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Effects of Elemental Mercury Exposure at a Thermometer Plant

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This study compares 84 mercury-exposed workers at a thermometer manufacturing facility with 79 unexposed workers for evidence of chronic mercury toxicity. Personal breathing-zone air concentrations of mercury ranged from 25.6 to 270.6 $\mu g/m^3$ for thermometer workers. Urinary mercury levels in the study population ranged from 1.3 to 344.5 $\mu g/g$ creatinine, with eight (10%) participants exceeding 150 $\mu g/g$ creatinine and three workers exceeding 300 $\mu g/g$ creatinine, which indicates increased absorption of mercury among the thermometer workers. All urine mercury levels in the comparison group were compatible with normal background levels in unexposed adults (<10 $\mu g/g$ creatinine). Thermometer plant workers reported more symptoms than did controls; in general, these differences were not statistically significant and could not be specifically associated with mercury exposure. Static tremor, abnormal Romberg test, dysdiadochokinesia, and difficulty with heel-to-toe gait were more prevalent among thermometer workers than control workers, which could not be associated with recent mercury exposure; there was some suggestion of an association with chronic exposure. There were no intergroup differences for the standard clinical tests of renal function except for a significantly higher mean specific gravity among the thermometer workers. A positive correlation was found, however, between urinary N-acetyl-b-D-glucosaminidase (NAG) and urinary mercury. There was no consistent evidence for intergroup differences in proximal renal tubule function, as measured by urinary β_2-microglobulin (B2M) or retinol binding protein (RBP).

Key words: occupational diseases, kidney diseases, neurologic manifestations, N-acetyl-b-D-glucosaminidase, β_2-microglobulin, retinol binding protein, SIC 3829

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INTRODUCTION

Elemental mercury can enter the body through the lungs following inhalation of the vapor, through the skin by direct contact, or through the digestive system [OSHA, 1975]. Acute or short-term exposure to high concentrations of mercury causes tightness and pain in the chest, difficulty in breathing, coughing, inflammation of the mouth and gums, headaches, and fever [OSHA, 1975; NIOSH, 1981]. Acute mercury poisoning has become relatively rare in industry in recent years [Harrington and Gill, 1983].

Chronic exposure to lower concentrations of elemental mercury is more common. Manifestations of chronic mercury poisoning are protean and include kidney damage, neurological toxicity (especially tremor), inflammation of the gums, metallic taste, increased salivation, weakness, fatigue, insomnia, allergic skin rash, loss of appetite and weight, and impaired memory [OSHA, 1975; NIOSH, 1981]. These symptoms generally occur gradually and may be associated with personality changes such as irritability, temper outbursts, excitability, shyness, and indecision [OSHA, 1975; NIOSH, 1981]. Finally, there is theoretical potential for adverse reproductive effects [Clarkson et al., 1972; Koos and Longo, 1976].

Occupational exposures to mercury are usually assessed by monitoring urine mercury levels. The reported correspondence of air levels (in $\mu g/m^3$) to urine levels (in μg/liter) varies from a 1:1 ratio to a 1:2.6 ratio. There is no generally accepted value, although a World Health Organization study group used 1:2 (i.e., exposure to an air level of 50 $\mu g/m^3$ would tend to result in a urine level of 100 μg/liter on the average) [WHO, 1980].

Classically, air levels of mercury vapor below 100 $\mu g/m^3$ were thought to be safe [NIOSH, 1973], but recent data suggest that renal and neurobehavioral effects may appear with air levels in the 50–100 $\mu g/m^3$ range, and there are reports of effects at even lower levels [WHO, 1980]. Correspondingly, toxicity was not thought to occur in individuals with urinary levels of mercury below 300 μg/liter, but recent reports suggest that neurobehavioral and subclinical renal effects may be detected in individuals with urinary levels as low as 50–100 μg/g creatinine [Roels et al., 1985].

The National Institute for Occupational Safety and Health (NIOSH) and the American Conference of Governmental Industrial Hygienists (ACGIH) currently recommend that exposure to inorganic mercury be limited to 50 $\mu g/m^3$ as an 8-hr time-weighted average (TWA) [NIOSH, 1973; ACGIH, 1982]. The Occupational Safety and Health Administration (OSHA) standard for inorganic mercury in effect at the time of the study was a ceiling level of 100 $\mu g/m^3$ [OSHA, 1980]. There are no established standards for urinary levels of inorganic mercury.

