PROSPECTIVE STUDY OF PSYCHOMOTOR FUNCTION AND URINARY MERCURY OF MERCURY CELL CHLOR-ALKALI PLANT WORKERS

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ABSTRACT

A retrospective study of psychomotor functions and urinary mercury has shown reversible changes in the tremor spectrum of the forearm under light load (285 g) that appear to correlate with urinary mercury concentrations.

Results of an ongoing prospective study in which baseline psychomotor function and urinary mercury measurements have been made in workers before and periodically after work involving potential exposure to elemental mercury vapor in mercury cell chlor-alkali plants will be presented. Preliminary results appear to confirm that changes in the tremor spectrum of the forearm under light loading may be one of the earliest reversible psychomotor changes that can be used for control of occupational exposure to elemental mercury vapor.

Excessive exposure to elemental mercury can result in neurotoxic effects manifested in signs and symptoms such as tremor, abnormal reflexes, motor coordination disturbances, insomnia and erethism[1,11,14]. Tremor is the sign most frequently reported in serious cases of frank mercury intoxication, and is clinically observable as fine trembling of fingers, eyelids, lips and tongue which may be interrupted by coarse shaking movements[15]. Modern industrial hygiene practices in chlor-alkali plant operations have made such clinical intoxications with obvious mercurial tremors extremely rare or nonexistant. However, it is still necessary to control the possibility that chronic exposure to mercury vapor may cause insidious subtle impairments in the neurological function of some sensitive workers which may not be apparent in ordinary clinical examinations or to the worker himself.

In the authors' previous work in two different studies, large groups of chlor-alkali workers with potential exposure to mercury vapor were tested by means of quantitative tests of neuromuscular and psychomotor functions[3,9]. In this previous work, measurement of forearm tremor by computerized power

spectrum analysis showed best sensitivity for detection of the earliest subclinical changes due to mercury exposure. In cross-sectional correlation analyses, trends were found which indicated that some workers with urinary mercury histories over 0.5 mg/l tended to show greater power in the forearm tremor signal at frequencies above 4 Hz[9,10]. The mercury related tremor effects which were detectable by power spectrum analysis were not observable in clinical examinations, and tremor spectrum changes were found to be reversible upon reduction of the affected workers' mercury exposure.

Past work did not show any significant correlation between workers' most recent urinary mercury excretions and their tremor spectra results. However, it was found that workers whose urinary mercury histories showed peaks over 0.5 mg/l in the previous year tended to display excessive power in the high frequency range of their tremor spectra. This observation was in good correspondence with an earlier prediction of Henderson and co-workers[5], that urinary mercury over 0.5 mg/l may indicate accelerated mercury absorption in the nervous system and greater probability of neurological effects.

In general, the authors' previous cross-sectional retrospective studies have concluded that a urinary mercury program which removes workers from exposure if urine levels exceed 0.5 mg Hg/l should be very effective in controlling neurological effects in the large majority of chlor-alkali workers. However, because of the possibility that some sensitive individuals may be affected with urine mercury levels below 0.5 mg/l and because of the lack of complete reliability of single urinary mercury determinations, direct neurological examination of exposed workers is still necessary. The objective of the work reported here was to determine the potential value of quantitative tremor measurement as a part of the routine examination of workers with potential exposure to mercury vapor.

In this work, baseline tremor measurements were made early in new workers' exposure to mercury and at approximate three-month intervals thereafter. Likewise workers who had previously worked in mercury exposure areas were examined while still in exposure, and later at three-month intervals after job transfer to non-exposure areas. The specific study objective was to determine if a dose-response relationship could be discovered between urine mercury levels and objective tremor measurements. The results given here represent the first year of longitudinal observations in an on-going study which will be carried out over a total period of three years.

SUBJECTS AND METHODS

Subjects were 54 worker volunteers from two chlor-alkali plants. Table 1 gives age statistics of subjects as a function of their highest urinary mercury levels observed over the period from January 1977 to July 1978.

Urinary mercury samples were obtained at least once per month from workers in exposure areas. Samples were obtained from non-exposed workers at the time of tremor tests at approximate three-month intervals. The chief interest

TABLE 1
Subject ages classified by urinary mercury levels.

