sectioned.

Changes in amalgam status and other patient detoxification regimens were recorded and analyzed. Prior to the study, most subjects had adhered to a low dietary intake of Hg and some had attempted chelation. Urine Hg excretions in $\mu g/day$ were measured using MetPath (Teterboro, NJ) Standard Test No. 136. Creatinine or skilled supervision assured completeness of the 24 hr collections. Environmental Hg exposure was ruled out by Jerome Model 411 Mercury Vapor Analyzer (Arizona Instrument Co., Phoenix, Arizona, USA) and histories. For comparison to our results, data from a MetPath database (2083 tests) were normalized from 2083 to 18 to match the number of subjects in our study.

Table 1. Urine Mercury Distribution of MetPath Data Base (db) and 18 Subjects (S) (see note immediately below table).

Urine Hg	0-5 µg	6-15 µg	16-25 µg	26-60 µg
(db) µg/L	15	1	1	1
(S) µg/L	4	3	5	6
(S) µg/day	4	0	0	14
(S*) µg/day	2	0	0	16

Note the distribution of the normalized MetPath data base (1st row) suggests ca 83% of the patients were in retention toxicity (i.e., had very low urine Hg). Also, note that use of µg/d (obtained by multiplying µg/L by L/day) resolves our subjects (S) into two peaks showing clearly that 4 of the 18 were in "retention toxicity" (when all 4 of these low excreters still had amalgams) and that 14 were not in this state S* is the distribution after 2 of 4 subjects in Population One (urine Hg < 5) had amalgams replaced with composite and moved to Population Two (urine Hg > 25).

RESULTS AND DISCUSSION

Initially, urine Hg in four subjects (22%) was very low, falling between 0 and 5 µg/d (Table 1). All of these subjects were amalgam wearers and were identified as members of Population One. The 14 subjects in Population Two (urine Hg of 26-60 µg/d) consisted of the 10 who had all, or at least all of their occlusal, amalgams removed prior to the study and the 4 with very aged amalgams. During the study, 2 of the 4 subjects originally in Population One had all amalgams replaced with composites and urine Hg determined about 1 year later. These 2 subjects moved to Population Two (urine Hg of 26 - 60 µg/ day, Table 1) and appeared to have recovered from retention toxicity. This shows that low urine Hg alone does not rule out MM but, in fact, is diagnostic for MM if there has been occupational inhalation exposure (as in dentistry or industrial settings) or amalgam history! Authors who attribute such low urine Hg values in dentists to low intoxication may have ignored retention toxicity.

Our findings showed that total Hg (µg/d) rather than concentration (µg/L) was the quantity indicative of MM. The distinct bimodal distribution observed in µg/d urine Hg was not seen when results were expressed in µg/L [i.e., the distribution was a featureless continuum (Table 1)]. This difference could be attributed to a very high variability in 24-hr urine volumes in subjects with MM (i.e., the total urine output in our subjects ranged from 0.75 to 6.1 L/d). The wide range could tentatively be related to the effects of Hg on the hypothalamus

since variable polyuria seems common in MM.

Notice that the total range in urine Hg was from 0 to 60 µg/d, but none of the 18 values fell in l/3 of the range (i.e., between 5 and 25). This bimodal distribution is highly significant; the probability of any such pattern (i.e., all 18 values in a given 2/3 of the range and none in the remaining l/3) occurring purely by chance is simply that of 18 unrelated numbers all falling in 2/3 of the range (i.e., 2/3 multiplied 18 times) or p = (2/3)**18 <0.001. Thus, it is highly improbable that the subjects in this study could be a randomly chosen unrelated group; they clearly represent two distinct highly selected populations. Subjects in transition between States must be expected and would be seen if urine Hg assays were measured often enough (i.e., once per month).

