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AN EVALUATION OF THE EFFECTS
OF CHRONIC MERCURY EXPOSURES
ON EMG AND PSYCHOMOTOR FUNCTIONS

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National Institute for Occupational Safety
and Health

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-ABSTRACT-

This is primarily a cross-sectional study involving both neurological and psychomotor skill assessments of 142 male industrial workers from four different plants. None of the workers reported being clinically ill from mercury at the time of the study. Of the 142 workers in the study, 77 were routinely exposed to inorganic mercury vapor in the course of their jobs, while the remaining 65 served as unexposed controls drawn from the same plants.

The primary health status indicators employed in the study were: forearm tremor, surface electromyography and discrete positioning eye-hand coordination. The following specific changes in these were significantly correlated with elevated levels of both blood and urine mercury burdens:

- * Mean frequency of forearm tremor increased.
- * Surface EMG bandwidth increased.
- * Discrete positioning hand motions became more erratic.

When the workers displaying these effects were placed in a reduced exposure for from four to six months, the adverse effects returned to more normal population levels.

Some psychomotor tests were also included in the study. These indicated that finger and toe tapping rates were significantly decreased in workers having elevated blood and/or urine mercury levels. When workers with these adverse findings were removed from exposure for four to six months their tapping rates returned to more normal levels. Other additional psychomotor tests also suggest that forced-choice decision times could be sensitive to chronic exposure to inorganic mercury.

Thirty-two of the workers volunteered for a clinical neurological examination. Though this was not a large enough sample to perform adequate statistical analysis, it was determined that in a group of workers having elevated urine mercury burdens (averaging 787 $\mu\text{gm/L}$ of urine), the prevalence of both eyelid fasciculations and dermatographia were much higher than expected in a normal population. It was also found that the symptoms did not remit after these people were removed from exposure for from four to six months.

The statistical findings of the study are used as the basis for a recommendation that specific quantitative neurological and psychomotor tests, such as those described in this study, be utilized in various industrial medical departments to routinely evaluate the health of workers exposed to inorganic mercury. It is shown that such a health evaluation program is warranted due to the large variation in individual tolerance to mercury documented in this study.

Acknowledgements

This project was initiated as the result of a feasibility study made possible by a small grant from the University of Michigan Institute for Environmental Quality. The initial work was carried out in May and June of 1971. In July of 1971, the Behavioral Studies Laboratory, Division of Laboratories and Criteria Development of The National Institute for Occupational Safety and Health (NIOSH) established a contract with the University of Michigan for the effort herein reported. During the ensuing 18 months of research, various people have been involved in the study. Their participation is acknowledged in the following areas:

- * Development of the test equipment and data reduction computer programs was supervised by Mr. James Foulke with assistance from Messrs. John Buckenberger and Robert Wolters.

- * Further refinement of the methods for analysis of mercury in blood and urine and for completing the evaluation of the many samples gathered in this study was accomplished by Professor Ralph Smith assisted by Mr. Thomas Armstrong.

- * Administration and reduction of the data from the various tests used in this project was carried out by Professor James Miller, Dr. David Zontine, Mr. Shashikant Kelkar, Mr. James Foulke, and Mr. Leonard Westra.

- * Major data reduction and analysis was directed by Mr. Shashikant Kelkar with assistance from Mr. David Murray, Miss Sue Nemeth, Mr. David Bowerman, Miss Peggy Reed, Mr. Joseph Washnock and Mr. Dilip Bhagwat.

* The animal experiments were conducted by Messrs. David Foust and Shashikant Kelkar.

* Typing and editing of this and earlier reports has been accomplished by Mrs. Vivian Ladd, Miss Joni Ann Benelli, Mrs. Sharon Marr, Mrs. Gloria Crosswait and Miss Nancy Knepper.

It should be noted that a separate analysis of some of the project data is currently being performed by Mr. Shashikant A. Kelkar as part of his Ph.D. thesis. This analysis will include further statistical evaluation of the tremor, EMG, and eye-hand coordination test results to determine: 1) if plant groups consistently varied, 2) if muscle fatigue could be assessed by means other than EMG mean frequency changes, and 3) if the performance on the eye-hand coordination tests varied during the testing period.

The writing of this final report has been a combined effort of the following people, with major responsibilities for the sections as indicated:

- * Sections I, III, IV and VI were drafted by Professor Chaffin.
- * Section II was drafted by Professors Dinman and Smith.
- * Section V was prepared by Professor Miller.
- * Section VII was written by Dr. Zontine assisted by Mr. David Murray.

The project staff also wishes to acknowledge the excellent cooperation of the NIOSH project officers, Drs. Charles Xintaras and Barry L. Johnson.

Don Chaffin and Bertram Dinman
Co-Project Directors

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AN EVALUATION OF THE EFFECTS OF CHRONIC
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Section I

Introduction

It has been well recognized that chronic exposure to mercury can result in complex alterations in a person's physiological status. Primary effects are to the central nervous system. These manifest themselves in varied symptoms and signs, as well as in altering the person's performance capabilities. If the chronic exposure is incurred as part of the person's job, both an occupational health and safety problem can exist, depending upon both the amount of exposure (dose) and the length of time exposed.

The current general problem is to prevent mercurialism by means of adequate monitoring of both the air and the exposed workers to assure that even the earliest signs of deterioration in the person's health are detected and prevented from progression. The challenge, therefore, is to devise the means to recognize preclinical evidence of overexposure in order that appropriate corrective action can be taken.

The thrust to date of most past research which has contributed to the setting of safe exposure levels for any toxic substance has relied on correlations between either clinical findings and exposure levels, or tissue pathology following

controlled exposure of animals. Descriptions of some of the major mercury related past efforts of these types are described in the following section (Section II) of this report. It suffices to say, however, that such approaches have resulted in widely differing answers to such basic questions as follow:

- * How long can a person be safely exposed to a given level of mercury?
- * What are the most prevalent symptoms and signs related to chronic exposure to inorganic mercury?
- * If some adverse mercury related symptoms or signs are manifested in an individual, which effects are reversible, and on what basis can a person be returned to exposure?
- * How frequently should a person be evaluated for the potential adverse effects of mercury?
- * What are the population variations (individual tolerances and sensitivities) that can be expected with given levels and durations of exposure to mercury?

Significance of Project

This report describes the research conducted as one attempt to compile the information necessary to gain more definitive answers to these questions. As such it represents a new approach, wherein a person's health status is monitored by non-invasive, quantitative tests of specific neuromuscular and psychomotor functions. In this study, the test results are correlated with the person's current blood and urine mercury burdens, as well as with his age, height, weight, cigarette smoking rate, and the length of time exposed to mercury. Re-

tests of some people whose exposures to mercury had been reduced for a period of time is also reported, thus indicating the reversibility of some of the positive findings.

It is demonstrated that some of the neuromuscular and psychomotor tests developed and used in this study are sensitive to the effects of mercury, and therefore can be used to assess the degree of individual response to given doses of mercury. These tests are proposed as a major means of diagnosing and controlling the effects of mercury (as well as other related neurotoxins) before a person's health and safety are jeopardized. This is believed to be a reasonable and necessary requirement in the control of neurotoxic substances, due to the large normal variations in response that are known to exist.

It is now realized to be economically infeasible - and thus damaging to the majority of the people - if an air or biological standard is set unreasonably low, based on the most sensitive person in the working population. Yet without objective knowledge about a person's health status, and thus his individual response to the toxic agent, this must be the rule in order to provide the greatest health protection for all. This project demonstrates that if the working population as a whole is to be free of any adverse subclinical changes in their neuromuscular or psychomotor functions, a low level of urine mercury (e.g., about 100 $\mu\text{gm/L.}$) would be necessary as an action level (i.e., that point where quantitative functional tests of health status are instigated on a routine basis). The worker would

be removed from exposure when the combination of the periodic biological tests and health status tests indicate deterioration in his health and well-being. If such health status tests also determine that a number of people in a certain work area are showing adverse effects, and atmospheric sampling discloses a level above a prescribed atmospheric level, then the operation would require immediate corrective action.

With further research and development, it is proposed that such a procedure could become feasible for control of many environmental agents. Indeed, it is analogous to the noise control procedure, wherein a person's hearing acuity must be routinely tested for adequate health protection. By developing such a health status monitoring procedure for toxic agents, maintaining the individual worker's health becomes the primary concern, with a secondary concern being to comply with a standard based on indirect indices of atmospheric and biological concentrations of the toxic agent.

Study Overview

The primary accomplishments of this project were as follows: First was the establishment of a set of quantitative, non-invasive tests of a person's neuromuscular and psychomotor functions which from past data could be expected to be sensitive to the adverse effects of mercury. The result of this effort was the administering of the following primary test measures to 142 people, 77 of whom were exposed to mercury in their jobs. (The specific test methods and results are

described in Sections IV and VI).

- * Surface Electromyography-- Earlier tests (Vroom and Greer, 1972) indicated that the power spectrum of the EMG was significantly altered in persons and animals having elevated mercury body burdens (Chaffin and Dinman, 1972).¹ A separate clinical needle EMG study of persons having elevated mercury burdens confirmed changes which would correspond to the surface EMG power spectrum changes due to denervation.
- * Forearm Tremor--Earlier studies by others (Neal, 1941 and Kazantzis, 1968) have indicated tremor to be one of the most sensitive functional manifestations of mercury intoxication.
- * Localized Muscle Fatigue--Earlier studies (Chaffin, 1969) indicated that "fatigue" is a general symptom of mercury intoxication, thus a specific submaximal weight holding endurance test was devised using surface EMG frequency changes as a measure of the resulting fatigue rates.
- * Discrete Positioning Eye-hand Coordination-- Other studies (Neal, 1941) have indicated that eye-hand coordination in manipulative tasks is adversely affected by exposure to inorganic mercury. A test of this was selected which also relates to general industrial skill levels (Pooock, 1968).

A secondary test battery was also developed to augment the findings from the primary battery. This included the following tests that were subsequently administered to 87 people, 47 of whom were exposed to mercury, and are described in Section V:

- * Simple reaction time
- * Two-choice decision time
- * Four-choice decision time
- * Finger tapping speed
- * Toe tapping speed
- * Blind toe point accuracy
- * Pencil flipping speed

¹ Appendix G describes preliminary animals studies performed under this contract.

A standard clinical neurological status evaluation was administered to 37 people in the study. The measures, which are described in Section VII, included the following:

- * History of neurological symptoms
- * Mental status
- * Cranial nerve evaluation
- * Sensory modality status
- * Motor system functions
- * Cerebellar functions
- * Involuntary movements
- * Deep tendon reflexes
- * Autonomic functions

Retesting of some of the workers was accomplished after a four to six month period. The results of the retests are described at the end of Sections IV, V, VI and VII. Section III describes the study population and gives a general protocol for the test administration. Section VIII summarizes the major findings and recommendations of the study.

Section II

Information Acquisition for Health Protection of Mercury Exposed Workers

The Occupational Safety and Health Act of 1970 has as its primary intent the protection of the health and safety of the worker. Since health protection is the focus of those activities required of employers and government under the Act, it would appear that any approaches necessary to meet these responsibilities should ultimately revolve about specific assessment of health status. In order for an indicator to achieve this full measure of health protection, it must possess several qualities. Ideally, it should be:

1. Sufficiently sensitive to provide adequate pre-danger warning capacity,
2. An indicator of specific health alternation,
3. Closely correlated to the relative health threat to the worker,
4. Reproducibly indicative at any time or place,
5. Capable of operation by available personnel.

Given such requirements, a variety of approaches to health surveillance of potentially exposed workers can be considered. However, further discussion of each makes it apparent that many of these do not meet the criteria noted above.

1. Atmospheric Measurement of Occupational Mercury Exposure

Although mercurialism is an ancient occupational disease, attempts to prevent over exposure by the application

of modern industrial hygiene methodology is a relatively recent phenomenon. In the United States, serious efforts to prevent mercurialism date from the landmark work of Neal et al., in the classic work entitled "A Study of Chronic Mercurialism in the Hatters' Fur-Cutting Industry", which appeared in 1937 and the subsequent publication, "Mercurialism and Its Control in the Felt Hat Industry" (Neal et al., 1941). These studies were the principal basis for the establishment of a threshold limit value (TLV), or time-weighted average exposure for mercury of 0.1 milligram per cubic meter, which remained the standard in the United States until approximately 1970. When it is realized that the methods for evaluating atmospheric mercury levels that were available 30 years ago were far less convenient and reliable than those in use today, it is surprising that the standard remained unchanged for as long as it did. It is interesting to observe that although the TLV has been lowered to 0.05 milligram per cubic meter, the supporting evidence for the most part does not really contradict the data used in the establishment of the original standard. In the 30 or so years which have elapsed since the hatting industry study, a large number of publications dealing with both toxicological and epidemiological studies have appeared, but none have presented findings which are dramatically different than those of the early studies.

The present standard evolved over a period of approximately five years as a result of findings on the part of several investigators that early signs and symptoms of mer-

curialism could be noted in workers exposed to levels very close to the previous TLV of 0.1 milligram per cubic meter. Perhaps the largest body of data of this kind resulted from The Chlorine Institute sponsored study in which approximately 600 workers in the chlorine industry exposed to mercury were examined (Smith et al. 1970). This study used essentially the same epidemiological approach as that used by Neal, et al., but had the advantage of more sophisticated means for measuring air and biological levels of mercury. It is ironic that the medical criteria on which judgments could be based were not appreciably different in the recent study than those used 30 years previously. The Chlorine Institute sponsored study in large measure confirmed the findings of the earlier study, but did suggest that the old TLV was perhaps a borderline value with little, if any, margin of safety.