Highest urinary mercury concentration January 1977 to July 1978 (mg/l)	Number of subjects	Mean age (years)	Standard deviation (years)
< 0.15	23	40.7	14.3
0.16 to 0.25	5	29.0	3.5
0.26 to 0.50	10	37.2	12.6
> 0.50	16	33.4	14.7

in obtaining subjects was to find those who underwent sharp changes in mercury exposure, either entering or leaving exposure areas due to new employment or job transfer. Since many new employees subsequently developed high urinary mercury levels, the age distribution of subjects in higher urinary mercury classes tended to be younger than those classed as controls (peak urine Hg not more than 0.15 mg/l during the entire study period). This was not a detriment to the longitudinal study, since in this design, each subject served as his own control.
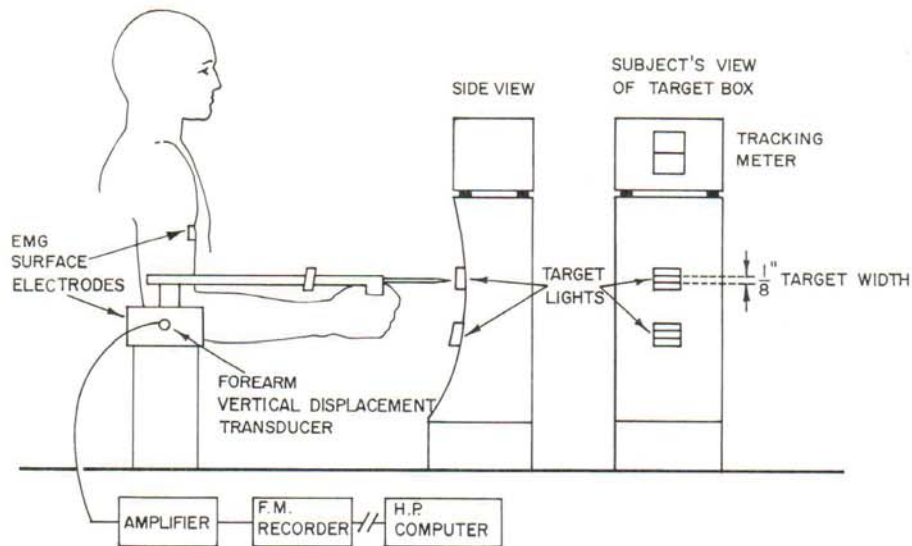

FIG. 1 – The forearm tremor measurement apparatus.

The apparatus used to record forearm tremor is shown in Figure 1. Two separate forearm tremor measurements were made. First the subject was instructed to simply hold a lightweight pointer (285 g) aiming as steadily as possible at an illuminated target. A linear potentiometer was used to change tremor to an electrical signal which was recorded on an FM instrumentation tape

recorder (Hewlett-Packard 3910). Tremor was recorded for a total of 4 minutes in two 2-minute trials. Tests were conducted in medical departments at the plant sites.

The four-minute sample of forearm pointing tremor was later subjected to frequency spectrum analysis by means of analog to digital conversion and a fast Fourier transform program on a Hewlett-Packard 2100 computer. The recorded tremor signal was sampled at a rate of 50 Hz in four successive 51.2 second intervals.
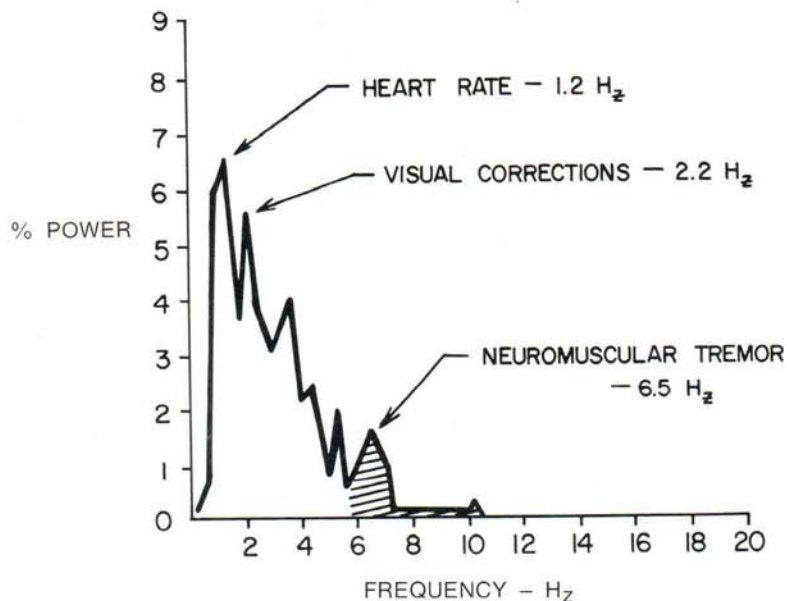

FIG. 2 – Normal forearm pointing tremor spectrum.

Figure 2 shows a typical tremor power spectrum from a normal control subject. (The spectrum is normalized so that it represents an estimate of the percentage signal power present in successive frequency bands of 0.2 Hz width.)

Three primary spectral peaks are most often present. The first peak at approximately 1.2 Hz is apparently due to ballistic effects of the heart beat and in normal subjects this represents the major power peak in the tremor spectrum. A second peak at about 2.5 Hz is often present and is due to subjects' visual corrections of pointer position, each correction occurring at minimum intervals of 200 msec[12].