In this article, we report the results of a study we conducted in 1984 at a small, rural manufacturer of mercury thermometers and glass scientific products. In this study, we assessed self-reported symptom prevalences, neurological status (by physical exam), and renal status. We also assessed performance on a battery of neurophysiological tests, which will be reported separately.

MATERIALS AND METHODS

Participation in the study was offered to all current thermometer manufacturer employees and to former workers who had recently left employment; 122 individuals

were eligible for participation. The comparison population worked at a nearby electronic instrument manufacturer, which employed 98 persons at the time this group was surveyed. No control participant had ever worked at the thermometer manufacturing facility, nor did any report previous mercury exposure.

The environmental survey entailed area and personal breathing-zone sampling for mercury vapor. This sampling was conducted for 7–8 hr over the work shift and provided full-shift TWA concentrations. The environmental samples were collected on hopcalite sampling medium using low-volume gas sampling pumps calibrated at a flow rate of 200 cc/min. The samples were analyzed for mercury by flameless absorption spectroscopy [NIOSH, 1984]. Ten blank samples were also submitted for analysis as a quality assurance procedure; all were reported as negative for mercury. In addition, a hand-held mercury vapor detector (limit of detection 10 $\mu g/m^3$) was used to pinpoint localized sources of mercury and areas of potential contamination.

The medical portion of the study consisted of a questionnaire and a neurological exam. Eighty-four thermometer plant employees completed the questionnaire, and 83 underwent the neurological examination; 79 workers at the comparison facility completed the questionnaire and underwent the examination. The questionnaire obtained demographic information, detailed occupational history, medical history, and a symptom survey. The examination included assessments for evidence of abnormal ocular movements, tremor, dyscoordination or balance disturbance, and elicitation of deep tendon reflexes. An individual was termed hyperreflexic or hyporeflexic if at least two reflexes (e.g., patellar and biceps) were symmetrically increased or diminished, respectively. All examinations, with one exception, were performed by the same examiner, who is board certified in internal medicine. The examiner was unaware of job status among thermometer plant workers, but knew whether examinees worked at the control or thermometer plant. We also administered a battery of three neurophysiological tests (for tremor, vibratory sensation, and grip strength), which will be reported separately.

We obtained blood and urine specimens to assess renal function. We measured urinary levels of mercury [Littlejohn et al., 1976], total protein [Cooper, 1977], albumin [Fielding et al., 1983], N-acetyl-b-D-glucosaminidase (NAG) [Leaback and Walker, 1961], β_2-microglobulin (B2M) (Pharmacia Diagnostics Phadebas, Uppsala, Sweden), and retinol binding protein (RBP) (Calbiochem-Behring, LaJolla, CA). We also measured specific gravity [Roth, 1976] and urinary creatinine [Larsen, 1972]. In the serum, we measured creatinine [Larsen, 1972], B2M (Pharmacia), and RBP (Calbiochem-Behring) for clearance ratio calculations. Finally, we measured urinary levels of cadmium [Pruszkowska et al., 1983], arsenic [Ediger, 1975; Slavin et al., 1983; Voellkopf and Grobenski, 1984], and lead [Ediger, 1975; Slavin et al., 1983; Voellkopf and Grobenski, 1984] to assess potential confounding exposure to these other metals. The urine specimen was a morning first-void specimen that was collected at home in a clean plastic container that was sealed in plastic wrap until the time of collection. The specimen was delivered to the survey trailer by the participant at the start of the work shift, prior to entering the plant. Processing of the specimens was performed in the trailer in a manner that minimized the possibility of contamination with any mercury inadvertently brought into the trailer from the plant. Analyses were performed at the Clinical Biochemistry Laboratory, Center for Environmental Health, Centers for Disease Control. We collected blood specimens from 83 thermometer plant employees and from 74 control plant employees. We obtained urine specimens

TABLE I. Results of Environmental Sampling, Thermometer Plant (Mercury Vapor as an 8 hr Time-Weighted Average [TWA])*