At an international meeting held in Stockholm, Sweden, in 1969, a committee reviewed all available evidence and essentially agreed with the findings of The Chlorine Institute sponsored study (Joselow and Goldwater 1967). On this basis, a recommendation was made that an international TLV (or MAC, as the committee elected to call it) of 0.05 milligram per cubic meter be adopted for elemental mercury vapor exposures. (The committee also recognized that the toxicity of inorganic mercury salts was different from that of elemental mercury vapor due to the reduced rate at which oxidized mercury enters

the brain, and suggested that the previous TLV remain in effect for the inorganic compounds of mercury and the non-alkyl organic compounds. The unique toxicity of alkyl mercury compounds was further recognized and these substances were considered to be very much more toxic, and best controlled by measurements of blood mercury levels.)

In the United States, the American Conference of Governmental Industrial Hygienists (ACGIH) TLV Committee in essence agreed with the Stockholm Committee findings except that as a matter of convenience a single TLV of 0.05 milligram per cubic meter was adopted for all forms of mercury except the alkyl compounds. This standard, which was originally tentative, has now been adopted as the permanent TLV by the ACGIH TLV Committee.

After passage of the Occupational Safety and Health Act, a mercury standard was published which in essence was that promulgated by the American National Standards Institute (ANSI) 237 Committee, and which consisted of a 0.1 milligram per cubic meter maximum time-weighted average 8-hour exposure. This standard, which was set by ANSI in 1942, was the standard changed to agree with that adopted by the ACGIH. Presumably, OSHA will make note of the most recent ANSI change, and alter its recommended standard to conform with it. Currently, of course, the National Institute for Occupational Safety and Health is in the process of preparing a criteria document for mercury and its compounds, and although this

document has not yet been released, it appears likely that it will be consistent with the standards adopted by the ACGIH and ANSI.

No matter which standards are respected, certain problems unique to the industrial usage of mercury will remain and make reliance upon an air standard as the sole criterion of control difficult. These problems include the possibility of some skin absorption of mercury compounds, the varying amount of absorption of mercury depending on its chemical and physical state, the ever-present problem of ingesting mercury due to contamination of the hands and clothing of exposed workers, the takeup of mercury by tobacco with its subsequent introduction into the system when smoking takes place, and finally the great variability in individual response to identical doses of mercury.

The relatively recent concern with mercury in the environment, and in particular the problem of ingesting sea food containing mercury has served to focus attention on mercurialism, and demonstrates that there are many opportunities for mercury intake other than the occupational environment. It appears that some of the anxiety attending the discovery that fish contained mercury has subsided, but remaining is the awareness of the probable exposure to mercury outside the work place.

Every study in the literature, including that by the Chlorine Institute group, suffers from one major shortcoming,

the difficulty in detecting early signs of mercurialism. Inasmuch as the central nervous system is the target organ, most of the nervous function changes which occur at low mercury levels are subtle and subjective and difficult to detect and differentiate from similar problems unrelated to mercury exposure. Even though our methodologies for sampling air, urine, blood, etc., are not yet perfect, they are much better than the comparable methodologies available for evaluating the appearance of early signs of mercurialism. It is in this latter area that substantial progress must be made if the provisions of the Occupational Safety and Health Act are to be intelligently administered.

Since it is well established that the primary route of entry for inorganic mercury and its compounds in the working environment is by inhalation, the measurement of mercury in air has always been an important aspect of any occupational exposure studies. Mercury is unique among metals in having an appreciable vapor pressure at ordinary temperatures, hence a toxic level of mercury can exist as a vapor. For this reason, many mercury measurements have been made using so-called mercury vapor meters, which respond only to mercury in the vapor phase. It is erroneous, however, to rely completely on such instruments, for there are many circumstances that can lead to the production of mercury-bearing dusts, to which these instruments are not sensitive. It is therefore necessary to perform atmospheric sampling in such a

manner as to ensure that the total airborne mercury is being measured. In many instances, it can be demonstrated that virtually all the mercury is present as a vapor, and the use of mercury vapor meters is justified without recourse to other means of sampling.

Certainly mercury vapor meters are the most attractive means of measuring atmospheric levels, for they are direct reading, fast responding devices which under most circumstances give reliable indications of mercury vapor levels. Certain precautions are essential for their correct use, however, and failure to observe them can result in erroneous data. The most common failing of these instruments is simple instrumental error caused by failure to properly calibrate them. Although there are certain internal checks built into the instruments, they cannot be considered reliable unless calibrated against known levels of mercury vapor. The meters operate on the principle that ground state mercury atoms absorb resonant energy of 2537 angstroms wavelength emitted by a mercury vapor lamp, but there are circumstances when other substances in the air may be present in sufficient concentration to absorb at this wave-length also. A number of substances, primarily aromatic compounds, do absorb appreciably at this wave-length, and their presence should be ruled out before readings are interpreted as being due to mercury.

Mercury vapor meters are often used in cell rooms, where brine is undergoing electrolysis to produce chlorine. In such circumstances intense magnetic fields usually exist due to large DC currents, and meters will frequently perform erratically or not at all. Good shielding, in most instances, will enable the instruments to be used, but circumstances can arise when the instruments appear to be functioning properly, but are actually being influenced to an unknown extent by the magnetic field. This influence can be demonstrated by observing the instrument reading at a given point, then slowly rotating the instrument to determine whether or not the reading changes due to orientation of the instrument with respect to the magnetic field. If a change is noted, then the reading cannot be trusted. Other problems related to the use of mercury meters include the necessity to obtain a reliable zero reading, either by means of taking the instruments to "fresh" air, or by passing the air through a carbon filter or other device to remove mercury vapor.

Whenever mercury aerosol is known or suspected of being present, some other sampling means must be used. The method most widely used is to pass the air sample through an acid solution of potassium permanganate, which traps both the gas and particulate mercury. Analysis then may be performed by a variety of means, with the long-time standard method being one based on the formation of a colored complex with the reagent dithizone. In recent years, this method has been rendered obsolete by the so-called cold vapor methods of analysis in which mercury is reduced to elemental mercury by the add-

ition of a reducing agent such as stannous chloride, and thereafter flushed into a measuring cell, which is basically similar to a mercury vapor meter in construction. Numerous other analytical schemes for mercury measurements have been used (Smith 1972).

In keeping with the provisions of the Occupational Safety and Health Act, increased emphasis has been placed on the measurement of mercury in the work place in such manner that a true eight-hour time-weighted average value can be obtained. Heretofore, air sampling has been performed primarily as previously described, and time-weighted averages have been computed on the basis of data from several locations and time studies of workers under consideration. Investigators at NIOSH and elsewhere have sought to devise a method of attaching a small sampling unit to the individual worker so that personal samples can be taken in the same fashion as widely practiced now for dust exposures. To date these approaches have been based on the use of activated carbon, silver wool, and other substances which effectively collect mercury vapor. In addition, a filter may be included for the retention of mercury present as an aerosol. There is no standard procedure as yet widely accepted for this type of sampling, but there are indications that this will be the preferred method of sampling by OSHA. Once the mercury has been collected, most procedures will complete the determination by some modification of the cold vapor procedure previously mentioned.

There is one problem related to the use of these samplers which is perhaps unexpected, and which is unrelated to the technical problems inherent in the use of the method. It has been stated that individuals working around mercury tend to retain a certain amount of mercury on their clothing, which thereafter acts as a secondary source of mercury vapor. It is further maintained that the actual exposure of the individual with contaminated clothing is therefore somewhat greater than usually indicated by standard methods of sampling. The personal sampler approach does tend to measure the "microenvironment" which the worker breathes, and could, therefore, be considered a more accurate measure of exposure than conventional sampling methods. The problem arises, however, that the present mercury-in-air standards are based upon traditional sampling methods and not on the personal samplers which measure the microenvironment. It is argued, therefore, that the present standard (.05 milligram per cubic meter) must be interpreted by conventional sampling, or else that a higher standard is required for use with the newer sampling methods. As yet there is little published evidence to support this view, but work is in progress at several locations to confirm the observations just noted.

2. Medical Monitoring

While assuredly part of the program of health protection,

the problem remains that presently utilized indicators of mercury absorption suffer from lack of sensitivity. That is, early changes are not sufficiently specific to take definitive action until relatively severe disorders occur. A modality or device capable of providing other substantiating data would increase specificity and sensitivity of medical detection and would enhance the value of medical surveillance. Complicating the nonspecificity of symptomatology in the early stages of mercury induced health change is the phenomenon of biological variability. For reasons that are unclear, individuals subject to similar mercury exposures develop health alterations of variable degrees. Such is manifest by evidence suggestive of either remarkably increased uptake or excretion rates as compared with other workers similarly exposed (Dinman et al. 1958). In other cases, inordinately high urinary levels usually associated with symptomatology in most individuals result in no symptoms in a few individuals. Although the term "sensitive" might be applied to persons in the first category above, and "resistant" to the latter, in actuality these probably represent both tails of a gaussian distribution which describes the occurrence of symptomologic response within a population. Although such individuals can ultimately be detected within a population, increasing the number and quantitative character of such descriptive parameters increases the likelihood of definitively arriving at such determinations.

Another constraint upon medical monitoring arises from the relative paucity of physician manpower resources. Because medical evaluation takes considerable time expenditures in the realm of minimal biological response, resource allocation is of primary importance. Thus if a screening device could safely eliminate a number of individuals in a suspect population, the utilization of scarce physician resources would be enhanced.

3. Use of Biological Samples

Given the difficulties of air sampling and medical surveillance which have been described, biological sample analysis should make the actual quantity of mercury absorbed the desirable vehicle to measure, in contrast to quantification of the variable environment in which the worker must operate. Biological sample analyses, particularly those involving urine and blood, are, in fact, quite useful but may also exhibit inconsistencies that can prove troublesome.

A definitive basis for these inconsistencies cannot clearly be established. Nevertheless, it would appear that mercury excretion from the kidney consists of two phases: (1) clearance from the blood and its accumulation in renal tubular elements, and (2) excretion from such cells into the urine. However, these two processes do not appear to proceed either synchronously or simultaneously. At the onset of mercury exposure, there is an initial delay of maximal

excretion until the kidney accumulates some burden. Thus in occupational exposures (usually intermittent in nature) this delay mechanism may result in dysynchrony of peak exposure with exposure peaks (Gage 1961). Gage further demonstrated that following cessation of exposure mercury continues to be excreted for a considerable period of time. This suggested that mercury was bound irreversibly to renal tubular cell protein. Accordingly, the ultimate excretion would tend to reflect metabolic turnover of protein rather than exposure.

For these reasons, the use of biological samples has not proven to be a highly useful indicator of work exposure. Although this is particularly applicable to spot samples, Gage has suggested that this problem could be greatly overcome if it were possible to collect a total seven-day sample of urine. For obvious reasons, the practicality of this suggestion is minimal.

While the urinary mercury concentration is subject to variations in renal handling of the element and probably has no parallel in other organs, the blood level of mercury is not quite as variable. However, at this time a somewhat tenuous and variable relationship between blood and urine mercury levels and either exposure or toxic effects still applies. Further, there is relatively little data available to assess transfer kinetics between the blood-brain barrier for mercury. For these reasons, a functional assessment of neural function would augment the usefulness of analyses of biological media for control of mercury exposure.

4. Evaluation of Functional Neurophysiologic Activity

The ancient Greeks and Romans had extensive familiarity with the concomitants of chronic mercury intoxication. The latter sent criminals and war prisoners to their mercury mines, near present-day Almaden, Spain, with full recognition that such was tantamount to a death sentence. While Ramazzini also recognized and described grossly the signs and symptoms of occupational mercurialism, the earliest definitive description was published in 1861 by the famed clinician Adolp Kussmaul in his book Untersuchungen Uber den Konstitutionellen Mercurialismus.

Since that time, the signs and symptoms of mercurial intoxication (or erethism) have been frequently observed and reported in detail. These symptoms are commonly subjective and have been referred to as "non-specific" constitutional changes in the Western World, and in the USSR as the "asthenic vegetative syndrome". (Trachtenberg 1969). While the former do not attempt mechanistic explanations of such symptoms, the Russian viewpoint regards such peripheral and central changes as due to imbalances of cortical and subcortical control centers. This control imbalance permits peripheral stimuli (exteroceptive and interoceptive) to act upon the "vegetative" nervous system (or in U. S. parlance, the autonomic nervous system), unbalanced or unmodulated by central, controlling centers. Indeed, consistent with such disturbances in the autonomic nervous system is the finding of

Smith (1972) of a decreased diastolic blood pressure in occupational mercury exposure. Although mechanistic explanations are not available, several investigators also report insomnia or altered sleep patterns, emotional instability and "nervousness".

There is considerable relevance of these emotional aberrations to motor performance decrements. For an understanding of these emotional disturbances characteristic of erethism, it is necessary to refer to certain consistent signs of chronic mercurialism, e.g., tremor and other objective manifestations of neuromotor defects, as well as memory alterations. The first, i.e., tremor, is the gross manifestation of the second; the defects seen here largely refer to aberrations in small hand muscle coordination and control. The combination of these motor and memory defects results in the affected worker experiencing difficulty in performing the simple and expected functions required of daily living, e.g., writing, execution of fine finger and hand manipulations necessary for buttoning, holding a grasped object steadily, etc. The net effect of these defects upon reactive behavior has been graphically reported by Benning (1958) as well as Chaffin and Dinman (1972).

Essentially, the patient becomes aware of these defects and demonstrates exasperation at his being unable to perform what formerly were automatic, natural activities. In part from this perception, plus the fatigue induced by impaired sleep habits, the patient becomes irritable with his maladroit per-

formance and also anxious that others are aware of his incapacibilities. This leads in part to withdrawal from contact with others and irritability secondarily caused by the anxieties engendered by unsatisfactory interpersonal relations. This drawing inward, coupled with anxiety concerning the perceptions of others, ultimately leads to what has been described frequently as a "paranoid" personality pattern. Thus the emotional components of erethism emerge. To what degree cerebral cortical aberrations are responsible for this pattern of behavior is not clear, nevertheless the contribution of the perceived neuromotor disabilities appears significant.