The final peak at approximately 6.5 Hz is due to basic neuromuscular tremor processes, and it is this high frequency component which is observed as tremor in clinical examinations. This high frequency spectral peak is very small in individuals who are "steady", and this peak will be called "neuromuscular tremor" in further discussions in this report.

The device shown in Figure 1 was also used to record tremor under the conditions of a compensatory tracking task. Here the subject was instructed to slowly move the pointer arm so that a meter needle was always kept as close as possible to the center mark. The tracking input signal was a very low frequency 0.1 Hz sine wave, and it was necessary for the subject to move the pointer arm over a range of ± 3 cm in order to keep the meter needle centered. This tracking tremor measurement was used to standardize the visual corrections behavior of the subjects, and to introduce a further element of intention in the steadiness task. A total of three minutes (3 one-minute trials) of tracking tremor was recorded, and spectral analysis was later carried out as in static pointing tremor. The appearance of the tracking tremor spectrum is not markedly different from that shown in Figure 2 since the 0.1 Hz tracking behavior was effectively removed by bandpass filtering (0.5 to 15 Hz).

Other neuromuscular and psychomotor tests were also performed, and these included surface electromyogram, arm drop reflex, finger tapping, finger tremor, critical tracking and Michigan Maze test. Only forearm tremor results will be discussed in this paper, however.

The first testing sessions in the longitudinal study occurred in May 1977 and subsequent sessions were carried out in August 1977, January 1978, and April 1978. Because of the intervals between testing sessions, it was generally not possible to obtain true baseline measurements on newly employed individuals. In the future two years of the study this difficulty will be alleviated by placing duplicate testing equipment in the medical department of one plant, and baseline pre-employment tremor recordings will be taken by a trained nurse.

RESULTS

Results from the previous 1975 cross-sectional study showed that workers whose urinary mercury had exceeded 0.5 mg/l in the previous year tended to show alterations in the neuromuscular component of the forearm tremor spectrum. These changes were: increase in the neuromuscular peak power, and reduction in the neuromuscular peak frequency. These changes are exemplified by the spectrum of the worker shown in Figure 3 who had 5 months in the previous year with urinary mercury exceeding 0.5 mg/l. Figure 3 also shows the spectrum of the same worker 10 months after he was removed from exposure.

The results of the current study confirm the pattern of mercury related tremor changes noted in the earlier work. First, it must be noted that there was no evidence of a correlation between urinary mercury and any overall amplitude measure of tremor (RMS level, percentage of time outside arbitrary amplitude limits, etc.). Therefore, the mercury related tremor effects are impossible to detect in visual examination of the outstretched limb. Only the relative composition of the tremor spectrum has been found to be sensitive to these early mercury effects.

Figure 4 shows a scatter diagram of the neuromuscular peak tremor power versus urinary mercury history of subjects in the current study. Note that for both
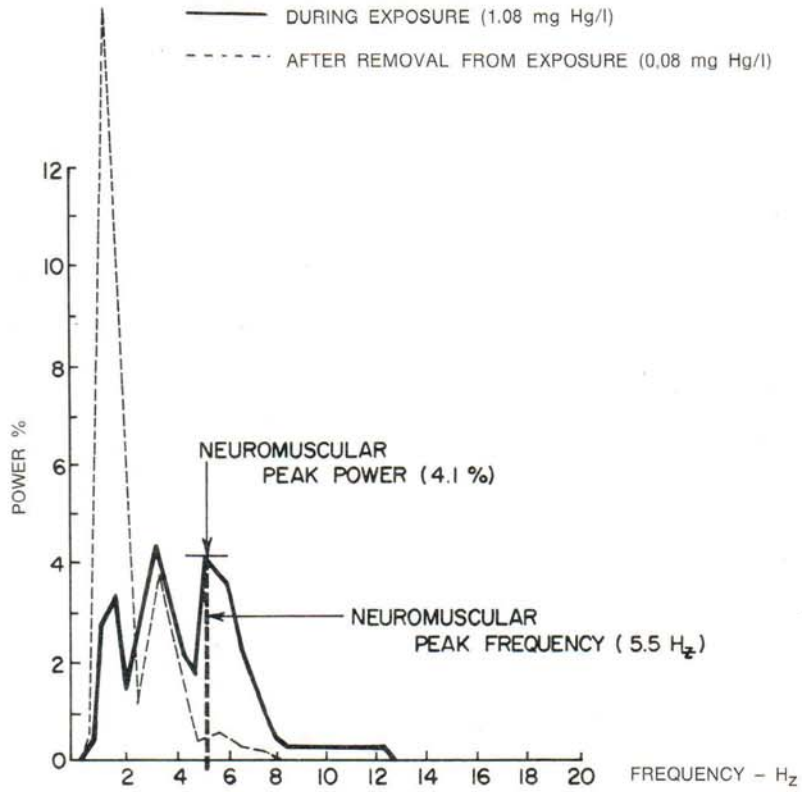
DURING EXPOSURE (1.08 mg Hg/l)

AFTER REMOVAL FROM EXPOSURE (0,08 mg Hg/l)

FIG. 3 – Forearm pointing tremor spectrum from a subject with urinary mercury history frequently exceeding 0.5 mg/l.

