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ELEMENTAL MERCURY EXPOSURE:
CORRELATION OF URINE MERCURY INDICES WITH ULNAR NERVE CONDUCTION STUDIES



Running Title: ELEMENTAL MERCURY NEUROPATHY

Authors: Simon P. Levine
G. David Cavender
Gary D. Langolf
James W. Albers

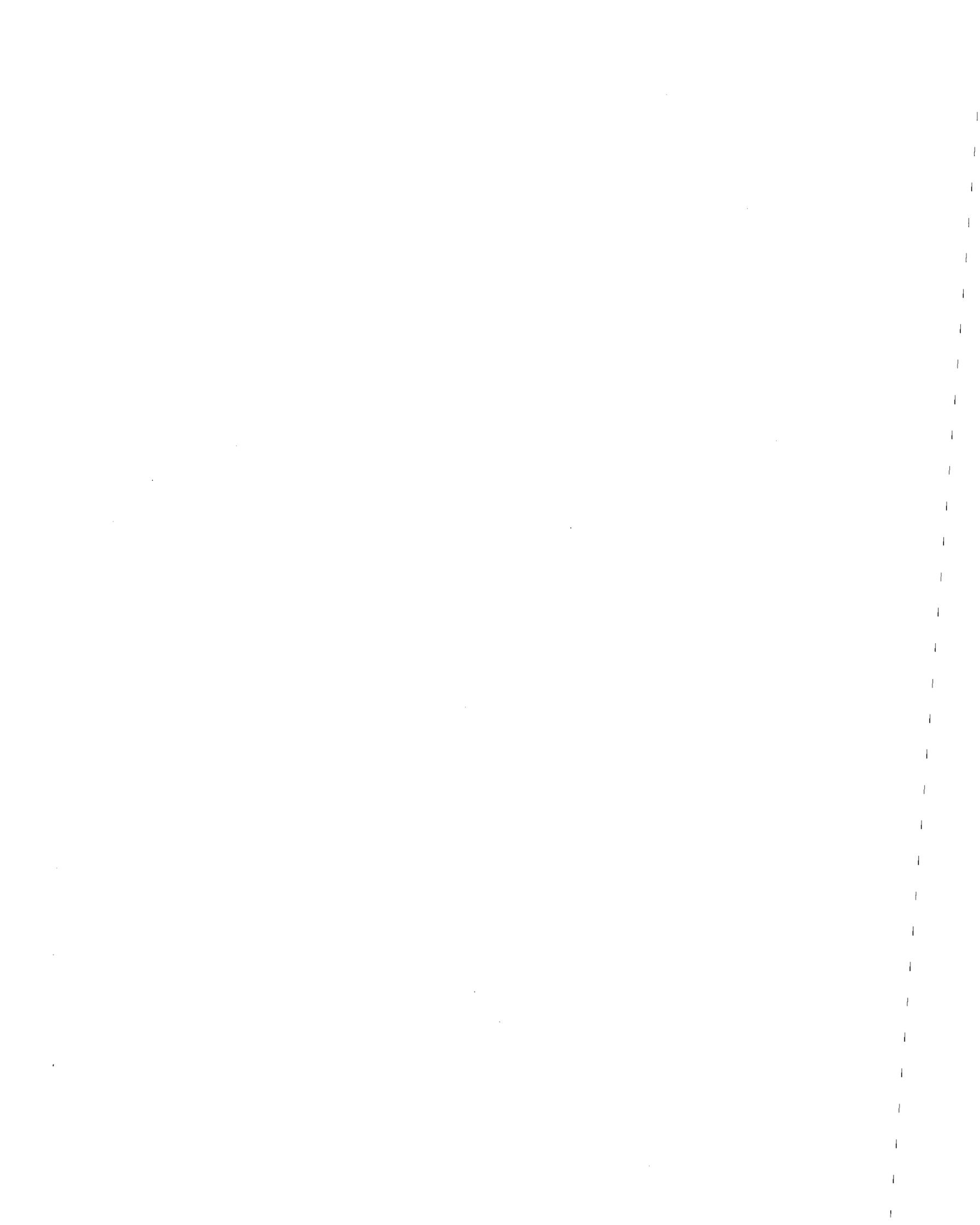
From the Department of Physical Medicine and Rehabilitation, Department of Industrial and Operations Engineering, and the Electroneuromyographic Laboratory, University of Michigan, Ann Arbor, Michigan.