Pathologic description within the central nervous system in chronic mercurialism has infrequently been available in man. Most of the accumulated pathologic data have been derived either inferentially from clinical testing or by use of animal models. Grossly, the pattern of deposition and distribution in animals exposed to low doses of ionic mercury indicates that relatively high levels are present in the cerebellar cortex, part of the hypothalamus, and the posterior portion of the floor of the fourth ventricle (Berlin et al. 1966). Microautoradiographic investigations following vapor exposures (Cassano et al. 1960) have demonstrated more specific localization in the Purkinje and dentate nuclear cells of the cerebellum, the spinal cord, medulla oblongata, pons and the mid-brain. There also appeared to be a relatively greater concentration in grey matter than in white matter.

In contrast to the distributions seen following alkyl mercury administration (Takeuchi 1970), there was relatively little mercury-induced damage found in the calcarine area. This may account for the contrasting lack of visual disturbances seen in inorganic mercury intoxication. Further, relatively less specific localization in the pre-central gyrus (as seen with alkyl exposure) was noted in these low-dose mercury vapor exposure experiments.

Given the predilection for the cerebellar cellular elements, certain of the symptomatic changes noted in inorganic mercury intoxication are accordingly explicable. Disturbances in the fine motor coordination and intention tremor can be attributed to lesions of the cerebellum, since granular cells of the central regions of the hemisphere and vermis are destroyed. Changes in the Purkinje cells are subsequently also noted (Cassano et al. 1966).

In contrast to the low-dose studies of Berlin and Ullberg (1963) (which suggest that the cerebellum, hypothalamus, medulla oblongata, pons and mid-brain were more severely affected than were the cerebral cortices) are the clinically derived pathologic inferences of Vroom and Greer (1972). These latter authors suggested involvement of the cerebral cortices and basal ganglia. However, differences in dose probably play an important role in determining the extent (both severity

and diffuseness) of brain involvement, for it should be noted that these clinical evaluations were based upon heavily dosed human cases.

While the foregoing descriptions emphasize the functional neurologic manifestations of chronic mercurialism, it should be recognized that other organ systems are also affected. Nevertheless, such emphasis reflects the relatively high risk to which nervous tissue is susceptible. Following single doses of labelled mercuric chloride, Berlin and Ullberg(1963) demonstrated that while mercury was taken up very slowly in the brain, once deposited, the rate of elimination was exceedingly slow. They concluded that while accumulation risks were high in kidney and liver, the same net result of excess cumulative risk applied to nervous tissue because of slow elimination from that site.

Subsequent work by the same authors studied mercury vapor exposure and resultant organ uptake. The uptake was even greater for the vapor exposure than with the injected chloride, i.e., approximately ten-times more mercury was found in the brain of vapor exposed animals. Although the elimination rate of mercury from the brain was higher following vapor exposures, the net result of high uptake and relatively slower excretion compared to other organs puts into perspective the central nervous system risk to the following mercury vapor exposure.

Given the above observations, plus clinical reports of neurologic risk, and considering the fact that pathologic deficits of central nervous system cells are essentially permanent, it would seem that early diagnostic indicators of changes in this organ system represent a critical need.

Because functional changes in the nervous system do not readily permit objective evaluation of its state, other indirect indicators of risk have been assayed. While organ loading by other metals may be adequately reflected in their blood or urine concentrations, the ability to generate such correlations are poor for mercury. One reason lies in the reports of wide differentials in specific localizations and turn-over rates both within an organ, e.g., the brain, as well as between various organs. This makes it less likely that excretion of mercury in urine--or its blood concentration--can be successfully correlated with mercury concentrations in all the organs. It is also clear that the slow turn-over in the brain represents a considerable risk for those structures of the brain where mercury is deposited. Ultimately, one must conclude that the likelihood is minimal that urinary excretion or blood concentration will reflect the brain concentration of mercury (e.g., see Vroom and Greer 1972).

Given these considerations, it would appear that an important need in mercury exposure assessment lies in the area of functional testing of nervous system function. This is

especially the case with the brain, since it represents the most sensitive part of the central nervous system as regards mercury effects.

Yet another reason for study of central nervous system function relates to the need for correlating neuropathologic function alterations with mercury localizations as indicated by animal models. Although differences of opinion regarding these localizations probably stem from dose-dependent considerations, the need to elucidate such localizations remains important nevertheless. That is, if early diagnosis is to be achieved, the low-dose animal models suggest the direction neurofunctional testing should take. Since these models consistently indicate cerebellar localizations, testing of that organ's capabilities is indicated in the early--and hopefully reversible--stages. Finally, if such testing could suggest an absence of other sites of localization in what are purported to be low-dosing cases, the significance of more widespread involvement would augment those findings associated with minimal dosing. Combining these differences in the extent of involvement, one can arrive at a dynamic conceptualization of the natural history of chronic mercurialism.

The final value of functional testing rests in its possible ability to delineate the course of toxicity following removal from exposure. If indeed the low-dosing type representation is valid, sequential testing should indicate its validity by demonstrating some degree of reversibility.

For this additional reason, neurofunctional testing can be of importance in and of itself.

The Role and Importance of Functional Testing

Given the foregoing problems, plus the primary goal of health protection, a practical solution is required of the problem of protection of workers exposed to mercury. Given all the possible avenues of approach, several possible courses of action are open:

- (1) Correlate air sampling with health status.
- (2) Validate biological sampling with health status,
- (3) Validate functional testing with health status, or
- (4) Use any combination of the foregoing.

Of each possibility, it can be seen in general that the various possibilities for control might be progressively less difficult and more feasible on a routine basis. Although the first possible course of action is highly desirable, such would require an extremely extensive study, e.g., the Smith, et al. (1970), study carried out in conjunction with the Chlorine Institute. In addition, questions have been posed regarding the validity of area sampling as an adequate reflection of microenvironments associated with each worker and ultimate mercury loadings. As regards the second alternative, consideration of mercury distribution kinetics places validity of this approach in question. Given the foregoing, ultimate health status cannot readily be defined except as direct measures of function or its alteration. It is for

these reasons that emphasis is placed upon the need to develop such measures of function or its alteration. Implicitly, these measures are only practical insofar as they are easily administered, reproducible, quantifiable and sufficiently sensitive as indicators of reversible change. While each of these pre-requisites is crucial, present realities require that especially the last criteria be met. Thus for validation of the latter criterion, neurologic evaluation should indicate sensitivity compatible with minimal non-specific change seen in the toxic states. The emphasis placed by the Soviet Union upon the desirability of setting action levels at such non-specific, pre-toxic stages requires that we seriously consider comparable worker protection efforts if it can be shown that such change represents other than a homeostatic response. While competent Western authorities may be reluctant to set action levels on the basis of non-specific alteration, if relevant, associated functional change can be demonstrated, this should also constitute a acceptable warning indicator in the U. S. for worker protection.

Section III

Description of Study Population and General Protocol

This study involved 142 male volunteers from four different plants. Seventy-seven of these people were working in jobs where daily exposure to inorganic mercury was incurred, thus resulting in them being identified for this study as the Exposed Group. The remaining sixty-five people were classified as Controls, based on the participating plant's industrial hygiene and safety personnel designating that they were not currently, nor had they been recently (within six months) working in areas where mercury exposure could take place.¹ Age matching was requested and was best achieved in the last two plant groups visited.

The first three plant groups (Groups I, II, and III) were engaged in chloralkali manufacturing, while the fourth group (Group IV) worked in a patented process for the manufacturing of magnetic materials. Groups I and II were revisited during the study period. This provided the opportunity to collect some retest data on people who had demonstrated marked reductions in their urine mercury levels as a result of changes in climatic conditions, industrial hygiene

1 The Controls from the first two plants were later found to have excessively high blood and urine mercury levels and can not be classified as "normal" controls in general. More will be mentioned about this in subsequent sections.

controls, and/or jobs which reduced their exposure to mercury. In total, 198 tests were conducted during seven site visits by three investigators.

General Test Protocol

The following is a general description of events at each site visit:¹

1. Set up test apparatus in quiet area of plant (usually Medical Department).
2. Coordinate scheduling of volunteers with plant nurse or medical technician to achieve an approximate interval of between 30 to 45 minutes for each volunteer.
3. Ask each volunteer to read and sign a statement regarding the purposes, risks, and data confidentiality of the study (Appendix A).
4. Have each volunteer fill in a standardized medical questionnaire (Appendix A), and have him designate a physician to whom his personal test results should be sent.
5. Obtain a urine sample in an acid washed bottle.
6. Attach electromyogram (EMG) surface electrodes to the biceps brachii of dominant arm.
7. Instruct the volunteer as to the eye-hand coordination test procedure and have him perform the test four times while recording his performance.

-
1. Details of the data gathering procedures are included in the Methods sub-section in each of the major sections of this report. (Sections IV, V, VI, and VII.)

8. Strap a 15-pound weight and tremor measuring device to his wrist and ask him to hold the weight for five minutes while recording both tremor and EMG signals.
9. Perform the eye-hand coordination test a fifth time immediately after the subject had set the weight down.
10. Obtain a blood sample using 10 ml. vacutainers containing potassium oxalate preservative.

If either the clinical neurological examination described in Section VII or the psychomotor examination described in Section V was performed, as was the case with plant Group II and III, then these tests took place between steps nine and ten in the above sequence of events.

Summary of Independent Variables

A major objective of this study was to gather the necessary data to indicate how specific neurological functions correlate with changes in blood or urine mercury levels. Thus, the current blood and urine mercury levels are the two major independent variables in this investigation. The method of determining the value of each is described in Appendix B.

Other secondary variables that could intervene in any such correlations with blood or urine mercury levels are as follows, along with the arguments for their inclusion in the subsequent data analyses:

1. Height and Weight were included based

on the assumption that these could indicate:
A) a state of physical fitness (weight), B)
a change in muscle loading performance during
the weight holding test, or C) a change in
the motion dynamics required during the eye-
hand coordination test.

2. Age was included based on its potential of indicating: A) a state of physical fitness, or B) a slowed simple decision and motor performance capability as indicated by other studies.
3. Smoking was included based on: A) its potential for reducing the person's endurance capacity (through the CO effect on the oxygen disassociation from hemoglobin), B) the heavy smoker possibly absorbing more mercury vapor by the increased ventilation required of him when moderately physically active (due to his reduced oxygen diffusion capacity in the lungs).
4. Duration of Exposure was included based on the assumption that those people exposed for a short period may react biologically differently from those exposed over many years.

A summary of the resulting values for each of these independent variables is presented in Table I and is based on the first visit to each plant. It should be noted that much of the other data gathered in the "yes/no" questions presented in the medical questionnaire (Appendix A) was to assure that the person was not suffering from any illness, under medication, or had a recent accident which could affect his performance on the tests. In addition, the questions

Table I

Summary of Independent Variables from First Visit Studies

Plant	I			II			III			IV			ALL (I, II, III, & IV)		
Group	Control	Exposed	Combined	Control	Exposed	Combined	Control	Exposed	Combined	Control	Exposed	Combined	Control	Exposed	Combined
Sample Size	15	20	35	14	23	37	26	24	50	10	10	20	65	77	142
Height (inches)	70.2 (3.08)	69.5 (2.42)	69.8 (2.70)	69.3 (3.15)	70.6 (2.98)	70.1 (3.7)	69.7 (2.68)	69.5 (2.66)	69.6 (2.64)	69.3 (2.16)	69.7 (2.67)	69.5 (2.37)	69.7 (2.74)	69.8 (2.71)	69.8 (2.72)
Weight (pounds)	172 (18.7)	174 (30.0)	173 (30.8)	166 (32.4)	172 (31.2)	169 (31.3)	177 (23.6)	184 (26.0)	181 (24.9)	179 (20.2)	183 (19.9)	181 (19.6)	173 (24.6)	178 (30.2)	176 (27.8)
Age (years)	31.2 (7.0)	27.2 (7.3)	28.9 (7.4)	49.9 (6.4)	41.5 (7.4)	44.7 (8.0)	33.6 (9.6)	36.4 (8.9)	35.1 (9.3)	37.9 (6.45)	36.9 (6.67)	37.4 (6.41)	37.1 (10.39)	35.7 (9.47)	35.4 (9.89)
Dur. of Exp. (months)	--	30.8 (26.7)	--	--	93.2 (85.4)	--	--	25.2 (16.1)	--	--	90.6 (49.1)	--	--	55.9 (62.5)	--
Cigarette (packs/day)	0.29 (0.49)	0.0 (data on 6 subjects only)	0.21 (0.48)	0.79 (0.55)	0.83 (0.68)	0.81 (0.63)	0.42 (0.56)	0.42 (0.56)	0.42 (0.56)	0.45 (0.60)	0.20 (0.34)	0.33 (0.49)	0.52 (0.58)	0.48 (0.60)	0.50 (0.59)
Blood Mercury (ug/100 ml)	2.17 (1.10)	6.25 (3.66)	4.45 (3.47)	5.89 (2.71)	17.11 (5.77)	12.74 (7.32)	0.90 (0.45)	3.97 (3.04)	2.56 (2.72)	0.93 (0.38)	4.51 (2.54)	3.49 (2.70)	2.49 (2.51)	8.56 (6.90)	5.97 (5.22)
Urine (ug/liter)	68 (53)	288 (240)	197 (216)	152 (100)	787 (471)	547 (486)	18.3 (22.1)	143 (104)	84 (99)	7.11 (3.26)	129 (69.7)	71.5 (79.8)	62.6 (78.1)	374 (399)	240 (342)

Note: Numbers in parentheses indicate Standard Deviation

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concerning the existence of general neurological symptoms were hoped to be of direct use in the study as dependent variables. These, however, were answered in the negative by all but a few people (less than 10% had any positive responses), thus not providing enough contrasting data to be useful in the subsequent statistical analysis.