STATIC POINTING   TRACKING

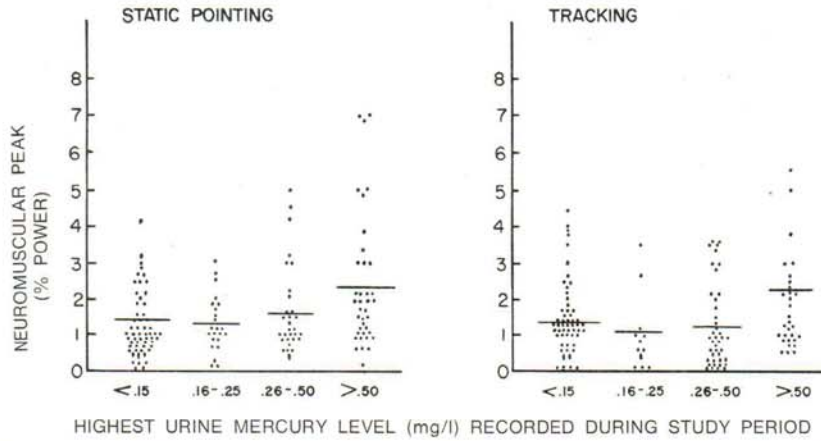HIGHEST URINE MERCURY LEVEL (mg/l) RECORDED DURING STUDY PERIOD

FIG. 4 – Neuromuscular tremor power as a function of subjects highest urinary mercury level.

static pointing and tracking tremor spectra, the neuromuscular power increased noticeably only for the group of subjects whose urinary mercury had exceeded 0.5 mg/l during the study period. The statistical significance of this change was marginal at $P < 0.08$; however, significance reached $P < 0.005$ in previous work with a larger group.

Statistical analysis of tremor spectra parameters also showed a trend toward reduction of the neuromuscular peak frequency in subjects whose urinary mercury history had exceeded 0.5 mg/l. (The statistical significance of this frequency trend was much greater at $P < 0.001$.)

With only four testing sessions to date, it is impossible to perform formal statistical analysis on individual subject case histories. However, illustrations from individual cases will be presented here, and these do confirm an impression of correlation between urinary mercury history and tremor spectra history.
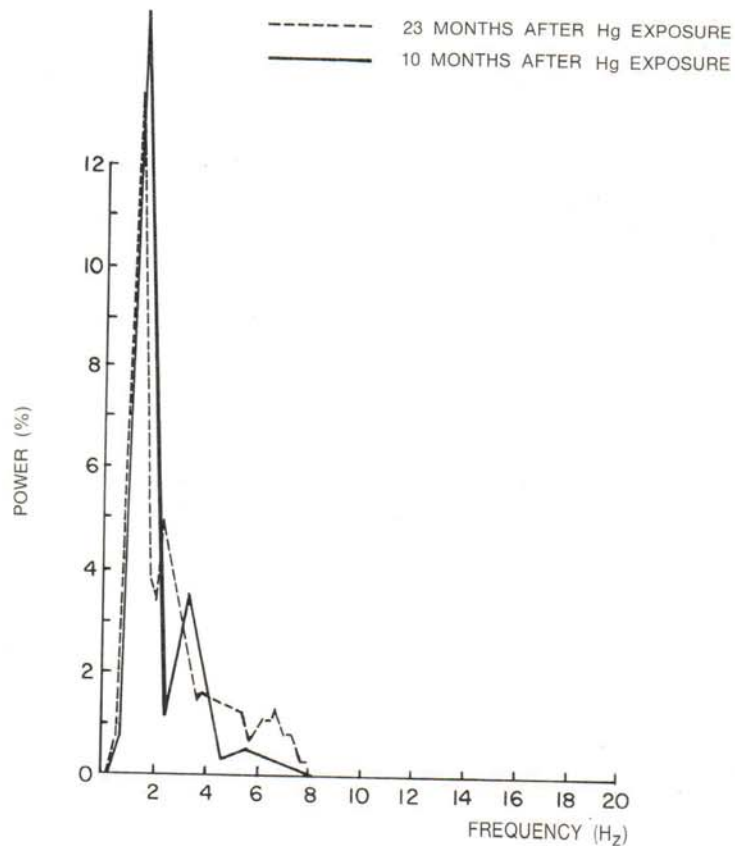

FIG. 5 – Retest tremor spectra after subject was removed from mercury exposure.