Sample type/location	No. samples	Mean (range)[a]	No. (%) exceeding NIOSH REL
Personal[b]/thermometer bldg.	17	75.6 (25.6–270.6)	9 (53)
Personal/glass bldg.	10	9.3 (2.8–24.4)	0
Area[c]/thermometer bldg.	11	56.7 (23.7–118.5)	7 (64)
Area/study trailer	2	22.5 (21.5–23.4)	0

*Then current OSHA Permissible Exposure Limit (PEL) = 100 $\mu g/m^3$, ceiling; NIOSH Recommended Exposure Limit (REL) = 50 $\mu g/m^3$, 8 hr TWA.
[a]$\mu g/mg^3$.
[b]Personal breathing-zone sample.
[c]General area sample.

from 80 thermometer plant employees and from 70 control plant employees. We could not perform all intended assays on all urine specimens because some individuals' specimens did not contain a sufficient volume of urine. One thermometer plant worker did not provide sufficient urine to measure a urinary creatinine level; consequently, a creatinine-standardized urinary mercury level could not be calculated, and results for this individual are not reported here or included in the analyses.

Based on industrial hygiene data and the physical layout of the plant, jobs at the thermometer plant were divided into four categories: 1) mercury (i.e., thermometer) process; 2) glass process and general labor, located in the thermometer building; 3) glass process, located in an adjacent, attached building; and 4) other miscellaneous. We also constructed an index to estimate cumulative mercury exposure over time. To each of the four job categories, we assigned a weighting factor calculated as the mean urine mercury level for all current workers in that category divided by the mean urine mercury for all employees at the thermometer plant. For each employee, we then calculated his or chronic exposure index by summing the time (in months) spent in each job category multiplied by the weighting factor for that category. Because there was no exposure to mercury at the control plant, this index could not be calculated for the comparison population.

Statistical analysis was performed on an IBM mainframe computer using the Statistical Analysis System (SAS) programs (SAS Institute, Cary, NC). Statistical significance was indicated by a two-tailed p value <0.05 or by Miettinen test-based 95% confidence intervals (95% CI) that excluded 1.00 [Schlesselman, 1982]. The Wilcoxon rank sum test was employed when outcome variables were not normally distributed.

INDUSTRIAL HYGIENE RESULTS

We collected 40 air samples at the thermometer facility (Table I). Seven (64%) of 11 area samples exceeded the NIOSH recommended exposure limit (REL), and one (9%) exceeded the OSHA permissible exposure limit (PEL) then in effect. Personal breathing-zone levels for nine (53%) of 17 monitored mercury workers exceeded the NIOSH REL, and four (24%) exceeded the OSHA PEL. None of the glass process workers exceeded either criterion. Finally, we obtained two area samples in the survey trailer; these averaged 22.5 $\mu g/m^3$ and suggested that, despite the brief

TABLE II. Sociodemographic Characteristics of 84 Thermometer Plant Workers and 79 Control Plant Workers

	Thermometer plant (72 [86%] female)			Control plant (69 [87%] female)		
	Age range (years)	No.	Percent	Age range (years)	No.	Percent
Age distribution	<20	6	7	<20	2	3
	20–29	26	31	20–29	35	44
	30–39	22	26	30–39	19	24
	40–49	22	26	40–49	18	23
	50–59	5	6	50–59	2	2
	≥60	3	4	≥60	3	4
Overall	18–68 years (mean = 35)			17–63 years (mean = 33)		
Education	8–16 years (mean = 12)			8–16 years (mean = 12)		
Employment tenure	mean = 65 months (s.d. = 48.8)			mean = 63 months (s.d. = 48.1)		
Current smokers	41 (48%)			40 (51%)		

duration of the study, some contamination may have occurred from workers inadvertently bringing mercury in on their shoes and clothes.

Environmental sampling at the control facility was conducted with a direct-reading mercury vapor detector. No mercury was detected (limit of detection 10 $\mu g/m^3$). We also obtained five full-shift area samples for airborne lead in the vicinity of soldering pots. None of the five samples had detectable amounts of lead (limit of detection 2 $\mu g/m^3$).

MEDICAL/EPIDEMIOLOGIC RESULTS

Any eligible individual who at least completed the questionnaire was considered to be a study participant. Eighty-four thermometer plant employees participated, including two former workers (aged 28 and 30 years) who had recently left employment; 79 control facility employees participated. Participation rates were 69% and 81%, respectively. Sociodemographically, the two groups were very similar. They resided in neighboring rural areas and had similar age and sex distributions, educational attainment, length of employment, and prevalence of smokers (Table II).