The MetPath database contains 2083 Test-136 (urine Hg) results which we have normalized to 18 to permit certain simple comparisons with samples of 18 drawn from it. Before and after normalization, the database exhibits the steeply falling distribution characteristic of Population One (ca 85% below 5 µg/L, and < 5% above 26 µg/L). However, when expressed in these units, there will, of course, be some loss of information because the quantity of interest is the Hg excreted per. day, long known to be independent of urine volume. Of course, if 24-hr volumes (L/d) had been available for these 2083 patients, their µg/d could have been calculated. Therefore, we assumed 1 L/d, an amount not as far from reality as it would have been for our mostly Population Two subjects whose advanced MM produced variable polyuria. Notice that the normalized values for the four concentration ranges (bins) are 15, 1, 1, 1 for the database (db) in Table 1. This states that if samples of 18 were drawn at random from the db, the average value (p) for the highest bin (26-60) would be 1 (i.e.,~5.5%). However, our 18 patients had 14 (i.e., ~78%) in the highest bin; is it probable they could have been drawn as a sampie from the database? We show the answer is no. Using Poisson statistics to calculate the probability that a sample of 18 (from such a steeply falling distribution) can have x=14 (78%) in the highest bin if db samples average only 1 in this bin is: $P(x,\mu) = e^{-\mu}\mu^{x}/x!$ The probability is less than one in 100 million! [$P(14,1)= (e^{-1}) 1^{14}/14! = 1/(14!e) <10^{**}(-11)$].

Remembering that ca 90% of patients in the data base have amalgams, we conclude that many (possibly nearly all) of the db 85% (1771) below 5 µg/L may have been missed diagnoses because of retention toxicity (i.e., were truly Population One) and, hence, were quite different from our 18 patients of whom only 22% were in Population One. We conclude that the vast majority of urine Hg tests may result in missed diagnoses for lack of this paper's findings. Larger scale studies are encouraged.

Bone is a significant depot for Hg in MM. Evidence for this is the observation of high bone Hg measured by x-ray fluorescence in living dentists at scientific meetings. In 20% of 300 dentists, Hg in the skull temporal bone measured by x-ray fluorescence (xrf) ranged from 20, the method detection limit, to 200 ppm (Bloch and Shapiro 1981). It has been shown by animal studies that bone is the major reservoir for Hg in MM (Young et al. 1930). When inhalation intoxication occurs (as in dentists, or in mouth-breathing subjects with large amalgam eflux), 80% of the Hg^0 is absorbed by the lungs (Klaassen 1990) and circulates, diffusing out of the blood into all tissues for ~2 min until oxidation to Hg++ in erythrocytes terminates its ability to diffuse freely. A first order estimate of skeletal Hg stores in some working dentists is ~1g, found by multiplying the approximate concentration found by xrf, ~100 µg/g (i.e., 100 ppm), times 7 kg/skeleton. It is interesting to note that a very similar value (~0.6 g) for bone stores is obtained from our MM subjects. At urine Hg of ~ 40 µg/day, subjects in Population Two excrete ~15 mg Hg per year; multiplying by Sugita's (1978) 20 year excretion half-time, gives 300 mg Hg as one half the starting average body burden. These two cases suggest that Hg body burden in MM is much greater (-50 times) than the often cited unintoxicated soft tissue body burden value of 13 mg (Schroeder 1973; Casarett and Doull 1975). In view of the large body burden in MM, it is now clear why sweating, used for 300 years (Sunderman 1988), is the preferred excretion route for MM (i..e., to spare kidneys) instead of the chelation route so useful with the much smaller burdens encountered in acute intoxication (Wedeen 1983).

Note that our concern in this study was the common failure to diagnose MM due to misinterpretation of urine Hg test results. Hence, we did not measure the fecal and sweat routes of excretion. Although these latter routes offer greater potential for detoxification, their testing is complex, inaccurate, expensive, slow, difficult to interpret, and they have no value in clinical diagnosis at first presentation as considered here. We anticipate that x-ray fluorescence (xrf) measurements of skeletal Hg at mid-tibia or skull temporal bone can offer a quick simple check on detoxification progress of MM patients with large skeletal burdens. Of course, xrf is only likely to become widely available after large numbers of such patients are recognized (i.e., 80% of the four million US Alzheimer patients who are estimated to have amalgam Hg as a possible etiological factor (Pendergrass and Haley 1997)). Understanding retention toxicity and bone storage of Hg will result in successful diagnosis of MM. This in turn will enable study of MM and testing the validity of reported associations with serious idiopathic disorders.

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