First, cases will be considered where urinary mercury reached a very high level above 0.5 mg/l, and the subject was removed from exposure. Figure 3 has already shown a subject whose urinary mercury reached 1.08 mg/l. Originally, his neuromuscular tremor peak power was very high, but this was markedly reduced 10 months after removal from exposure. However, his neuromuscular peak frequency remained low in the retest condition (5.5 Hz versus 6.5 Hz average for the control group). When the on-going study began, the subject was again retested after a total of 23 months since last mercury exposure. Figure 5 shows a shift in his neuromuscular peak frequency from 5.5 to 6.7 Hz in the latest test. Possibly, the change in neuromuscular tremor frequency reverses much more slowly than the change in neuromuscular peak power.

During the August 1977 testing session of the longitudinal study, a 23 year old worker whose urinary mercury had reached a very high level of 1.30 mg/l was brought to the attention of the study team. He was removed from mercury exposure, and received the tremor test approximately one week after removal from exposure. Figure 6 shows his tremor test results related to his urinary mercury history. Initially his tremor spectrum showed a very strong neuromuscular tremor peak located at an abnormally low frequency of 4.6 Hz.
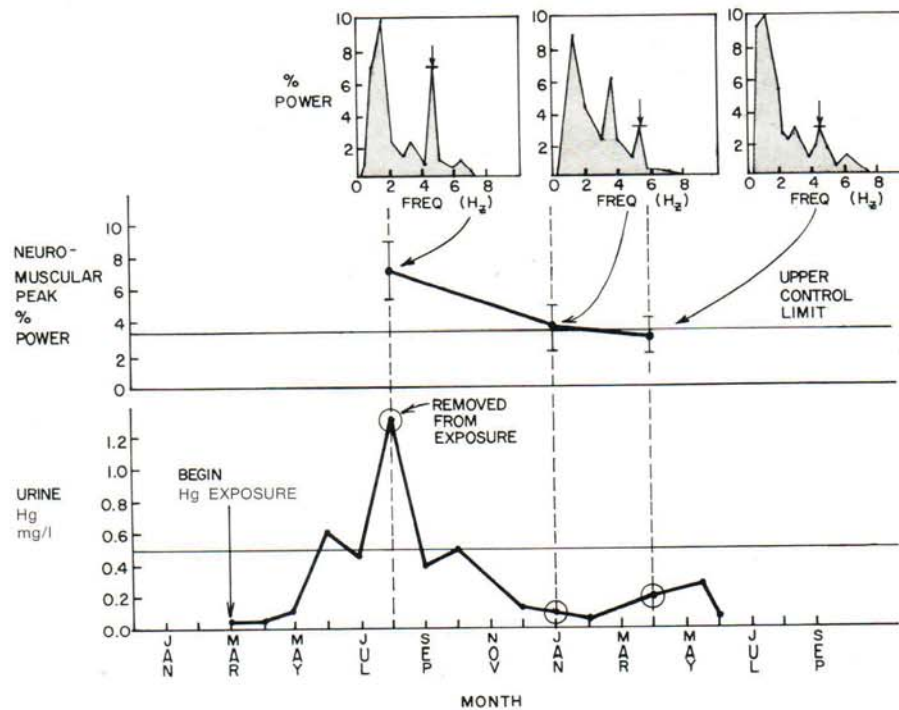

FIG. 6 – Urinary mercury and static pointing tremor history – subject removed from mercury exposure.

His neuromuscular peak power of 7% was markedly higher than the 95% upper control limit established for observations of the control group. (The ±2 sigma measurement error limits or neuromuscular peak power are shown for each point on the upper graph. Even if the maximum measurement error is considered, the first value is clearly outside control group limits.)

After his removal from mercury exposure in August 1977, his urinary mercury levels decreased progressively to 0.10 mg/l in January 1978. At this time his neuromuscular peak power decreased to 3.2%, which was borderline compared to the control group high limit. In a subsequent test in April 1978 his neuromuscular tremor power was further slightly reduced to 3.0%. While this appears to indicate reversal of a mercury exposure effect, note that the frequency of the neuromuscular peak remained low (4.4 to 5.2 Hz) throughout the testing period. As noted before, the frequency effect may reverse later than the peak power effect.