Section IV

Neuromuscular Measures of Tremor and Surface Electromyograms

This section describes two neuromuscular functions which were quantitatively assessed in the study. The first is the measure of both the frequency and magnitude of forearm tremor when statically loaded. The second is the surface electromyogram power spectra obtained from an isometric contraction of the biceps brachii. What follows is a description of the method used in obtaining both types of data, followed by the results of the analysis of the data. In general, the results in this section describe the correlations between the subjects' blood and urine mercury levels at the time of testing and the following neuromuscular characteristics:

- * The frequency distribution of the forearm tremor for eight seconds when holding a 15-pound load strapped on the wrist.
- * The magnitude (RMS Voltage) of forearm tremor for eight seconds while holding a 15-pound load strapped on the wrist.
- * The power spectral distribution of the surface electromyogram obtained for eight seconds from the biceps brachii while holding a 15-pound load strapped on the wrist.
- * The magnitude (RMS Voltage) of the surface electromyogram obtained from the biceps brachii for eight seconds while holding a 15-pound load strapped on the wrist.
- * The localized muscle fatigue rate as judged by changes in the surface electromyogram power spectral distribution while holding a 15-pound load strapped on the wrist for a period up to five minutes.

This section also includes the results of a retest of some of the people who on first testing had high blood and urine mercury levels. In essence, this retest of people was performed to determine if any of the above listed neuromuscular characteristics that were abnormal on first testing of those people having elevated blood and urine mercury levels were still abnormal after four to six months when their blood and urine mercury levels had decreased. In other words, is there a recovery in these functions?

The section ends with conclusions and recommendations regarding these neuromuscular characteristics and mercury body burdens as measured by blood and urine levels.

Methods of Data Collection and Analysis

Equipment. Both the forearm tremor and biceps surface EMG were obtained simultaneously. To accomplish this a four-channel FM tape recorder (Hewlett Packard Model 3960) having a bandwidth from DC to 312 Hz. (at 15/16 IPS) was utilized. A specially constructed preamplifier (10^{11} ohms input impedance, 5K Hz. response) was used to amplify the signals with known gains. The EMG electrodes were Hewlett Packard Model 14057. The tremor transducer was specifically constructed to detect changes in a force load of less than two ounces. An oscilloscope was used to monitor both the EMG and tremor signals during the tests to assure that peak clipping did not occur.

Data Collection Procedure. The data were collected by the following procedure:

1. The subject was shown the test apparatus with an explanation of the procedure to be employed.
2. The subject was seated and his dominant arm was supported by an elbow rest which allowed a 90° elbow angle with the forearm unsupported.
3. Three surface electrodes were applied to his dominant arm in the following configuration after vigorously rubbing electrode past into the skin at the following sites of application:
 - * Ground Electrode, over the medial epicondyle of the elbow.
 - * Reference Electrode, over the lateral epicondyle of the elbow.
 - * Active Electrode, over the anterior center of the biceps brachii when contracted to give a 90° elbow angle.
4. A padded wrist cuff was strapped around the wrist to which both the force sensing transducer and a 15-pound load were attached.
5. The subject was instructed to pick up the load by flexing his arm to a 90° elbow angle and hold it there for five minutes, or until he was fatigued¹ if this occurred before five minutes had elapsed.

During the five-minute holding task both the EMG and tremor signals were recorded continuously, along with 15-second timing comments. A picture of a typical test set-up is depicted in Figure 1.

Data Analysis Procedure. Both the EMG and tremor signals were analyzed by first digitizing the signals over a period of eight seconds into 14 successive blocks of data and then performing a Fast Fourier Transformation to yield the power

1. Normally a load of this magnitude could be supported for over 15 minutes (Chaffin 1969).

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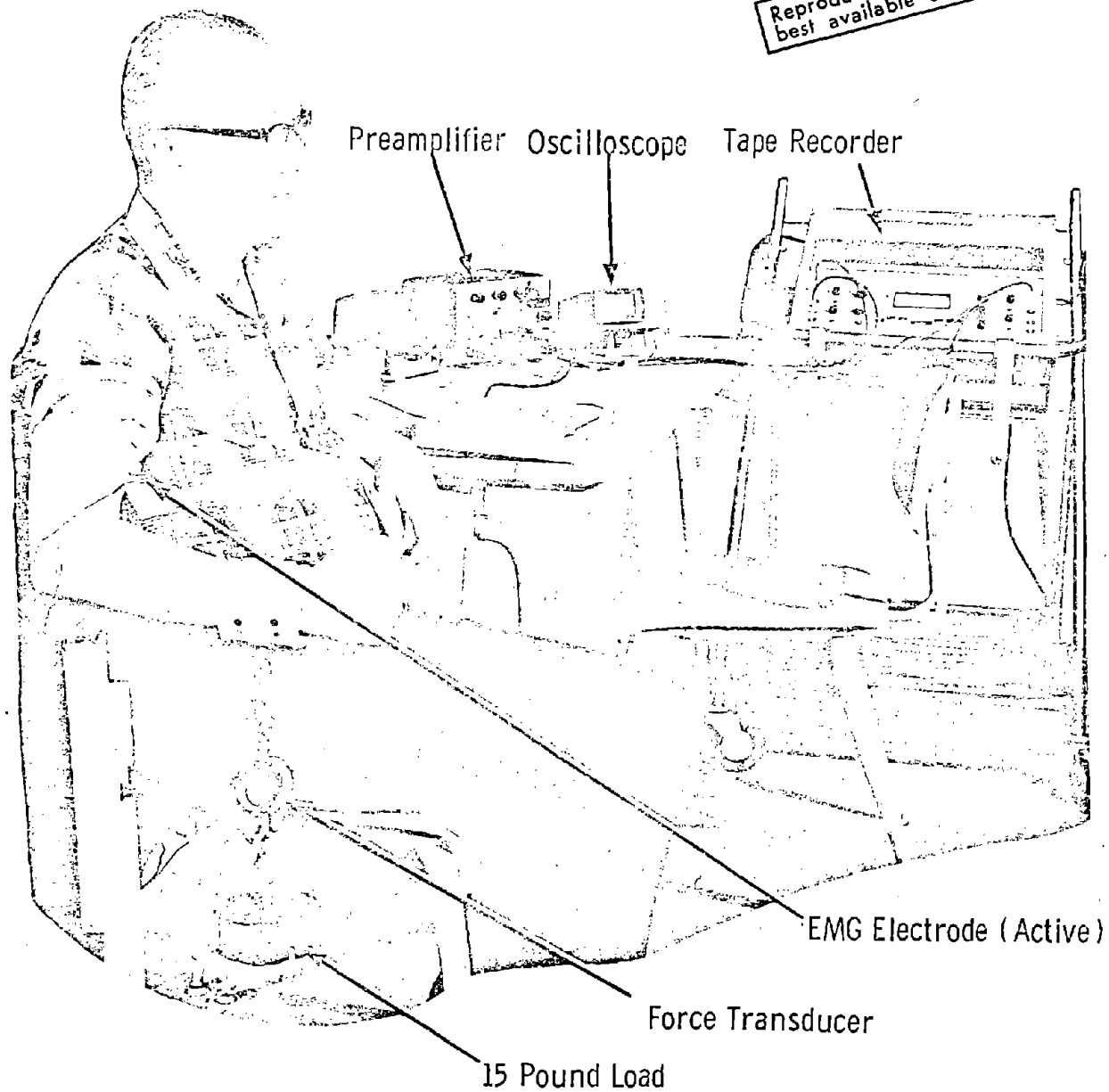


Figure 1. Typical Test Setup for EMG and Tremor Measurements

spectrum. The total power of the signal was then divided into the power within preselected frequency bands which resulted in a normalized power spectrum where the percentage of the total power in each spectral band was a function of the frequency of each band. In the case of tremor, the power spectra were computed over the frequency range from 5.5 hertz to 24.5 hertz in 0.25 hertz increments. The EMG power spectrum analysis was performed from 4.0 hertz to 200 hertz in bandwidths of 2.0 hertz.

The following statistical characteristics were then computed to parameterize the power spectra for subsequent correlation with blood and urine mercury levels:

- * Central tendency of the frequency of the signal was estimated by modal, median, and mean frequencies of the power spectrum.
- * Band width of the signal was estimated by the standard deviation of the power spectra, and by percent power within selected bands.
- * Lack of symmetry of the frequency of the power about the mean frequency was estimated by the skewness coefficient of the power spectrum.
- * Magnitude of the signal was estimated by the RMS of the EMG voltage.

Each of these parameters was regressed onto the independent variables described in Section III, Table I, (e.g., blood and urine mercury levels at the time of testing, duration of occupational exposure to mercury, age, weight, height, and cigarette smoking rate). A stepwise least-squares-error algorithm was used to determine the singular and combinatorial correlations of each of the independent variables with the

tremor and EMG parameters. A value of $\alpha \leq 0.10$ was chosen for acceptance or rejection of any one variable in explaining the variance observed in the parameter values for the population studied.² Both the order that the variables were brought into the resulting prediction equations and the effects on the resulting multiple correlation coefficients were tabulated. In the case of the blood and urine mercury levels, a simple correlation was also performed on both the tremor and EMG data to disclose any general effects of mercury on the populations regardless of the secondary population variables of age, height, weight, and cigarette smoking.

The stepwise multiple regressions were performed on all the people in the study, entitled a combined group (i.e., a group containing both the exposed people and their controls), as well as on the exposed group only. The latter evaluation was necessary to ascertain the effect that the variable, "duration of exposure to mercury" had on the EMG and tremor parameters.

As it turned out, due to missing or poorly recorded data, the combined group contained data from 133 people (9 fewer than the total people visited) and the exposed group had 75 people (2 less than visited). With a sample of 133 people, a correlation coefficient above about 0.15

²The α level of 0.10 was used to assure that secondary variables were included to disclose their potential additive effect, thus disclosing the potential for future research of them.

indicates the two variables are significantly correlated, a universally true result with a 90% probability, and if above approximately 0.18, it indicates the variables are significantly correlated at 95% probability of being universally correct.³

Results of Tremor Analysis

As has been discussed earlier in this report, tremor is a major clinical finding associated with mercury intoxication. Since quantitative measures of tremor frequency and magnitude have recently been developed (Chaffin 1969, Kazantzis 1968, Stern 1971), it appeared reasonable to use such measures to determine if the various blood and urine mercury levels found in the chronically exposed working population correlate with consistent changes in tremor frequency and magnitude.

This was accomplished by regressing the initial tremor power spectrum parameters (i.e., mean, mode, median, standard deviation, skewness and RMS voltage) onto the population variables (i.e., current blood and urine mercury levels, duration of occupational exposure to mercury, age, weight, height, and cigarette smoking rate). The results of such a correlation are depicted in Tables II and III, for both the combined group of 133 people and the exposed group of 75 people, respectively.⁴ The following was concluded from this analysis:

³ Since the exposed group had 75 people, correlations of about 0.20 and 0.24 for 90% and 95% significance, respectively, are required.

⁴ The first number in a table cell indicates the order that the variable entered the resulting prediction equations, with the number in parentheses being the multiple correlation coefficient, and the sign indicating the direction of effect of the variable brought into the regression.

TABLE II

Significant Multiple Correlation Coefficients
of Tremor Spectra Parameters

Combined Group (Exposed and Control) Cases=133

Stepwise Regression Summary

Independent Variables					
Dependent Variables	Height	Weight	Age	Smoking Rate	Mercury Level
Blood Study					Blood
Median Frequency	3 (.55)+	-	2 (.51)+	-	1 (.46)+
Modal Frequency	3 (.50)+	-	2 (.48)+	-	1 (.42)+
Mean Frequency	2 (.52)+	-	3 (.55)+	-	1 (.47)+
Std. Dev. Frequency	-	-	-	-	1 (.29)+
Skewness of Frequency	-	3 (.43)-	2 (.40)-	-	1 (.34)-
RMS Voltage	-	-	-	1 (.22)+	-
Urine Study					Urine
Median Frequency	3 (.55)+	-	2 (.52)+	-	1 (.45)+
Modal Frequency	3 (.53)+	-	2 (.51)+	4 (.54)+	1 (.43)+
Mean Frequency	3 (.53)+	-	2 (.50)+	-	1 (.45)+
Std. Dev. Frequency	-	-	-	-	1 (.23)+
Skewness of Frequency	-	-	2 (.39)-	-	1 (.30)-
RMS Voltage	-	-	-	1 (.24)+	-

RMS Voltage has a sample size of 102 people.

TABLE III
Significant Multiple Correlation Coefficients
of Tremor Spectra Parameters

Exposed Group

Cases=75

Stepwise Regression Summary

Dependent Variables	Independent Variables					
	Height	Weight	Age	Smoking Rate	Log Duration	Mercury Level
Blood Study						
						Blood
Median Frequency	2(.56)+	-	-	-	-	1(.46)+
Modal Frequency	2(.52)+	-	-	-	-	1(.45)+
Mean Frequency	2(.53)+	-	-	-	-	1(.43)+
Std. Dev. Frequency	-	-	-	2(.29)-	-	1(.21)+
Skewness of Frequency	-	2(.39)-	-	-	-	1(.29)-
RMS Voltage	-	-	-	-	-	-
Urine Study						
						Urine
Median Frequency	2(.52)+	-	-	-	-	1(.45)+
Modal Frequency	-	4(.61)+	-	3(.59)+	2(.55)+	1(.50)+
Mean Frequency	2(.49)+	-	-	-	-	1(.42)+
Std. Dev. Frequency	-	-	-	-	-	-
Skewness of Frequency	-	2(.33)-	-	-	-	1(.26)-
RMS Voltage	-	-	-	-	-	-

RMS Voltage has a sample size of 53 people.