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Reprint request to Simon Levine, Department of Physical Medicine and Rehabilitation, University of Michigan Medical Center, Ann Arbor, Michigan 48109.

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16. Abstract (Limit: 200 words) An electrophysiological evaluation was made of the ulnar nerve in 18 men who were exposed to elemental mercury (7439976) vapor in the course of their jobs at a mercury cell chlorine plant. The men averaged 31 years of age, ranging from 19 to 56. Urinary mercury levels were determined routinely at this facility and were thus available for 3 years prior to the evaluation of the ulnar nerve. Conventional techniques were used to measure compound muscle action potential and sensory nerve action potential (SNAP) negative peak amplitudes, motor and sensory distal latency, and maximum motor conduction velocity. Abnormal nerve conduction studies were obtained in five subjects, with three having prolonged sensory distal latency, one having prolonged motor distal latency and one having both prolonged motor and sensory distal latencies with a low normal SNAP amplitude. Over half of the mercury levels were significantly higher in this abnormal group. The highest correlation obtained was between sensory latency and the number of months urine mercury exceeded 0.50 milligrams/liter. The authors conclude that exposure to elemental mercury can affect both motor and sensory peripheral nerve conduction and that the degree of involvement can be related to time integrated urine mercury levels.			
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SUMMARY

Nerve conduction tests were performed on the right ulnar nerve of factory workers exposed to elemental mercury vapor. Time integrated urine mercury indices were used to measure degree of exposure. Workers with prolonged distal latencies had significantly higher urine mercury levels when compared to those with normal latencies. Significant correlations between increasing urine mercury levels and prolonged motor and sensory distal latencies were established. We conclude that elemental mercury can affect both motor and sensory peripheral nerve conduction and that the degree of involvement can be related to time integrated urine mercury levels.

Introduction

The neurologic manifestations of inorganic mercury intoxication are well documented. These include symptoms (weakness, numbness, paresthesias, muscle cramps) and signs (muscle atrophy, diminished muscle stretch reflexes, paresis, fasciculations, sensory loss) which may be associated with peripheral nervous system dysfunction (1-4). There is, however, limited information regarding the electrophysiologic effects of elemental mercury on the human peripheral nervous system.

Barber (4) and Vroom and Greer (5) suggested that the clinical and electrodiagnostic abnormalities of inorganic mercury intoxication are best explained by anterior horn cell involvement with subsequent axonal degeneration. Both studies emphasized the similarity between inorganic and organic mercury intoxication, where in the latter the existence of peripheral sensory nerve abnormality has been questioned (6). Levine and Cavender (unpublished) found a significant correlation between prolonged motor distal latencies and urine mercury levels, but did not perform sensory nerve conduction studies. Goldstein et al. (1) indicated that mercurialism can be associated with a sensorimotor polyneuropathy and described a patient intoxicated by inorganic mercury in whom nerve conduction studies confirmed the clinical impression of sensory polyneuropathy.

We report here results of an electrophysiologic evaluation of the ulnar nerve in subjects exposed to elemental mercury vapor. Our goal was to ascertain whether motor and/or sensory peripheral nerve was affected by mercury exposure and, if so, whether the degree of abnormality could be related to the degree of exposure.