The relationship between urinary mercury history and tremor for new employees who recently entered mercury exposure areas was interesting in cases where urinary mercury ultimately exceeded 0.5 mg/l. In these cases, neuromuscular peak tremor power often appeared at abnormally high levels
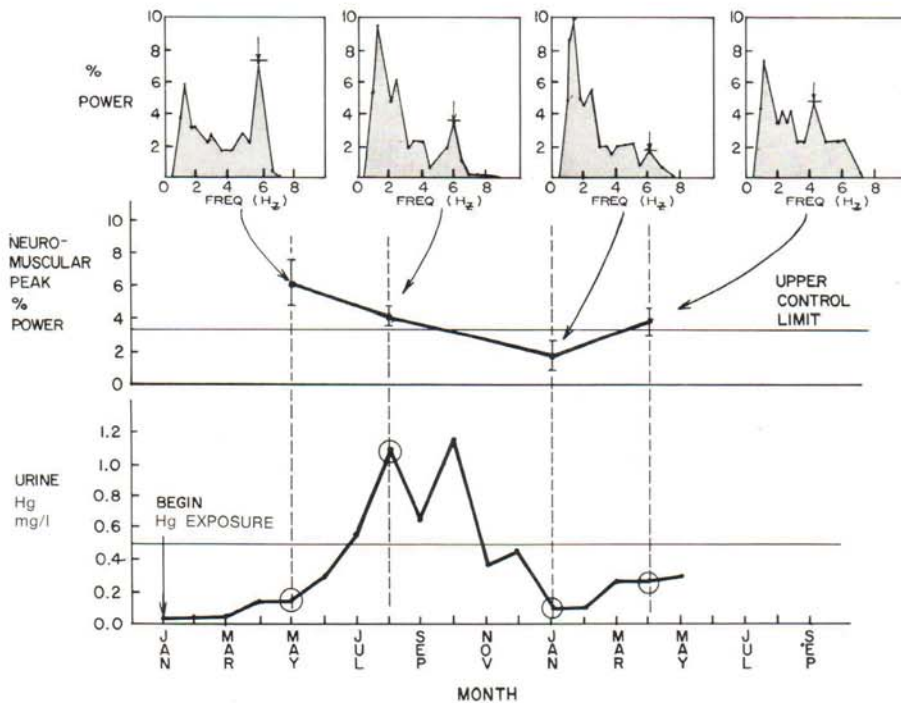

FIG. 7 — Urinary mercury and tremor history — subject entering mercury exposure.

before urinary mercury rose beyond 0.5 mg/l. Figure 7 shows the history for one 23-year-old worker who entered mercury exposure in January 1977. He was first tested in May 1977 at the beginning of the study. At this point his urinary mercury concentration was still low at 0.13 mg/l. However, his tremor spectrum shows a very strong peak at 7.0%, well beyond the high limit for the control group. When his urinary mercury had risen to 1.04 mg/l in August, his neuromuscular peak tremor power showed a decrease to 4.0%. Note that his neuromuscular peak frequency, however, was normal at 6.0 Hz for the first three testing sessions, but then dropped to 4.4 Hz a full 16 months after the beginning of mercury exposure.

Figure 8 shows a similar pattern for another subject who showed an abnormally high neuromuscular tremor peak before a marked increase in urinary mercury concentrations. In this case the 46-year-old worker had some mercury exposure in previous years, but his urinary mercury levels were consistently low ($\simeq 0.10$ mg/l) for the two years before the study.

Altogether, six employees at one plant showed a distinct "hump" in their urinary mercury records during the summer and fall months of 1977. Four out of the six workers showed higher levels of neuromuscular tremor power in the May
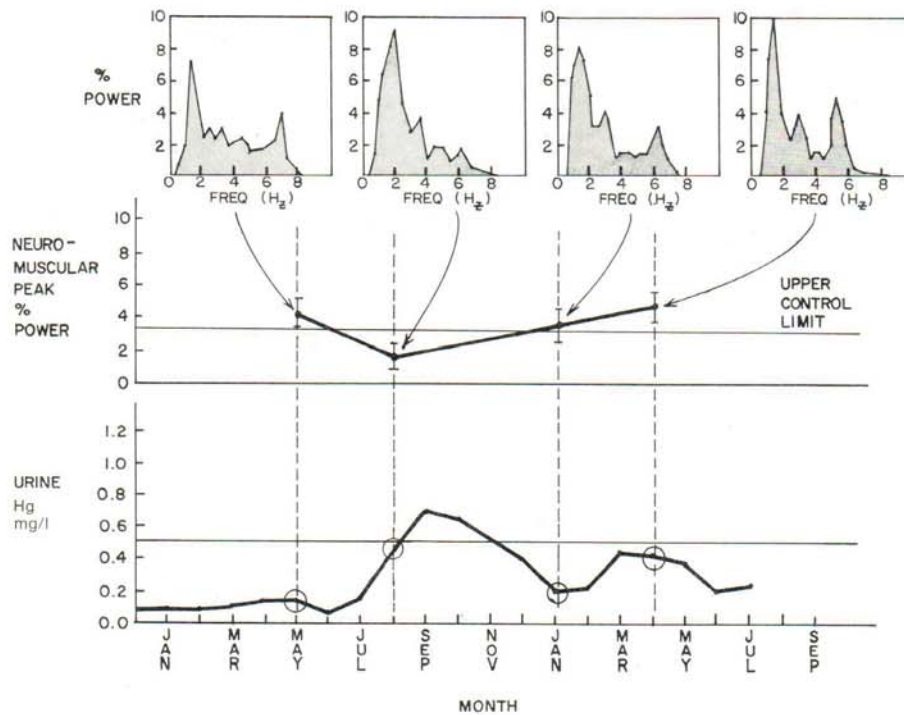