- * Elevated blood or urine mercury levels are significantly correlated with increased tremor frequencies, as measured by mode, median, and mean estimates of the central tendency of the power spectrum.
- * The magnitude of tremor did not appear to correlate with elevated blood or urine mercury levels or other population variables, with the exception of smoking rate which positively correlated in the larger combined group of people.
- * The taller and older people also had consistently increased tremor frequencies.

The resulting prediction equations to estimate the effects of each of the significant population variables on the tremor parameters are listed in Appendix C.

To illustrate the effect of elevated blood and urine mercury levels on typical tremor spectra, Figure 2 was developed. This depicts the mean tremor power spectra for two groups of five men each, matched on mean age and height, but with quite different blood and urine mercury levels, as indicated. What is clearly evident, as noted from the stepwise regressions for the total group of 133 people is that the tremor power spectra is generally of a higher frequency.

To further statistically define the generalized relationship between blood and urine mercury levels and tremor frequency in the study population, the best singularly correlated tremor parameter (i.e. mean frequency) was regressed onto the $\log_e$ transformation of the blood and urine mercury

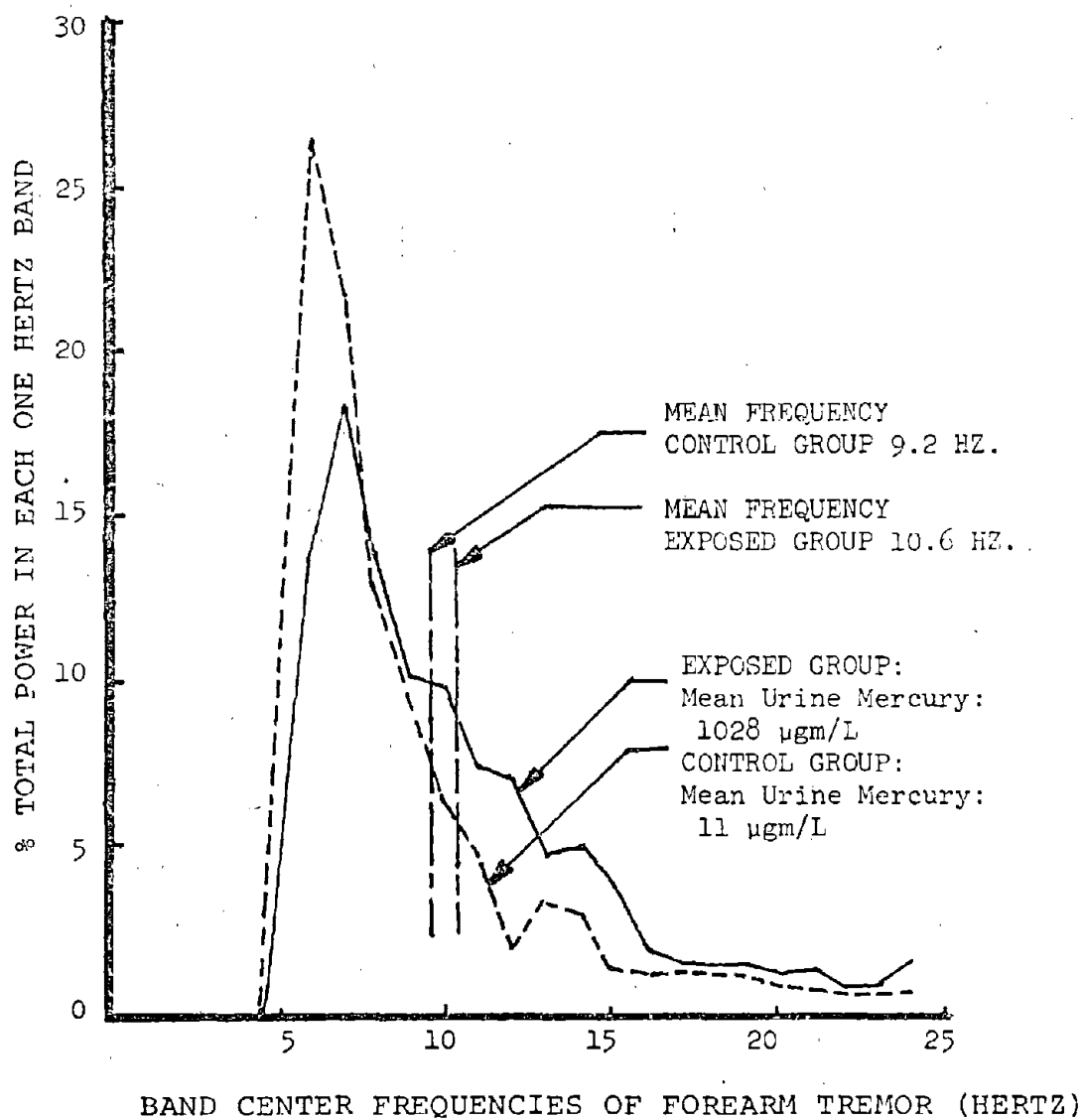


FIGURE 2

TYPICAL TREMOR SPECTRA FROM FIVE CONTROLS
AND FIVE EXPOSED SUBJECTS OF MATCHED
AGE AND HEIGHT

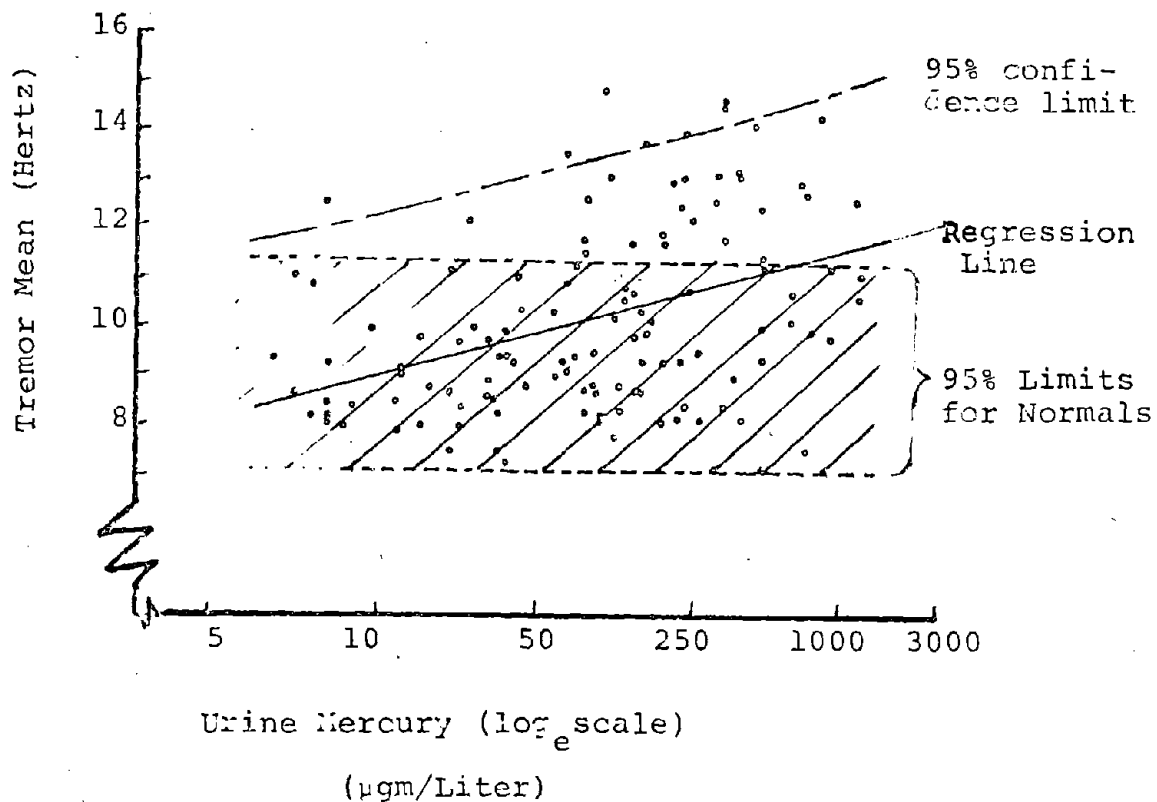
levels.⁵ The results of this regression using urine mercury levels (blood mercury disclosed the same relationship) is depicted in Figure 3. Both an average regression line (solid) and the 95% upper confidence limit (dashed) are plotted, along with the resulting prediction equation for the regression line.⁶

Also included for comparison is the normal range of mean tremor frequency (cross-hatched zone) based on the unexposed people with low current mercury burdens tested in Control Group III and IV (as summarized in Appendix D).

Figure 3 clearly depicts the general population effect on mean tremor frequency regardless of age and height of the people. It is believed to be the singularly most powerful result in this study. Much more discussion of this result will be developed later in this section.

⁵ The $\log_e$ transform was chosen to standardize the variance of the mercury measurement error, and to provide unbiased estimates of the effects of mercury due to most of the people having relatively low mercury levels. It should be noted that other transformations of blood and urine mercury levels were used but did not significantly change the resulting correlations.

⁶ The plot of urine mercury levels rather than blood mercury levels in Figure 3 is not meant to indicate that either is consistently better correlated with any of the dependent measures. Indeed, in all cases the correlations coefficients for both have been shown, as in the preceding Table II and III for tremor. In general, neither blood nor urine mercury levels are singularly better correlated with any of the dependent measures in this study, though Shashikant Kelkar is further evaluating this possibility as part of his Ph.D. dissertation.



Prediction Equation for Regression Line:

$$\text{Tremor Mean (Hz)} = 7.8 + 0.53 * \text{LOG}_e(\text{Urine})$$

Correlation Coefficient = 0.45

Figure 3

Regression of Tremor Mean Frequency
and Urine Mercury Level in
Combined Population

Results of EMG Analysis

As in tremor, the concern of the initial analysis of the EMG power spectra was to define the correlation that its characteristics might have with a person's blood or urine mercury levels. Once again the multiple step-wise regression approach was taken, where-in the parameters describing the EMG power spectrum obtained immediately after the person picked-up the 15 pound load were independently regressed on-to the population variables (i.e., current blood and urine mercury levels, duration of occupational exposure to mercury, age, height, weight and cigarette smoking rate.) The results are given in Table IV and V, for both the combined group of 133 people and the exposed group of 75 people, respectively. The following was concluded from this analysis:

The most consistent relationship is between blood and urine mercury levels and the standard deviation of the power spectrum. This shows a positive correlation, indicating a widening of the band width of the EMG with higher blood and urine mercury levels. The effect had some dependency on age in the combined group, Table X, but was a singular effect when just the exposed group was evaluated, Table XI. Central tendency measures (median, mean, and mode) displayed little sensitivity to mercury burdens. Aging tended to reduce the usual positive skew of the distribution slightly. The exposure duration had no effect on the frequency distribution of the EMG, but did correlate with increased EMG magnitude on a smaller sample size. Smoking rate tended to reduce the mean frequency slightly, but was not a consistent effect.

The resulting prediction equations from this analysis are given in Appendix C.

TABLE IV
Significant Multiple Correlation Coefficients of
EMG Spectra Parameters

Combined Group (Exposed and Control) Cases=133

Stepwise Regression Summary

Dependent Variables	Independent Variables				
	Height	Weight	Age	Smoking Rate	Mercury Level
Blood Study					Blood
Median Frequency	-	-	-	-	1(.21)-
Modal Frequency	-	-	-	-	-
Mean Frequency	-	-	-	-	-
Std. Dev. Frequency	-	-	2(.36)+	-	1(.28)+
Skewness of Frequency	-	-	1(.22)-	-	2(.27)+
RMS Voltage	-	1(.21)-	-	-	-
Urine Study					Urine
Median Frequency	-	-	-	1(.16)-	-
Modal Frequency	-	-	-	-	-
Mean Frequency	-	-	-	-	-
Std. Dev. Frequency	-	-	2(.42)+	-	1(.36)+
Skewness of Frequency	-	-	1(.23)-	-	-
RMS Voltage	-	1(.21)-	-	-	-

RMS Voltage is based on 82 cases.

TABLE V

Significant Multiple Correlation Coefficients of
EMG Spectra Parameters

Exposed Group

Cases=75

Stepwise Regression Summary

Dependent Variables	Independent Variables					
	Height	Weight	Age	Smoking Rate	Log Duration	Mercury Level
Blood Study						Blood
Median Frequency	-	-	2(.36)+	1(.27)-	-	3(.41)-
Modal Frequency	-	-	-	-	-	-
Mean Frequency	-	-	1(.24)+	2(.32)-	-	-
Std. Dev. Frequency	2(.38)+	-	-	-	-	1(.28)+
Skewness of Frequency	-	-	1(.26)-	-	-	-
RMS Voltage	-	-	-	-	1(.43)	-
Urine Study						Urine
Median Frequency	-	-	1(.26)+	2(.36)-	-	-
Modal Frequency	-	-	-	-	-	-
Mean Frequency	-	-	1(.25)+	-	-	-
Std. Dev. Frequency	2(.42)+	-	-	-	-	1(.35)+
Skewness of Frequency	-	-	1(.27)-	-	-	-
RMS Voltage	-	-	-	-	1(.43)	-

RMS Voltage is based on 35 cases.

Because the EMG bandwidth correlation to mercury burden remained a significant effect with the increased sample population, it was deemed worthy of a band-by-band analysis to determine which frequencies are significantly affected. Four frequency bands were selected for this analysis, based on earlier studies by the principal investigators: 1) A low frequency band of 4 to 30 Hz., which would be sensitive to synchronized recruitment of motor units, which also causes tremor; 2) Two middle frequency bands of 40 to 70 and 60 to 90 Hz. which would encompass the modal frequency with cutoffs where transitions in power distribution may be prevalent due to mercury, as indicated in earlier pilot studies; and 3) A higher frequency band of 100 to 200 Hz., which would be more sensitive to increased polyphasic action potentials and/or high frequency discharging units. The significant multiple correlation coefficients are depicted in Table VI.