Urinary Mercury Levels

We measured urine mercury (standardized to urinary creatinine) for 79 thermometer plant workers and 70 control plant workers (Table III). The mean urinary mercury level for thermometer plant workers (73.2 μg Hg/g creatinine [s.d. = 69.7]) was significantly higher than that for control plant workers (4.2 μg Hg/g creatinine [s.d. = 2.3]) ($p < 0.0001$, Wilcoxon rank sum test). All urinary mercury levels at the control plant were compatible with "normal" levels for unexposed individuals (<10 μg/g creatinine). The mean urinary mercury level at the thermometer plant was higher for males than for females (96.2 vs. 69.4), but the difference was not statistically significant. Mean urinary mercury was not affected by smoking status, age, educational level, or total duration of employment. There was a strong correlation between personal environmental monitoring results and urinary mercury values. For

TABLE III. Urinary Mercury Levels by Current Job Category*

	Mean (s.d.) (μg Hg/g creatinine)	Range (μg Hg/g creatinine)
Control plant		
All participants (n = 70)	4.2 (2.3)	nd[a]–10.0
Thermometer plant		
All participants (n = 79)[b]	73.2 (69.7)[c]	1.3–344.5
Mercury process (n = 29)	118.2 (87.5)[d]	27.2–344.5
Nonmercury process (n = 50)	47.0 (38.2)	1.3–156.3
Glass process		
Thermometer bldg. (n = 18)	65.4 (29.6)	19.0–156.3
Glass bldg. (n = 24)	30.3 (32.5)	1.3–120.5
Other misc. (n = 8)	56.0 (52.2)	1.9–135.6

*Normal range for unexposed adults <10 μg/g creatinine.
[a]Non-detectable (limit of detection 1.0 μg/liter).
[b]Eighty thermometer plant employees provided urine specimens. One provided insufficient volume to measure urinary creatinine, and a creatinine-standardized urinary mercury level could not be calculated; results for this individual are not reported here or included in the analyses.
[c]$p < 0.0001$, Wilcoxon rank sum test; comparison with workers from control plant.
[d]$p < 0.0001$, Wilcoxon rank sum test; comparison with non-mercury process workers.

the 25 workers from whom we obtained both urinary mercury levels and breathing-zone mercury vapor levels, the correlation coefficient (Pearson's r) for the two measurements was 0.88 ($p = .0001$) (Fig. 1). Because much of this association might be attributable to the results from one individual with both very high urinary mercury and breathing-zone vapor levels (see Fig. 1), the analysis was rerun after excluding this individual. The correlation remained strong ($r = 0.74$, $p = 0.0001$).

Mean urinary mercury levels for workers grouped according to current job category are shown in Table III. Mercury process workers had significantly higher urine mercury levels than did non-mercury workers ($p < 0.0001$, Wilcoxon rank sum test). Urinary mercury level was not significantly associated with tenure in current job. There was, however, a modest positive correlation of urine mercury with the calculated exposure index ($r = 0.23$, $p = 0.05$).

Symptoms

The questionnaire asked specifically about the presence of 28 symptoms. The most frequently reported symptom among thermometer workers were headache (29% of interviewees), difficulty sleeping (25%), nervousness (23%), skin rash/sores (20%), emotional lability (18%), and difficulty with memory or concentration (16%). Headache (24%), nervousness (22%), emotional lability (18%), and skin rash/sores (14%) were also the most frequently reported symptoms among control plant workers. Overall, thermometer plant workers reported a significantly greater mean number of symptoms (2.9/person) than did control plant workers (1.9/person) ($p < 0.02$, Wilcoxon rank sum test). When the prevalences of specific symptoms in the two groups were compared, prevalences among thermometer workers exceeded those among control plant workers for 21 of the 28 symptoms queried. Symptom prevalences among control plant workers exceeded those among thermometer workers for only three symptoms and were approximately equal for the remaining four symptoms. Prevalence differences were statistically significant for only two symptoms, metallic