Methods

Eighteen male worker volunteers from a mercury cell chlorine plant were evaluated. The mean age was 31 years (range of 19 to 56 years). All subjects were asymptomatic and routine physical examinations performed by the industrial physician at the time of testing were normal. Volunteers had no history of alcoholism, diabetes mellitus, or any known neurologic abnormality.

Urine mercury levels were used to assess exposure (7,8). Urinary mercury determinations were made once a month using the method of cold, flameless atomic absorption (9). Split samples were frequently employed for intra-laboratory validation and correlation was generally greater than $r = .95$ (10). All subjects were included in a urinary mercury control program at the plant wherein workers with spot sample urine mercury levels exceeding 0.50 mg/l were removed from mercury exposure. Urine mercury records were available for three years prior to evaluation or the duration of employment if less than three years.

The following time integrated, urine mercury indices were used as measures of body mercury levels and were designed additionally to detect any "threshold effect" that might exist (9,11): Spot sample urine mercury concentration (mg/l) at the time of testing; average urine mercury concentration during the previous 3, 6, 12, 24, and 36 months; the number of months urine mercury concentrations exceeded 0.25 mg/l or 0.50 mg/l during the previous 6, 12, 24, and 36 months.

The right ulnar nerve was studied in all subjects. Compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) negative

peak amplitudes, motor and sensory distal latency, and maximum motor conduction velocity (MMCV) were measured using conventional techniques. Minimum motor nerve conduction velocity was measured using a collision technique (12,13). The range of motor nerve conduction velocities (MCV range) was calculated as the difference between MMCV and mMCV. A Teca TE-4 electromyograph was used in the testing. Evoked responses were recorded on the TE-4 fiber optic recorder for subsequent analysis. Surface temperature was measured at the elbow and wrist (range of 31 - 34°C).

Urine mercury index values for subjects with abnormal nerve conduction studies (one or more abnormal values) were compared to those for the remaining subjects (t-test). Least square regression analysis was used to correlate urine mercury indices and nerve conduction test results.

Results

Average urine mercury concentrations ranged from 0.02 to 0.45 mg/l. The group mean for spot sample urine mercury concentration was 0.29 mg/l (range of 0.02 to 0.70 mg/l). Five subjects had abnormal nerve conduction studies when compared to normal values from our laboratory; three had prolonged sensory distal latency, one had prolonged motor distal latency and one had both prolonged motor and sensory distal latencies with a low-normal SNAP amplitude. While the mean CMAP amplitude was low (8.3 mv) when compared to normal values for our laboratory, no individual value was outside of our normal range. All other measurements were within normal limits.

Results of the comparison between urine mercury index values for "abnormal" and "normal" subjects are displayed in Table 1. Over half of the

Urine mercury indices were significantly ($p < 0.05$) higher in the abnormal group. The most significant differences between groups occurred using number of months urine mercury concentrations exceeded 0.50 mg/l in the previous 24 and 36 months ($p < 0.002$ and $p < 0.003$, respectively). The significance of differences between the two groups tended to increase with time up to 24 months with a decrease at 36 months.

Correlation coefficients between urine mercury index values and nerve conduction test results are presented in Table 2 with levels of statistical significance. Sensory distal latency was significantly correlated ($p < 0.05$) with over half of the urine mercury indices used. Motor distal latency also showed significant correlation with urine mercury indices. In both cases, positive correlations indicate an increase in distal latency with increasing mercury indices. The highest correlation obtained was between sensory latency and the number of months urine mercury exceeded 0.50 mg/l in the previous 24 months ($r = .72$, $p < 0.002$). Distal latencies tended to correlate best with 6, 12, and 24 month time indices. MNCV and mNCV were significantly correlated with a few urine mercury indices but no consistent relationship was exhibited. CMAP, SNAP, and MCV range had no significant correlations with any urine mercury index. Three scatter plots illustrating the relationship between urine mercury indices and nerve conduction values are presented in figure 3.