FIG. 8 – Urinary mercury and tremor history – subject with previous exposure, but increasing urinary mercury.
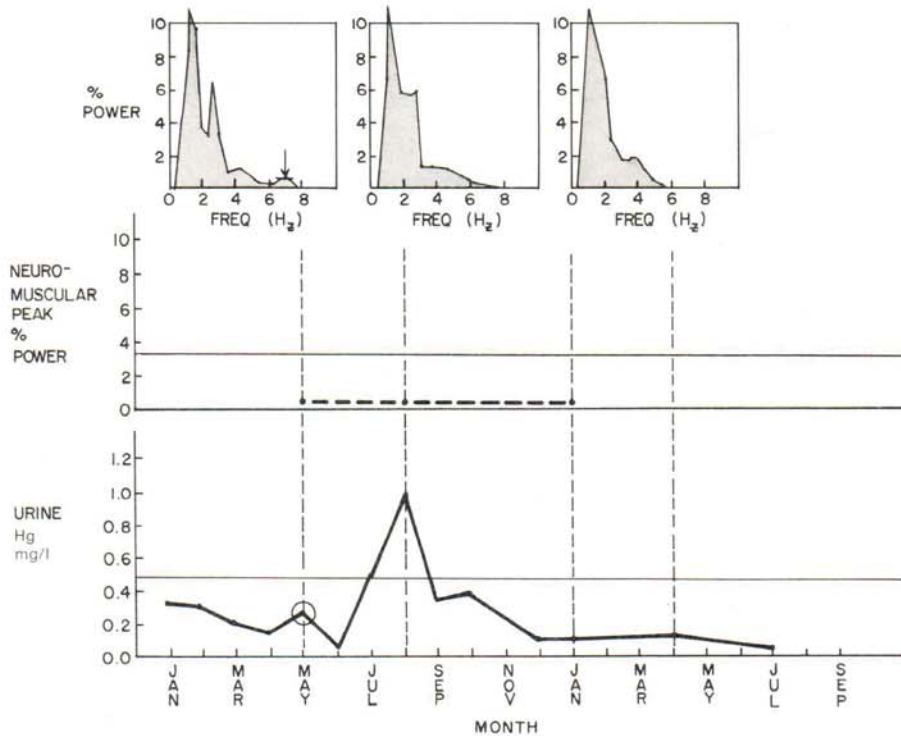
FIG. 9 — Urinary mercury and tremor history — subject who showed no tremor response related to elevated urinary mercury.

session which preceded their increase in urinary mercury. The other two showed no apparent response to mercury in their tremor spectra. Figure 9 shows the record of one of these exposed workers who showed a consistently normal tremor spectrum.

Emotional stress and anxiety may certainly cause an increase in tremor and one may wonder if employees may have been more anxious in their first testing session, making it appear as if their tremor had increased before excretion of large amounts of urinary mercury. In order to explore this question, the tremor spectra of the six exposed employees were compared to those of eight controls at the same plant. Figure 10 shows the results of this comparison. Here, the average urinary mercury for the exposed group reached 0.62 mg/l in August, and before this their average neuromuscular tremor peak power was significantly higher in May. The control group, however, showed no changes in neuromuscular peak power across sessions, indicating that there was no increased anxiety effect during the first testing session. The high neuromuscular power of the exposed group during the first session is of special interest since the group average value lies on the upper control limit for individual observations in the control group.
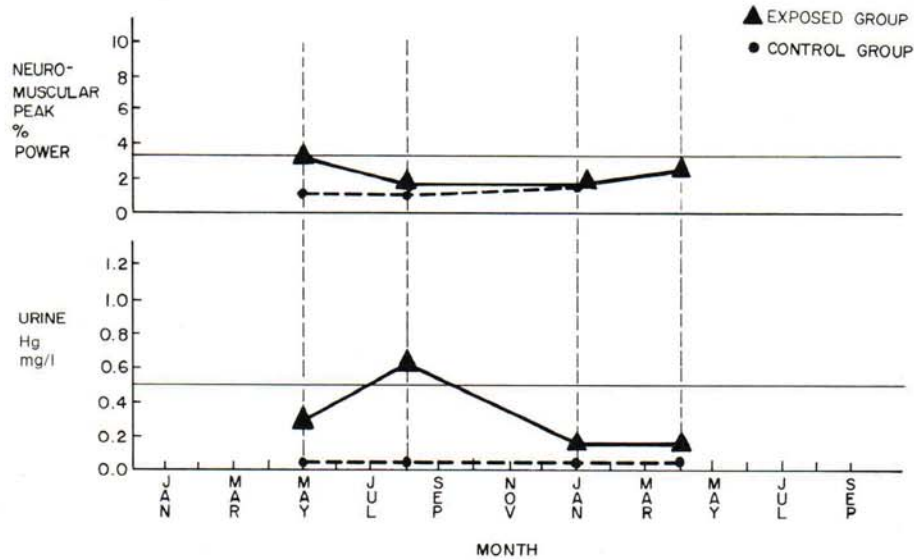
FIG. 10 – Urinary mercury and tremor history. Averages for exposed group versus averages for control group.