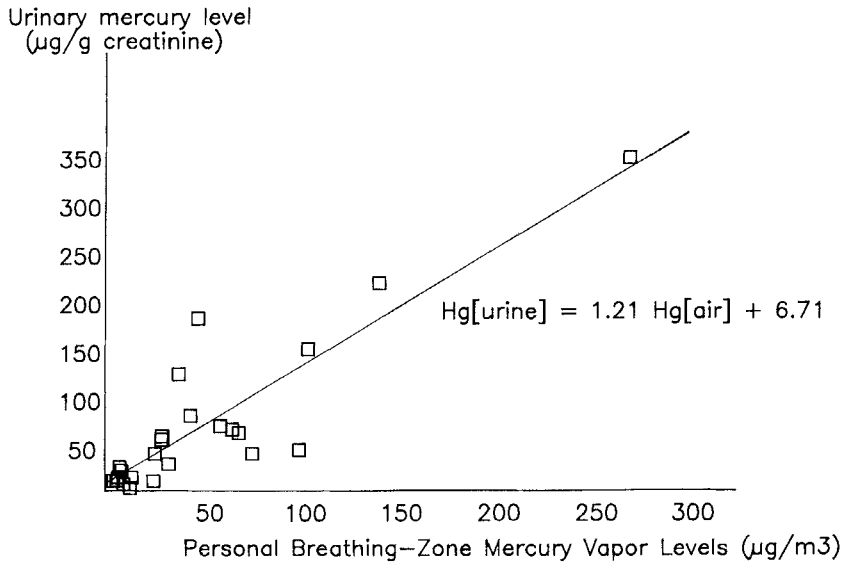

Fig. 1. Plot of urinary mercury levels and results of personal air sampling.

taste (relative risk [RR] = undefined [no control plant workers reported this symptom], p = 0.003, two-tailed Fisher's exact test) and difficulty sleeping (RR = 2.82, 95% CI 1.34, 5.95), but this overall pattern of greater symptom prevalence among thermometer workers was significant ($p < 0.02$, normal approximation to binomial). When analysis was limited to symptoms particularly suggestive of mercury toxicity, we found a similar (but not statistically significant) pattern, with greater symptom prevalences among thermometer workers for 12 of 17 symptoms and lower prevalences for only two of 17.

We also compared mean urine mercury levels and mean chronic exposure indices for thermometer workers according to symptom status. This analysis was restricted to the thermometer plant employees because: 1) all control plant personnel had urine mercury values at or below 10 µg/g creatinine, and any symptomatic control plant worker would necessarily have a low urine mercury and would tend to mask any association of symptoms with urine mercury level among the thermometer manufacturer employees; and 2) the chronic exposure index cannot be calculated for the control plant workers. No overall patterns of association were found between symptom prevalences and either urinary mercury level or the chronic exposure index. Only one individual symptom (chest pain/tightness) was associated with a significant difference in mean urine mercury level (in this instance, lower for symptomatic workers). A significantly higher mean index was found only for those reporting shortness of breath, chronic cough, and diarrhea, and none of these three symptoms would be particularly suggestive of chronic mercury toxicity.

Neurological Examination

The most commonly noted findings in the thermometer plant population were hyporeflexia (24% of the 83 examined), static tremor (19%), and difficulty with heel-to-toe gait (15%). Hyporeflexia (43% of 79 examined), static tremor (13%), and

TABLE IV. Mean Urinary Mercury Levels and Mean Chronic Exposure Index Among Thermometer Plant Workers and Control Plant Workers According to Results of Neurologic Examination

Neurological finding	Thermometer workers/ control workers[a] with abnormality	Mean urinary Hg[b] (Abnormals/normals)	Mean exposure index[b] (Abnormals/normals)
Rest tremor	1/0	42.1/74.1	228.2/73.0
Static tremor	16/10	94.2/68.4	99.0/69.1[c]
Intention tremor	1/0	72.1/73.7	50.0/75.2
Finger-to-nose	0/0	—/73.2	—/74.6
Dysdiadochokinesia	3/0	78.3/73.5	195.0/70.4[c]
Hyporeflexia	20/34[d]	58.9/77.2	58.0/78.9
Hyperreflexia	3/0	159.4/69.8	127.1/72.6
Gait disturbance	0/0	—/73.2	—/74.6
Heal-to-toe walk	12/2[d]	73.7/74.8	109.4/68.6[c]
Abnormal Romberg	3/0	56.0/74.4	96.2/74.1