What is striking is that the middle frequency bands did show reduced power while the low and high frequency bands had increased power. This suggests that elevated mercury burdens cause a compound effect on neuromuscular function. One functional change is probably in the temporal recruitment pattern of the motor units wherein they become more phasic, thus causing both the increased low frequency EMG power and the mercury-related tremor modifications. A second effect of mercury on the EMG power spectrum is to increase the high frequency power (above 100 Hz.), which

TABLE VI

Significant Multiple Correlation Coefficients
of EMG Band Analysis

Combined Group (Exposed and Control) Cases=133

Stepwise Regression Summary

Dependent Variable (% Power in each Band:)	Independent Variables				
	Height	Weight	Age	Smoking Rate	Mercury Level
Blood Study					Blood
4 to 30 Hz.	-	-	-	1(.34)+	2(.42)+
40 to 70 Hz.	-	-	1(.28)-	3(.39)-	2(.38)-
60 to 90 Hz.	-	-	-	2(.34)-	1(.28)-
100 to 200 Hz.	-	-	1(.21)+	-	-
Urine Study					Urine
4 to 30 Hz.	-	-	-	1(.34)+	2(.37)+
40 to 70 Hz.	-	-	2(.35)-	3(.38)-	1(.26)-
60 to 90 Hz.	-	-	-	1(.23)-	-
100 to 200 Hz.	-	-	2(.26)+	-	1(.19)+

could easily be attributed to increased polyphasic muscle action potentials which have been recently associated with clinical studies of mercury intoxication (Vroom and Greer, 1972).

To further illustrate the effect of mercury on the EMG power spectrum comparative spectra were developed based on the average spectra from five controls and five exposed individuals. These two groups were matched on average age and height. Figure 4 depicts the results. As indicated statistically in the preceding Table VI, the power in both the low and high frequency EMG components is higher in the exposed individuals than in the unexposed, thus causing a wider band width (as indicated by the standard deviation increasing from 27.4 to 32.2 hertz).

In an effort to determine if elevated blood and urine mercury has a general effect on EMGs from people chronically exposed to mercury, a simple correlation of the EMG power spectra standard deviation and the $\log_e$ transformation of blood and urine mercury values was developed. The results of the urine mercury correlation are depicted in Figure 5. As in the earlier analysis of tremor, both a general regression line, 95 upper confidence limit, and normal values from control groups III and IV (Appendix D) are depicted. What is concluded is that EMG power spectra band width increases significantly as the current blood or urine mercury

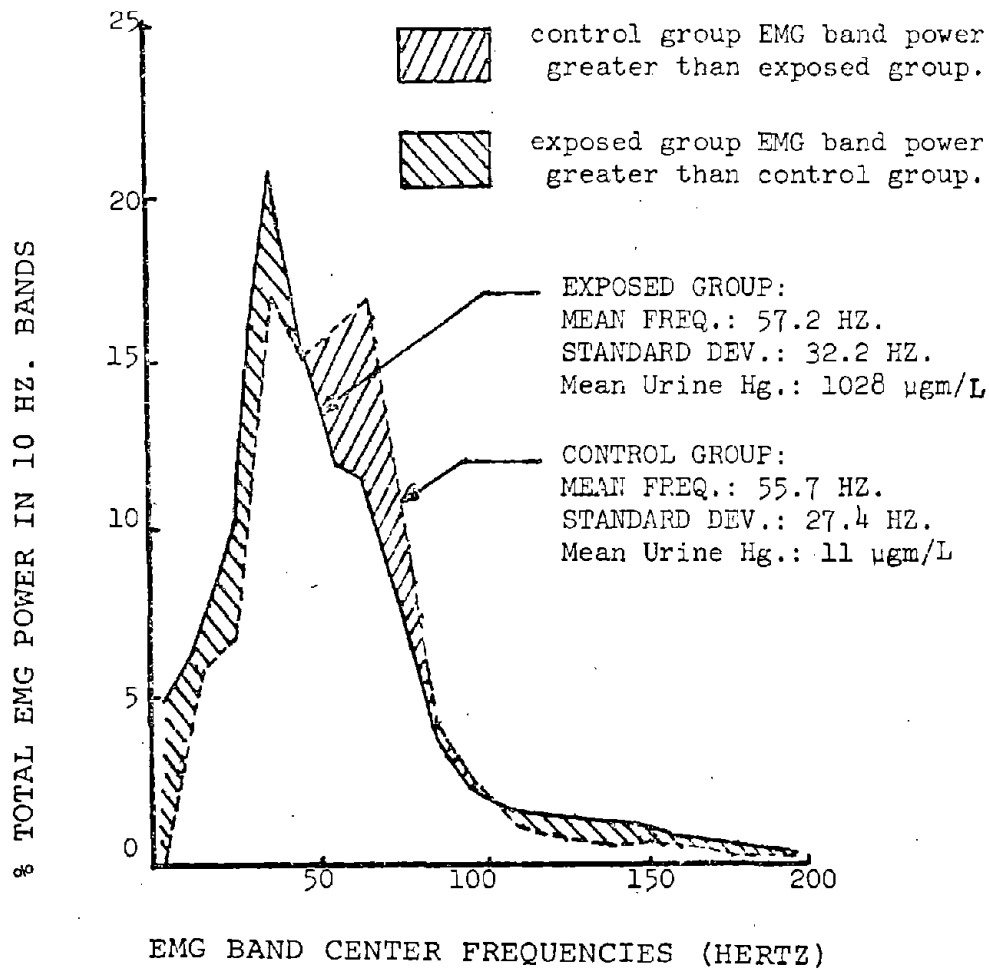
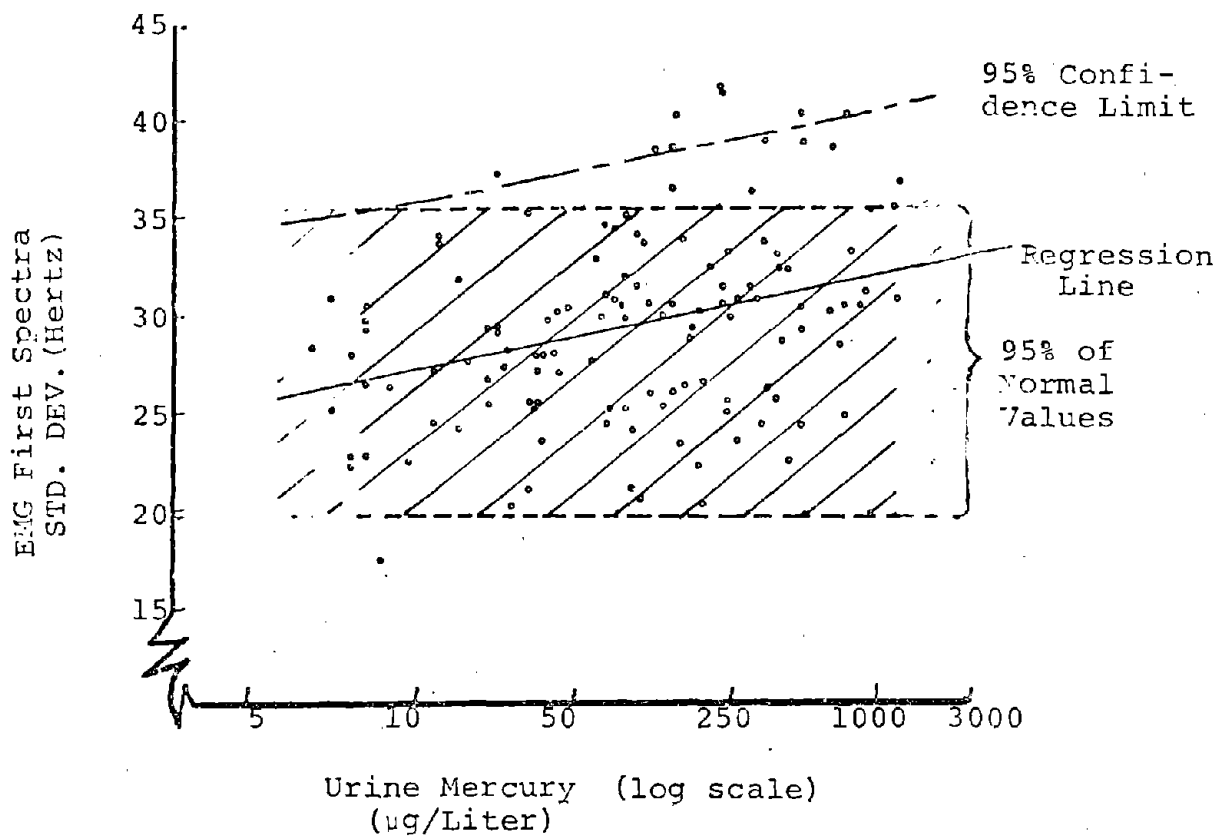


FIGURE 4

TYPICAL EMG SPECTRA FROM FIVE CONTROL AND
 FIVE EXPOSED SUBJECTS MATCHED ON AGE & HEIGHT

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Prediction Equation for Regression Line:

$$\text{EMG First Spectra STD. DEV. (Hz)} = 24.87 + 1.05 * \text{LOG}_e(\text{Urine})$$

Correlation Coefficient = 0.34

Figure 5

Regression of EMG Band Width (Standard Deviation)

and Urine Mercury Levels in

Combined Populations

level increases in chronically exposed workers regardless of their age, height, weight, and cigarette smoking. The length of the exposure time necessary for this effect to occur appears to be not significant (i.e., even an exposure of four months could cause this change).

Results of EMG Mean Frequency Changes During the Five Minute Holding Period (muscle fatigue)

A somewhat separate question concerning the effect of mercury on EMGs is to what extent does localized muscle fatigue, as measured by EMG mean frequency shifts toward lower frequencies during an exertion, correlate with elevated mercury body burdens? For this analysis successive 15-second EMG signals were analyzed over the entire five-minute period of weight holding. A linear regression of the mean frequencies of the successive power spectra with time of holding was then computed. The slope of these regressions was then used as a measure of fatigue, as described earlier by Chaffin (1969).

The significant correlation between the mean frequency slopes and the population variables are displayed in Table VII. What is concluded is that localized muscle fatigue is only slightly correlated with increased weight and body height, two variables that could easily be rationalized by the following: the height effect could be caused by its also indicating a larger mechanical loading of the biceps brachii, due to the forearm of a tall person providing a longer lever arm upon which the 15 pound weight on the wrist

TABLE VII

Significant Multiple Correlation Coefficients of the
Slopes of the EMG Spectra Mean Frequencies

Combined Group (Exposed and Control)

Cases=133

Dependent Variables	Independent Variables				
	Height	Weight	Age	Smoking	Mercury Level
Blood Study					Blood
EMG Spectra Mean Slope	-	-	-	-	-
Urine Study					Urine
EMG Spectra Mean Slope	1(.16)+	-	-	-	-
Exposed Group Cases=75					
	Height	Weight	Age	Smoking	Log Duration Mercury Level
Blood Study					Blood
EMG Spectra Mean Slope	-	1(.24)+	-	-	-
Urine Study					Urine
EMG Spectra Mean Slope	1(.23)+	-	-	-	-

can act. Similarly, the body weight also increases the weight of the forearm and hand, thus loading the upper arm more greatly for the heavier person or, possibly, the heavier weight individuals were, indeed, in poorer physical condition, at least as far as their arm endurance capabilities. At any rate, the major finding was that it could not be shown that those individuals with elevated body burdens did indeed suffer localized fatigue at a faster rate than those not having elevated mercury burdens.

Results of Neuromuscular Retesting of People After Reduction in Blood and Urine Mercury Values

The value of the test/retest approach has been widely recognized in the open literature during the last decade. This recognition has stemmed from the problems associated with small sample sizes and large individual biological and psychological differences. Considerably more understanding about human performance has been gained by following longitudinally the variations in functional abilities. With this as a motivation, workers were retested after being found to have greatly reduced mercury body burdens four to six months after their initial tests, due to either increased industrial hygiene controls or removal from exposure. A test/retest analysis was performed on the two sets of data obtained from these people. A student's "t" test of

mean differences between their two test results was used as a measure of change from the first to the second test.

The data for these comparisons were gathered by retesting 32 people who in first visits at Plants I and II were found to have elevated mercury burdens and/or some positive test findings. Some retest data were lost in recording of the second EMG, reducing this retest sample size to 24 people.

The means of the various EMG and tremor test parameters are displayed for both the first and second tests in Table VIII. As can be seen at the bottom of Table VIII, the mercury burdens were reduced significantly for the groups between the first and second tests. The significant concomitant changes in the EMG and tremor parameters are indicated by an asterisk on the second mean value.

What is concluded is that both the EMG power spectrum bandwidths (standard deviations) and the forearm tremor mean frequencies were reduced significantly on subsequent testing. In fact, the mean of the tremor measures was outside normal limits (see the earlier Figure 3) when first tested but on second testing was well within these limits. Apparently recovery of more normal neuromuscular function as measured by these parameters was associated with reduction in mercury body burdens brought about by a four to six month period of reduced exposure or removal from direct exposure.

Table VIII

Test/Retest Results for
Tremor and EMG Parameters

Sample Size	Test Means	Tremor Parameters ¹			
		Mode	Mean	Standard Deviation	Skewness
32	First Test	9.6	11.4	3.9	1.00
	Second Test	6.6 *	9.3 *	3.6 *	1.50 *
		EMG Parameters ²			
		Mode	Mean	Standard Deviation	Skewness
24	First Test	40.9	54.7	31.7	1.54
	Second Test	40.0	52.4	28.6 *	1.59

* Designates mean difference is significant at $\alpha \leq .10$.

¹ First test mean blood mercury level = 13.0 $\mu\text{gm}/100 \text{ ml}$.
 Second test mean blood mercury level = 7.4 $\mu\text{gm}/100 \text{ ml}$.