Discussion

Significant differences in urine mercury indices between groups with prolonged versus normal distal latencies implies that peripheral nerve conduction can be affected by elemental mercury even when average urine

concentrations do not exceed 0.50 mg/l. The number of significant correlations between both motor and sensory distal latencies and urine mercury indices (Table 2) supports this concept.

Barber (4) reported markedly prolonged sensory distal latencies and decreased sensory conduction velocities in two patients with mercuric oxide exposure. Motor conduction velocities were normal. Needle electromyography revealed frequent fasciculations. It was suggested that the clinical findings best resembled those found in organic mercury intoxication and amyotrophic lateral sclerosis.

Vroom and Greer (5) demonstrated mild slowing of motor and sensory conduction velocities, prolonged motor and sensory distal latencies, and a reduced CMAP in a group of nine patients with mercury vapor exposure. Needle electromyography demonstrated increased motor unit action potential amplitude, duration, and polyphasia. They attributed the reduced CMAP amplitude and prolonged sensory distal latencies to an inappropriately chosen control group. They concluded that inorganic mercury can cause abnormalities similar to organic mercury; namely, a disorder with both central and peripheral manifestations, the latter which may mimic amyotrophic lateral sclerosis.

Similarly, we show correlation between prolonged sensory and motor distal latencies and urine mercury indices in the ulnar nerve of asymptomatic individuals. These findings are most consistent with a sensorimotor neuropathy and inconsistent with motorneuron disease alone. This would suggest that reported sensory symptoms of elemental mercury intoxication may be, at least in part, due to a peripheral abnormality.

Miglietta (14) reported a reduction of MCV range in amyotrophic lateral sclerosis without any change of MMCV. Seppalainen et al. (15,16) found mMCV to be more sensitive than MMCV in detecting peripheral nerve dysfunction in individuals exposed to lead and carbon disulfide. We have previously reported significant correlation of mMCV and urine mercury levels (17). This result was obtained using multiple regression analysis techniques which included a number of seemingly independent variables. Further investigation has shown these variables to violate the independence assumption invalidating this result. We were unable to show any consistent relationship between either mMCV or MCV range and urine mercury indices in the present study using simple regression analysis.

Urinary mercury determinations commonly are used to assess and control industrial elemental mercury exposure. We have shown little correlation between spot sample urine mercury concentrations and electrophysiologic data. This concurs with previous reports noting little correlation between spot sample urine mercury concentrations and neurologic findings (7,8). Poor correlation with spot sample measurements may be due to daily variation in urine mercury concentration (18). We have attempted to overcome this problem by integrating urine mercury levels over time. The correlations shown in Table 2 suggest a dose - response relationship exists between the quantitative nerve conduction test results and time integrated urine mercury indices. Reduction in the significance of results for 36 compared to 24 month indices (Tables 1 and 2) may be due to short term effects of mercury and/or an artifact arising from variability in subjects' exposure time course.

Urine mercury concentrations greater than 0.50 mg/l may be associated

with increased central nervous system toxicity (9,11). Results obtained in the present study, using the number of months urine mercury concentration exceeded 0.50 mg/l as a measure of body mercury level, do not differ substantially from those obtained using concentrations exceeding 0.25 mg/l or average levels (Tables 1 and 2) and offer no support for a threshold effect in the peripheral nervous system.

We conclude that exposure to inorganic mercury can affect both motor and sensory peripheral nerve conduction consistent with a mild sensorimotor neuropathy. The degree of involvement can be related to mercury exposure as quantified by time integrated urine mercury concentrations. Additional electrophysiologic investigation including needle electromyography seems warranted on the basis of these results.