[a]Thermometer workers, 83 examined; controls, 79 examined.
[b]Among thermometer workers only.
[c]$p < 0.05$, Wilcoxon rank sum test.
[d]$p < 0.05$, Fisher's exact test.

difficulty with heel-to-toe gait (3%) were the only findings in the control plant population. Thermometer workers were significantly more likely to have an abnormal heel-to-toe gait (RR = 5.78, 95% CI 1.63, 20.50) and were less likely to be hyporeflexic (RR = 0.56, 95% CI 0.36, 0.87). For other components of the examination, differences between the two groups were not statistically significant, but again there was an overall pattern of higher prevalences of abnormal findings among thermometer workers, including three with positive Romberg tests, three with dysdiadochokinesia, and one each with resting and intention tremor (some persons had more than one abnormality). No other abnormalities were noted among control plant workers.

Among thermometer company workers, there were no significant differences in mean urine mercury levels between those with and those without any of the neurological examination abnormalities nor any overall pattern of higher urine mercury levels among those with abnormal findings (Table IV). Workers with static tremor, dysdiadochokinesia, or difficulty with heel-to-toe walk did, however, have significantly higher mean values for the exposure index ($p < 0.05$, Wilcoxon rank sum test) (Table IV). Also, there was a suggestion of an overall pattern of higher mean values for the index in those with other abnormal findings.

Biologic Markers and Renal Assessments

The results of the renal status assessments are shown in Table V. With the exception of specific gravity, there were no significant differences between the thermometer and control plant workers in mean values of any renal marker. Thermometer plant workers had a higher mean urinary B2M, but the difference was entirely accounted for by one worker with a very high value (7,674 μg/g creatinine). Thermometer plant workers had greater prevalences of abnormal (elevated) levels of serum B2M (RR = 6.24, 95% CI 0.79, 49.55) and urinary NAG (RR = 2.46, 95%

TABLE V. Results of Renal Function Markers, Thermometer Workers vs. Control Plant Workers

Test (reference range)	Mean value (std. dev.) and proportion abnormal[a]			
	Thermometer workers		Control plant workers	
NAG (0–1.48 μg/g creatinine)	0.81 (0.73)	6/56	0.71 (0.65)	2/46
Urinary B2M (7–200 μg/g creatinine)	164 (867.6)	1/77	89 (70.3)	3/63
Urinary RBP (0.03–0.19 μg/ml)	0.14 (0.25)	13/78	0.14 (0.25)	7/64
Serum B2M (<2,000–<3,100 μg/liter)[b]	1,613 (409.4)	7/83	1,536 (317.1)	1/74
Serum RBP (3.0–6.0 mg/dl)	6.2 (1.4)	44/83	6.2 (1.5)	42/74
Total protein (28–244.8 mg/g creatinine)	92.0 (99.2)	1/79	148.2 (472.9)	1/70
Albumin (2.02–12.01 mg/g creatinine)	8.4 (11.1)	9/77	7.1 (7.7)	5/64
Specific gravity (1.001–1.035)	1.020 (0.008)[d]	0/79	1.017 (0.006)[d]	0/70
Urinary creatinine (N/A)[c]	143 (69.1)	—[c]/79	129 (66.8)	—[c]/70
Serum creatinine (0.4–1.5 mg/dl)	0.9 (0.14)	0/83	0.9 (0.19)	0/74

[a]Number abnormal/number of samples examined (some individuals did not provide enough urine for all tests to be run).
[b]Normal range varies with age.
[c]Not applicable. Normal range for urinary creatinine is based on 24-hr collection of urine, which was not performed in this study. Results reported in mg/dl.
[d]$p < 0.05$, Wilcoxon rank sum test.

CI 0.55, 10.96), RBP (RR = 1.52, 95% CI 0.65, 3.56), and albumin (RR = 1.50, 95% CI 0.53, 4.21), but none of these differences was statistically significant.