DISCUSSION

Several investigators have noted the apparent lack of correlation between urinary mercury levels and appearance of signs such as tremor[6,8,11,13,14]. This may be because of complex lead-lag relationships between effects, such as tremor, and urinary mercury. While decreases in neuromuscular tremor power were consistently noted in direct relationship to decreasing urinary mercury in workers who were removed from heavy elemental mercury exposure, an increase in neuromuscular tremor may have preceded the rise in urinary mercury of newly exposed employees.

Possibly in the early history of chronic exposure, mercury accumulates in the nervous system before the appearance of significant excretions of urinary mercury. This, of course, is conjecture at the present time and Clarkson[4] has pointed out the need for isotopic tracer studies to elucidate the relationship between urinary mercury excretions and body burden in chronically exposed workers.

The apparently high neuromuscular tremor power which preceded high urinary excretions needs careful examination in the future two years of this longitudinal study. Unfortunately, true baseline tremor measurements could not be made for new employees during the first year of the study. In future years tremor will be recorded with a pointing device installed in the plant medical department. This will allow true baseline tremor measurements for new employees and retests at a minimum of one month intervals.

Tremor is a very nonspecific sign, in that it is affected by a host of factors. Therefore, one must be very careful in attributing tremor characteristics to elemental mercury exposure. Of course, muscle fatigue increases neuromuscular tremor, and care must be taken to assure that workers have not lifted heavy loads before forearm tremor recording. The authors and other researchers have noted that alcoholism, insomnia, and hypertension are also associated with increased neuromuscular tremor[2,9]. At the present time the abnormal tremor spectra of individuals with these conditions cannot be reliably distinguished from mercury related tremor spectra. However, the neuromuscular tremor frequency characteristics apparently do not change in alcoholism or hypertension[2,9]. Since there are statistical indications that neuromuscular tremor frequencies are reduced in workers with histories of urine mercury over 0.5 mg/l, the frequency characteristics may in the future allow a more diagnostic interpretation of the tremor spectrum. (It should be noted that none of the workers whose case histories were presented here were alcoholics, insomniacs or hypertensives.)

In 1968, Kazantzis[7] pointed out the need for closer definition of mercurial tremor. It is hoped that this work will succeed in fulfilling that need. Kazantzis informally observed that mercurial tremor had a frequency around 5 Hz similar to that of a Parkinsonian tremor, in contrast to the fine tremor of hyperthyroidism. Using an amplifier which "passed frequencies around 5 cycles per second", he showed that a group of heavily mercury exposed subjects showed greater average signal power at 5 Hz than a matched control group. In terms of the results of the present study, Kazantzis' definition was remarkably correct. Wood and co-workers[15] later showed complete tremor spectra of two subjects with excessive elemental mercury exposure. They showed excessive power in the 5 Hz region, which decreased in the months after cessation of subjects' mercury exposure. This again is in good agreement with the results presented here.

A urinary mercury control program is a valuable method for preventing excessive exposure to elemental mercury. Regular measurement and spectral analysis of tremor could provide additional protection when used in conjunction with a urinary mercury control program. Tremor measurements described here can detect changes in tremor before tremors become clinically observable. This could be valuable in detecting the few sensitive individuals who may show mercury effects before reaching the 0.5 mg/l urine mercury control limit. If tremor spectra changes do precede the development of high urinary mercury excretions, as suggested by initial research results, the value of tremor testing in controlling the earliest reversible mercury effects is obvious. Finally, tremor measurements are of extreme value in providing objective measurement of the progress of subjects who may have had excessive exposure to elemental mercury.

The tremor measurements described in this paper are extremely sensitive compared to clinical observations. None of the mercury exposed subjects, even those with urinary mercury exceeding 1.0 mg/l, showed clinically detectable tremors. None reported any unusual experience with tremor. In the authors' opinion, there were no functionally significant effects in any of the mercury

exposed workers. Indeed the value of the tremor spectrum measurement is its capability to detect the earliest subclinical effects at a stage when they are functionally insignificant and reversible.

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