First test mean urine mercury level = 562 $\mu\text{gm}/\text{L}$.
 Second test mean urine mercury level = 347 $\mu\text{gm}/\text{L}$.

² First test mean blood mercury level = 11.4 $\mu\text{gm}/100 \text{ ml}$.
 Second test mean blood mercury level = 6.7 $\mu\text{gm}/100 \text{ ml}$.

First test mean urine mercury level = 599 $\mu\text{gm}/\text{L}$.
 Second test mean urine mercury level = 292 $\mu\text{gm}/\text{L}$.

Summary, Discussion and Recommendations

The following are the major tremor and EMG related findings and recommendations for future research and applications:

Summary of Tremor Findings

Increased blood and urine mercury levels due to chronic exposure to inorganic mercury are significantly correlated with an increase in the mean frequency of static loaded tremor. The magnitude of the tremor, however, was not found to correlate with mercury blood and urine levels. Some individual effects due to age and height were observed, but these were secondary to the mercury effects. Recovery of elevated tremor frequency was demonstrated following four to six months at lower mercury exposure which greatly reduced the previously high blood and urine mercury levels.

Discussion of Tremor Findings

At present only theories exist as to the basis of physiological and pathological tremor (See Mardsen, et al., 1969 for a recent discussion). Whether mercury acts to modify the stretch reflex loop time, which is believed by many to be the basic controller of physiological tremor (see Chaffin, 1973), or whether it acts at the spinal cord or the cerebellar level in some more complex manner to

increase the synchronization rate of alphamotoneurons, is beyond the scope of this investigation. However, the latter theory appears to be more plausible than the loop time hypothesis, based on both the relatively high mercury uptake in the cerebellum and spinal cord, and due to a recent study by Vroom and Greer (1972). This study indicated that mercury may slow peripheral nerve action potential conduction velocities. The effect would be to then lower tremor frequency due to a delay in the stretch reflex loop time. On the other hand, a normal delay in the stretch reflex loop is provided by the speed of contraction of the muscle fibers. Vroom and Greer (1972) also indicated that increased mercury correlated with denervation. If denervation was of the larger and slower contracting motor units, then increased tremor frequency could result, due to increased activation of the remaining fast contracting motor units. Regardless of the specific neurological effects of mercury, the tremor frequency increase with mercury body burden provides both an excellent neurological research tool and a potentially useful diagnostic technique for establishing an objective index of health status in regards to suspected mercury intoxication.

Summary of EMG Findings

The surface EMG power spectra obtained during an eight-

second weight holding task indicated a complex neuromuscular effect due to mercury. EMG power increases in both low and high frequency bands were significantly correlated with elevated blood and urine mercury levels. In addition, the amplitude of the surface EMG was significantly correlated, though on a smaller sample size, with the length of time the person was exposed to inorganic mercury, but not with the body burden at the time of testing. Population variables of age, height, and smoking rate were found to also have secondary effects on the EMG power spectrum. A significant reversal of the initial EMG spectra changes in people having elevated body burdens was demonstrated when these same people were exposed to only limited amounts of mercury for a four to six month period, thus greatly reducing their blood and urine mercury levels. Muscle fatigue, as measured by prolonged exertion EMG changes, could not be shown to correlate with elevated mercury body burdens.

Discussion of EMG Findings

It has been well recognized in the literature that mercury exerts a complex effect on neuromuscular functions. The surface EMG power spectra changes reported in this investigation are consistent with these in the following ways: The increase in high frequency power in the EMG has been

demonstrated previously in pathologies where increased numbers of polyphasic muscle action potentials were present (Chaffin, 1969, Walton, 1952, and Gersten, et al., 1965). Polyphasic muscle action potentials are caused by a breakdown of the synchronized muscle fiber depolarizations in the motor unit. Their presence has been recently attributed in several case studies to denervation of the muscle fibers by mercury (Vroom and Greer, 1972). Polyphasic action potentials have also been documented in various myopathies where muscle fibers in a motor unit are not well synchronized in their membrane depolarizations (Walton, 1952). It would therefore appear that the increase in high frequency (100-200 Hz.) power in the surface EMG is probably due to increased polyphasic muscle action potentials. Whether these are due to denervation or alteration in the muscle fibers functions remains to be researched.

The increase in the EMG low frequency power is probably caused by increased synchronization of the motor units. Such "temporal bunching" in the motor units recruitment pattern has been related to increased EMG low-frequency power by Stern (1971) and has been correlated with tremor (Chaffin, 1969 and 1973). Since tremor changes are also correlated with mercury, increased synchronization of the motor units could explain both the low-frequency EMG increases and the tremor modifications. Whether such

synchronization is caused by increased anterior horn cell spatial summing, as proposed by Buchthal (1950) in fatigue, or by cerebellar dysfunction is beyond the scope of this investigation. It should suffice to say, however, that the surface EMG power spectra technique is a sensitive indicator of the type of neuromuscular functions affected by mercury and therefore should be included in further studies, as indicated in the recommendations to follow.

Recommendations based on Tremor and EMG Findings

Since the techniques are painless and relatively easy to perform, it is recommended that routine tremor and EMG monitoring of the type described in this report be instigated with a group of people who are exposed to measurable and periodically differing levels of inorganic mercury (due to job rotations, seasonal variations, and ventilation changes). It would be the intent of such a study to better establish the levels and durations of exposure that would be permissible for a population and for an individual based on consideration of neuromuscular health. Such a study should indicate: 1) the capability of a person to reverse the neuromuscular effects of an exposure to mercury, 2) how long such a recovery would take, 3) whether the neuromuscular effects are cumulative with repeated exposure/recovery periods, and 4) whether some workers'

neuromuscular functions are highly sensitive to even short periods of exposure at certain levels.

It is also worth noting for future study that on a subset of the population (35 exposed people) the length of time exposed to mercury did correlate ($r=.43$) with the EMG magnitude (RMS voltage), but not with the urine or blood mercury concentrations, as presented earlier in Table V. This finding is potentially important, in that it could indicate that longer term exposures result in decreased muscle fiber contractility, thus requiring greater motor unit recruitment. Exact measures of EMG magnitudes are difficult to ascertain, however, and thus even a speculative interpretation is not well justified until a greater data base is developed.

Finally, these quantitative measures of neuromuscular function should be used to study the effectiveness of such drugs as British Anti-Lewisite (BAL) in controlling the neuromuscular dysfunctions related to mercury intoxication.

Section V

Psychomotor Testing and ResultsIntroduction

In severe cases of mercury intoxication there are consistent clinical findings of gross psychomotor impairment. This has been characterized by tremor, rigidity, and mental dysfunction in patients. The neurological changes which occur in exposed individuals apparently can affect both the functions of the motor pathways and the psychological aspects of processing information. There have been indications that these dysfunctions may occur in possibly the cerebral hemispheres, the temporal lobe, or possibly in the transfer of information between the right and left cerebral hemispheres.

While gross psychomotor impairment has been found among the classical symptoms of severe mercury intoxication, it was of interest to this project to use psychomotor testing to try and identify the types of impaired functions in workers exhibiting lower levels of mercury intoxication. It would be desirable to find quantitative measures of worker performance which would be sensitive enough to indicate decrements in psychomotor capabilities long before they would be discovered through more traditional and qualitative clinical testing. The objective then of these tests is the development of psychomotor test measures which can give an early indication of small changes in a worker's psychomotor capability and which might also be linked to lowered productivity or safety on the job.

Test Selection

The Human Performance Laboratory at the University of Michigan has previously been involved in relating psychomotor testing to worker performance. The objective of earlier work done by Poock (1968) was the development of psychomotor tests that could be utilized in selecting workers with a particular ability to do given kinds of production tasks. Having already gained experience and baseline data as a part of this study it was logical that some of these same psychomotor tasks or adaptations of them be utilized in conjunction with this study. The classes of tests chosen for this study included: two and four choice decision times, simple reaction time, finger and toe tapping, discrete positioning eye-hand coordination, blind toe pointing, and finger manipulation (pencil flipping). All of the above tests are reported in this section with the exception of the discrete positioning eye-hand coordination which will be reported in Section VI. The rationale for selecting specific tests now follows.

The two and four choice decision time task can be utilized as a measure of the rate of processing information. Abnormalities in the ability to perform this task may suggest involvement of the temporal lobes.

The tapping task may offer indications of nervous system dysfunction or defects in transfer of information within the brain. Both finger tapping and foot tapping were utilized to detect deteriorations of the motor pathways which should be more obvious in the longer length pathways. Thus, any deterioration or abnormality in finger tapping ability should be magnified in toe tapping performance. Between these two tapping tasks then we have measures of both lower and upper extremity performance.

In our earlier research Pooock (1968), the finger manipulative task (pencil flipping) showed the best correlation with a worker's ability to perform manipulative type production tasks. It is also an easy task to administer. For that reason this particular test was included.

The tests were administered to three plant groups over a ten month period. All 11 tests were administered to the first group of individuals, but several of the tests were not administered to the second and third groups. This omission of certain tests during the latter studies was justified on the basis of the initial results obtained in testing Group 1, and also because of the necessity to decrease the amount of total time required for subjects to complete the test battery. The following section will describe these tests in detail with each test and its replication, if there was one, given a specific test number for reference throughout the reporting.

Description of Psychomotor Tests

Test No. 1: Two Choice Decision Time, Trial #1, (Figure 6). For the purposes of this experiment, decision time (or reaction time) is defined as that time which elapses between the onset of a visually displayed digit and the initiation of a response as measured by the subject's pressing a button with his finger. This definition is consistent with traditional and current experiments involving simple and choice reaction times.

For the Tests 1 through 5, the subject was seated such that he could observe a visually displayed number about 18 inches from his eyes and 1 inch by 1-1/2 inch in size (see Figure 6). In this first test, he was told that either a number 2 or a number 3 would appear with equal probability. As soon as the number appeared and he identified it, he was to push a correspondingly numbered button located between him and a visual display. Preceding the appearance of the number, his left forefinger was placed on top of the number 2 button, his right forefinger was placed on top of the number 3 button. It thus required only the slightest movement of either finger to indicate a response to the visual stimulus.



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Figure 6 Decision Test and Experimental Layout



Figure 7 Finger Tapping

Each subject was given five trials during which no data were collected. Thereafter, he was given twenty trials with the numbers 2 and 3 randomly appearing and with an intertrial interval for all Tests 1-5 ranging from 1 to 6 seconds randomly.

Test Nuber 2: Two-choice Decision Time, Trial #

2. Following Test Number 1, the subject was given a rest period of about 30 seconds. Thereafter, an additional 20 trials occurred as a replication to Test Number 1, with the learning trials omitted.

Test Number 3: Four-choice Decision Time, Trial

#1. In this test, the subject was told that the numbers 1, 2, 3, and 4 would appear equally often and he must again push the appropriate button that corresponded to the number which appeared visually. The index and forefingers of the right hand were placed on top of buttons 3 and 4. The subject was given 5 learning trials before the 20 trials during which data was collected.

Test Number 4: Four-choice Decision Time, Trial

#2. After a 30-second rest period, the previous test Number 3 was replicated with the learning trials omitted.

Test Number 5: Simple Reaction Time. To determine

simple reaction time only the Number 3 appeared on the visual display but with a random inter-trial interval of up to 6 seconds. The subject placed his dominant forefinger on the button Number 3 and was told to press that

button as soon as he saw the number appear in the visual display window. After 5 learning trials, 20 additional trials followed during which data was collected. This test was not replicated.

Test Number 6: Finger Tapping (Figure 7). Following Test Number 5, the subject was given a 2-minute rest period. The subject's dominant hand and arm were then rested on the table top in front of where he was sitting. With the hand and fingers in an unbended condition, the subject was able to rest his index and forefingers on a 1-1/2 inch diameter button. This button was raised above the plane on which the arm and hand rested about 1/2 inch (see Figure 7). The subject was then told that his task was to tap on the button as fast as he could, alternating between his forefinger and index finger. He was asked to keep his fingers and hands as straight as possible. He was told that each trial would last about 10 seconds and that there would be several trials. Initially, he was given one trial to learn the task. After he began tapping, the recorder was turned on and data were collected for 5 seconds after which he was told to stop tapping. Data were collected for a total of three trials and he was given about 10 seconds between trials. The data consisted of a time history of tapping over the five second period. These same data were collected for all tapping tests.

Test Number 7: Toe Tapping (Right Foot) (Figure 8).

Following Test Number 6, the subject rotated his chair 90°

until he could comfortably rest the heels of both feet on the floor while easily reaching 2 side-by-side 1-1/2 inch response buttons with his large toes. The buttons were elevated 1 inch off the floor with one quarter inch clearance between them. The subject was asked to tap the button on the right as fast as he could with his right toe, keeping the toe as straight as possible. The left foot was allowed to be placed anywhere comfortable to the subject. Similarly to Test Number 6, each trial lasted 10 seconds during which only five seconds of data were collected. Following one learning trial, he was given three subsequent data collection trials spaced about 10 seconds apart.

Test Number 8: Toe Tapping (Left Foot) (Figure 8). In the identical fashion as the previous experiment, the subject was then asked to perform the tapping tests with his left toe operating on the left button in front of him. He was free to place the foot not being used in any position comfortable to him.