Urinary NAG levels were positively correlated with urine mercury (standardized to urinary creatinine) levels. This was true both for the entire study population (Pearson's r = .36, p = .0002) and when the analysis was restricted to thermometer plant workers (r = .48, p = .0002). Regression analysis indicated that this relationship persisted after controlling for age, chronic exposure index, and known diabetes mellitus. There were no significant associations for any other biological marker with the creatinine-standardized urinary mercury levels.

Among thermometer plant workers, there were no significant associations between any of the urinary markers and the chronic exposure index. Apparently significant correlations of urinary B2M (r = 0.25, p = 0.03) and total urinary protein (r = 0.26, p = 0.02) with the exposure index were attributable to the results of one individual with extremely elevated values for these markers. Similarly, an apparently significant correlation between serum B2M (r = 0.31, p = 0.005), and the exposure index was primarily attributable to the confounding factor of age. For none of the biological measurements were abnormal (elevated) values associated with a higher exposure index, although there was a tendency in this direction for NAG, and one individual with substantially elevated urinary levels of B2M, RBP, total protein, and

albumin did have the fourth highest index in the cohort. Finally, all levels for urinary cadmium and lead in each group were compatible with background levels for unexposed populations (0.0–5.0 ng/ml and 0.0–80.0 ng/ml, respectively), as were all but two levels for urinary arsenic (normal range 0.0–80.0 ng/ml), which would exclude these heavy metals as likely confounders for any effects otherwise attributable to mercury.

DISCUSSION

The environmental data demonstrate significant exposure to inorganic mercury vapor at the thermometer plant. Many samples, both personal and area, exceeded the NIOSH recommendation of 50 $\mu g/m^3$ (TWA) and/or the then current OSHA standard of 100 $\mu g/m^3$ (ceiling). The measurements obtained in the survey trailer suggest that some contamination of the trailer with mercury occurred during the short duration of the study and support the possibility of off-site contamination by mercury inadvertently carried out of the plant on the workers' shoes, clothing, or persons. This concern has been addressed in a companion study [Hudson et al., 1987].

The urine mercury levels indicate substantial absorption of mercury in the exposed population and demonstrate greater absorption among mercury process workers (who presumably had higher exposure than did glass workers) at the thermometer company. Mercury levels among control plant workers were all compatible with normal background levels in unexposed adults (<10 $\mu g/g$ creatinine). Despite the documented levels of exposure among the thermometer company personnel, urine mercury levels were not exceptionally high. Mean (and median) levels were below 100 $\mu g/g$ creatinine. Although the correlation of signs of chronic mercury toxicity with urinary mercury levels is notoriously inconsistent and unpredictable, effects of mercurialism are usually reported at urinary levels in the range equivalent to 150–300 $\mu g/g$ creatinine or higher. Only 10% of the study population exceeded the lower limit of this range, and only three individuals exceeded 300 $\mu g/g$ creatinine. Finally, urine mercury levels generally reflect relatively recent exposures (within 2–3 months of the sampling time) and are not necessarily reliable indicators of long-term exposure [Gompertz, 1982].

In the symptom survey, only two symptoms suggestive of mercury toxicity were significantly associated with the thermometer plant group (metallic taste and difficulty sleeping), and this could be a purely statistical effect of our multiple comparisons. To attempt to compensate for such a phenomenon, we also looked at the overall pattern of the symptom prevalences, which did suggest higher rates of symptoms among thermometer workers. Within this group, however, we could not specifically associate symptoms (individually or overall) with exposure to mercury, whether estimated by urine mercury level or the chronic exposure index.

When compared with control plant workers in the neurological examination, thermometer plant workers had notably higher prevalences of certain abnormalities (static tremor and difficulty with heel-to-toe gait) and an overall tendency for higher rates of positive findings (including other cerebellar signs). The presence of examination abnormalities could not be clearly associated with recent mercury exposure, as measured by urine mercury level, but there was evidence of an association between examination abnormalities and the exposure index, suggesting some chronic toxicity. Prominent neurological abnormalities would not be expected at the mercury levels encountered by participants in this study, although more subtle effects have been

reported [Roels et al., 1985; Piikivi et al., 1984]. The increased prevalence of hyporeflexia in the control plant group and the generally high prevalences in both groups are not readily explained. The intergroup differences may represent some secular trend in the assessments of the examiner, and the overall frequencies may reflect too loose a definition for hyporeflexia.