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Table 1: Comparison of Urine Mercury Indices for Subjects
with Normal versus Abnormal Conduction Studies

Urinary Mercury Index	Group Mean		Significance Level of Difference
	Normal	Abnormal	

average urine Hg (mg/l) in previous:			
1 month (spot sample)	0.18	0.17	0.86
3 months	0.12	0.22	0.55
6 months	0.12	0.19	0.17
12 months	0.13	0.29	0.02
24 months	0.10	0.21	0.006
36 months	0.10	0.18	0.10

No. of months > .25 mg/l in previous:			
6 months	0.8	2.0	0.05
12 months	1.9	6.0	0.009
24 months	3.2	8.2	0.02
36 months	4.9	10.4	0.14

No. months >0.50 mg/l in previous:			
6 months	0.2	0.6	0.06
12 months	0.7	2.6	0.03
24 months	0.8	3.2	0.002
36 months	1.1	3.8	0.003

Table 2: Correlation Coefficients between Urine Mercury Indices and Selected Nerve Conduction Measures

Urinary Mercury Index	Sensory Distal Latency	Motor Distal Latency	MMCV	mMCV

average urine Hg in previous:				
1 month (spot sample)	+.07	+.07	-.47**	-.44†
3 months	+.28	+.32	-.51**	-.64***
6 months	+.49**	+.51**	-.37	-.44†
12 months	+.67***	+.36	-.13	+.05
24 months	+.52**	+.60***	+.10	+.18
36 months	+.28	+.44†	+.36	+.36

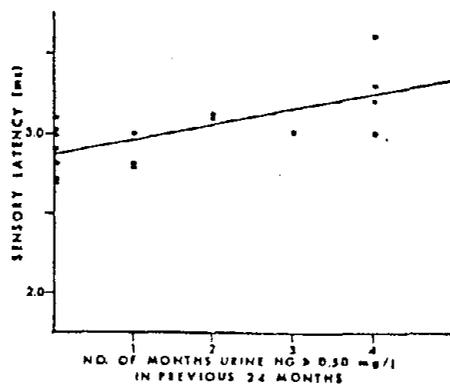
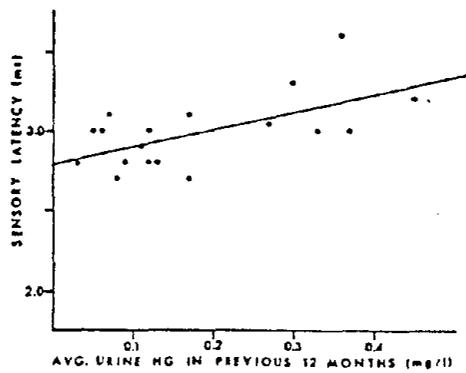
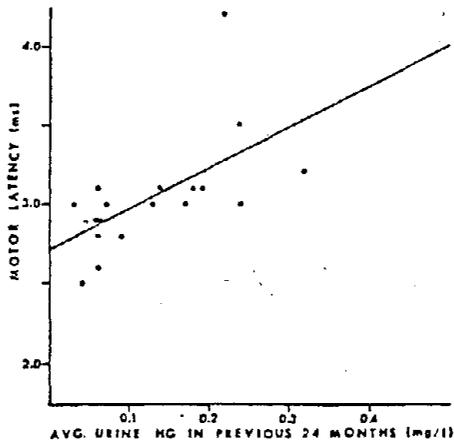
No. months > .25 mg/l in previous:				
6 months	+.51**	+.61***	-.42†	-.47**
12 months	+.61***	+.44†	-.21	-.09
24 months	+.43†	+.46†	+.13	+.22
36 months	+.22	+.33	+.32	+.46†

No. months > .50 mg/l in previous:				
6 months	+.41†	+.48**	-.27	-.50**
12 months	+.68***	+.35	-.16	+.09
24 months	+.72***	+.41†	-.03	+.16
36 months	+.60***	+.35	+.16	+.30

Significance Levels: † p < 0.1
 ** p < 0.05
 *** p < 0.01

FIGURE LEGEND

1. Selected scatter diagrams and regression lines for urine mercury indices versus ulnar motor and sensory latencies.



~~FIGURE 1~~

*Redrawn for
photos
(larger scale)*