Classically, chronic renal damage from elemental mercury toxicity has been considered to manifest itself by albuminuria or a nephrotic syndrome, with only minimal or late effects on creatinine clearance or tubular functions [NIOSH, 1973]. More recently, it has been recognized that there are two types of proteinuria associated with mercury toxicity; a glomerular proteinuria and a tubular proteinuria [Morgan, 1982]. The former is characterized by leakage of serum proteins (predominantly high molecular weight) through damaged glomeruli and is thought to represent an idiosyncratic immune-complex glomerulonephritis [Tubbs et al., 1982]. The latter consists of a variety of proteins and enzymes. Many of these markers are low-molecular-weight proteins (e.g., B2M and RBP), normally filtered through the glomerulus and then reabsorbed in the proximal tubule. Others (enzymes such as NAG) are released directly into the urine from damaged proximal tubule cells. Thus, this tubular proteinuria may reflect either dysfunction of or damage to proximal tubule cells [Morgan, 1982] and may be a more sensitive indicator of mercury toxicity.

Elevated urinary NAG levels have been demonstrated in a variety of clinical states, including drug toxicity, early rejection of transplants, heavy metal toxicity, diabetes, and hyperglycemia [Price, 1982], and may be more reflective of current activity of an injurious process than of chronic damage. Elevated urinary B2M levels have been demonstrated in many similar circumstances but may be more representative of chronic damage than of acute activity. Also, being freely filtered, urinary B2M levels are more sensitive to serum levels. RBP is thought to behave like B2M, except that it is not hydrolyzed by acid urine and, thus, is less susceptible to destruction in the bladder or following collection [Bernard et al., 1982]. Urinary pH measurements were not recorded, but aliquots of urine to be assayed for B2M were buffered with sodium carbonate (to an approximate pH of 7.5) after delivery to the survey trailer. This procedure would not have prevented any acid hydrolysis of B2M while urine was in the bladder overnight or while urine was being transported to the trailer.

The data demonstrate evidence of a dose-response relationship between urine mercury level and urinary NAG level and suggest an elevated relative risk for an abnormal NAG level among the mercury-exposed workers. No such findings were shown for urinary B2M, RBP, or any of the standard clinical measures of renal status. This is not inconsistent toxicologically because urine mercury is a measure of recent exposure and is less reliable as a measure of long-standing exposure or body burden. Thus, current exposure could well be associated with a measure of acute damage (NAG) without being associated with measures of chronic damage (B2M, RBP). The long-term index of exposure was not clearly associated with any measure of renal damage or dysfunction at the levels and duration of mercury exposure encountered in this population. Thus, mercury exposures sufficient to produce mild tubular damage (as indicated by the NAG results) might not be severe enough to overcome compensatory mechanisms or reserve capacity and manifest as tubular dysfunction (as would be indicated by increased excretion of B2M or RBP). These results are consistent with others reported recently [Stonard et al., 1983; Meyer et al., 1984]. It is not clear

whether acid hydrolysis of B2M (alluded to previously) occurred or affected study results. If it had, the effect would have been to reduce observed urinary B2M levels, perhaps masking an association with mercury exposures. Were this the case, it might be suggested by discordances between B2M and RBP findings, e.g., associations of urinary RBP with mercury exposure, but not of urinary B2M with exposure. This did not occur, although there was discordance to the extent that individual urinary B2M and RBP levels were not well correlated (as might have been expected), and there were considerably more elevated urinary RBP levels than elevated urinary B2M levels (Table V).

The lack of an association between serum B2M levels and any measure of mercury exposure is worthy of mention. Such associations have been reported in workers exposed to other heavy metals (e.g., cadmium and uranium) [Thun et al., 1985] and might have been expected for mercury as well.

Finally, one worker had substantial elevations in several of the renal function markers. The same individual also demonstrated several abnormalities on neurological examination and quite likely represented a true case of chronic mercurialism. Nevertheless, it should be noted, with respect to the renal markers reported here,that we are considering primarily subclinical effects. Even when there were associations between measures of renal status and indicators of exposure, test results remained, for the most part, within normal ranges. Furthermore, it is by no means clear at this time whether such elevations, when present, represent mere biochemical abnormalities or whether they have clinical significance to the individual, either currently or as predictors of future, more serious renal disease.

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