Test Number 9: Toe Tapping (Alternating) (Figure 9). After about 30 seconds rest, the subject was then asked to position his feet so that he could comfortably reach the left and right buttons before him with his left and right large toes respectively. He was then asked to alternate tapping between his left and right toes as fast as possible for a period of 10 seconds for each trial. After one learning trial, he performed three subsequent trials with 10 second



Figure 8 Single Foot Tapping

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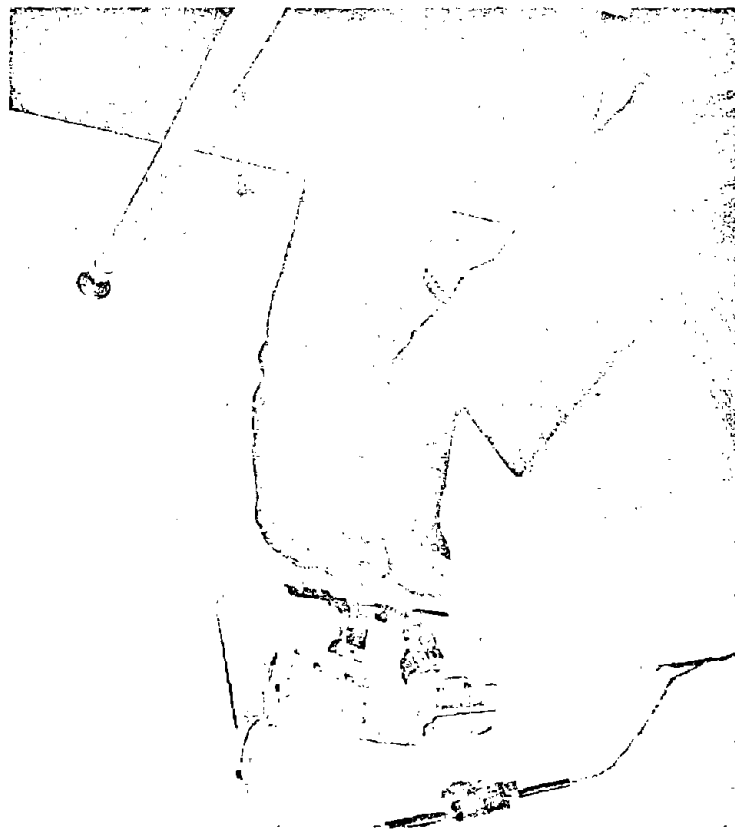


Figure 9 Alternating Foot Tapping

rest periods between each trial.

Test Number 10: Blind Toe Pointing (Figures 10 and 11). While seated in a straight-backed chair, the subject's dominant foot was placed such that his heel was vertically below his knee and resting in a horizontal V-block which was part of the toe pointing apparatus. The apparatus was flat and laid horizontally on the floor in front of the subject. There was a series of concentric circles displayed on the floor with the center located 11 inches to the right and 13 inches in front of the center of the V-block heel rest. The subject was asked to look down at these circles and fix in his mind the location of their center. The objective of the task was to move his foot such that the end of his big toe was exactly in the center of the concentric circles. For the five practice trials allowed, he was permitted to look at the target point while moving his toe to it. For the fifteen trials to follow, his vision of the target was restricted and the movement was made from memory. Between trials he was permitted to look at the target but no knowledge of results was provided.

Test Number 11: Pencil Flipping. Using a standard unsharpened Number 2 wooden pencil, the subject was asked to use his thumb, forefinger, and index finger and rotate the pencil 180°. The pencil was initially placed in a vertical position. After it was rotated 180°, the subject was to tap it on the table top once. This he

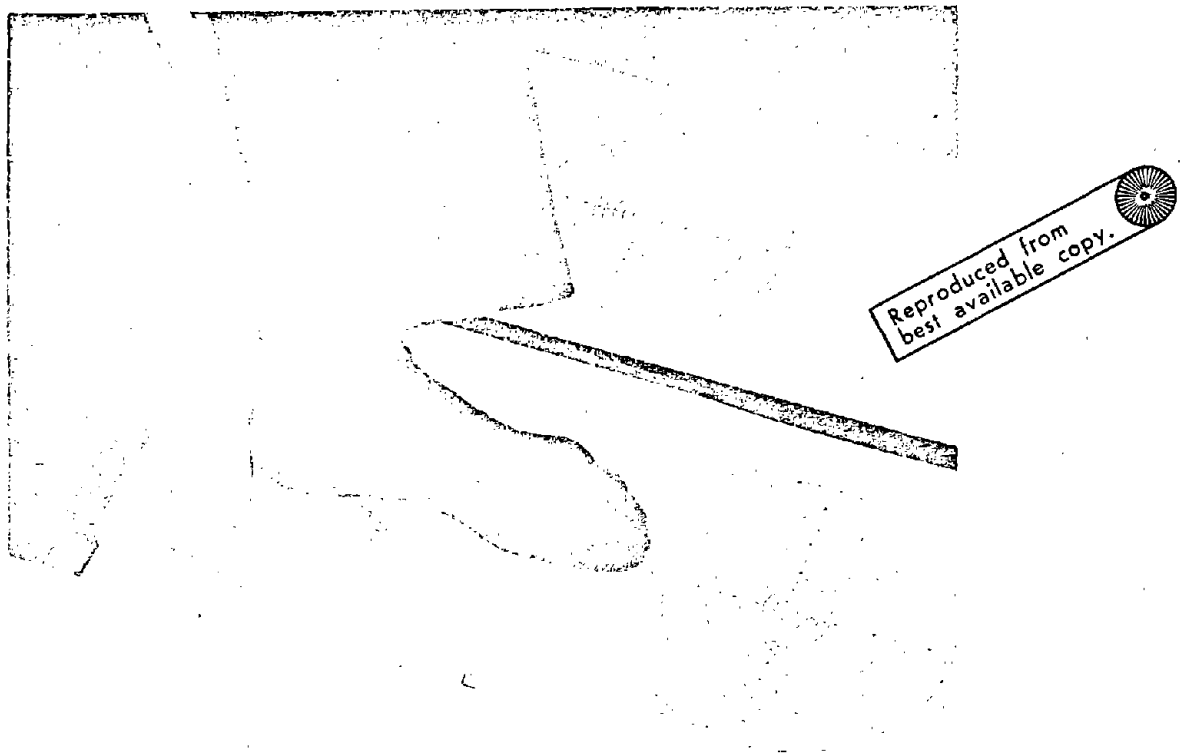


Figure 10 Blind Toe Pointing - Ready Position

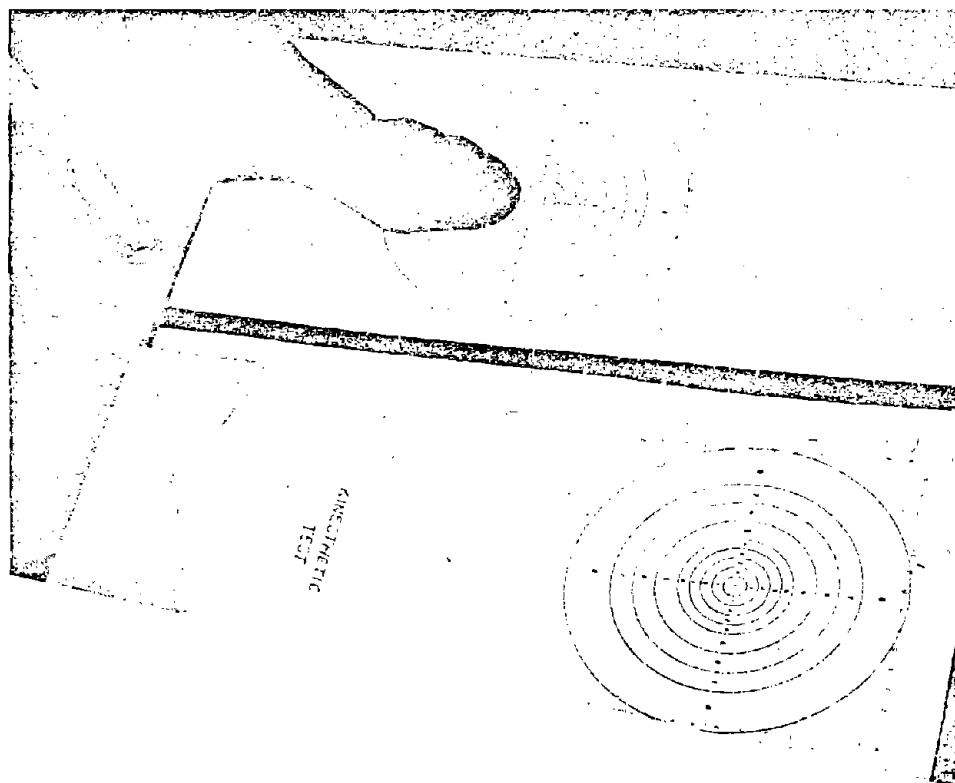


Figure 11 Blind Toe Pointing - Pointing Position

repeated after each 180° rotation. He was also asked to make the rotations in one direction only. The total number of rotations was 25. He was to do this as fast as possible without dropping the pencil. The data collected was the time to complete 25 rotations of 180°. If the pencil was dropped, the subject picked it up and continued while the stop watch remained running.

Psychomotor Tests Used vs. Subject Group

The psychomotor test battery described above was first used in the revisit of plant Group II. The second time the psychomotor tests were used was for the first visit to plant Group III. The third time a battery of psychomotor tests was administered was in the retesting of 11 subjects from plant Group II after they had been away from the mercury exposure for four to six months. Whenever reference is made to combined data in subsequent analyses, it is the data from plant Groups II and III which have been used. No new tests were added to the battery used in the study of plant Group III; however, there were some deletions. First, since plant Group II data indicated very high correlations between replications of decision tasks, it was not considered necessary to repeat the two and four choice decision tasks. Instead of two sets of data with twenty trials per set, the plant Group III data have only one set of twenty trials for the two and four-choice decision tasks. (Tests #2, #4 and #10 have been thus elimi-

nated.) Second, the blind toe pointing task provided no interesting results in the study of plant Group II and was thus eliminated. Table IX lists a comparison of the psychomotor tests administered to the various plant groups.

TABLE IX

STUDY GROUP VERSUS PSYCHOMOTOR TESTS USED

Test Number	Name	Group II First Test	Group III	Group II Retest
1	Two Choice Decision Time, Set #1	X	X	X
2	Two Choice Decision Time, Set #2	X		
3	Four Choice Decision Time, Set #1	X	X	X
4	Four Choice Decision Time, Set #2	X		
5	Simple Reaction Time	X	X	X
6	Finger Tapping	X	X	X
7	Toe Tapping (Right Foot)	X	X	X
8	Toe Tapping (Left Foot)	X	X	X
9	Toe Tapping (Alternating)	X	X	X
10	Blind Toe Pointing	X		
11	Pencil Flipping	X	X	X

NOTE: An "X" indicates tests administered versus subject group.

Data Analyses

Gross Performance "Results" of Plant Groups II (First Test) and III. In this first analysis, the gross performance data from all subjects in test Groups II and III were combined. These dependent measures were tested against seven independent factors using stepwise linear regression as described in Section IV. The independent factors used in the analyses included:

1. Height
2. Weight
3. Age
4. Duration of exposure
5. Number of cigarettes smoked per day
6. Blood mercury level
7. Urine mercury level

The significant results of these stepwise regressions performed on psychomotor data are listed in Table X. It will be noted therein that tests #2, #4, and #10 do not appear for reasons mentioned previously. It is seen that the important independent factors were age, mercury level in body, and height.

TABLE X

PSYCHOMOTOR STEPWISE REGRESSION RESULTS

Groups II and III Data (All Subjects and Trials Combined)

Test Number	Name	Statistic	Ref.	Independent Factors		
				Age	Mercury ¹ Level	Height
1	Two Choice Decision Time	Mean	2	1(.39)+	2(.48)-	--
		S.D.	2	1(.34)+	2(.40)-	--
3	Four Choice Decision Time	Mean	2	1(.42)+	--	--
		S.D.	2	--	--	--
5	Simple Reaction Time	Mean	2	1(.45)+	--	--
		S.D.	2	--	--	--
6	Finger Tapping Rate	Mean	2	1(.33)-	2(.42)-	--
		S.D.	2	--	1(.27)-	--
7	Right Toe Tapping Rate	Mean	3	1(.38)-	2(.42)-	--
		S.D.	3	--	--	--
8	Left Toe Tapping Rate	Mean	3	1(.40)-	2(.49)-	--
		S.D.	3	--	1(.21)-	--
9	Alternating Toe Tapping Rate	Mean	3	1(.32)-	2(.38)-	--
		S.D.	3	1(.25)-	2(.31)-	--
11	Pencil Flipping Time	Mean	4	1(.39)+	--	--
		S.D.	4	2(.35)+	--	1(.30)+

NOTE:

Number preceding bracket is the order in which variable enters the regression with significance at 90% confidence level.

Number in bracket is the multiple correlation coefficient after the variable enters regression.

Sign after bracket is the sign of the regression coefficient for that variable.

1. Blood or urine is used here, whichever has a higher correlation.
2. A plus sign means decision performance decreases as independent factors increase in value.
3. A plus sign means tapping performance improves as independent factors increase in value.
4. A plus sign means pencil flipping performance decreases as independent factor increases in value.

From inspection of the decision tasks (Tests #1, #3 and #5) it is noted that age effects explain most of the correlation. This is interpreted to mean that as age increases, there is poorer performance. Ironically, in the case of the two choice decision task, the mercury level tends to have a cancelling effect on the age factor (it reduced the decrement in performance due to age). Note that a similar effect in the mean performance was recognized with respect to the maze test data to be described in Section VI.

The finger and toe tapping tasks (Tests #6 and #9) also were affected by the age factor. However, mercury level was a strong second factor in the case of mean tapping rates and was of first importance in two out of three standard deviations of tapping rates. This result initiated a closer analysis of tapping performance which is reported in the following section.

Table X indicates the tapping tests in particular as being affected by the level of mercury intoxication. With increasing levels of body mercury, the mean rate of tapping capability apparently decreases. The fact that these results were significant in all tapping tests makes the test a prime candidate for further exploration.

Of further interest are the results concerning the standard deviation of tapping rates across the three trials. The indications are that with increasing levels of intoxication the subject tends to have less difference in his tapping rate

across the three trials for each test. There is no immediately obvious rationale for this finding. One theory to explain this could be that if mercury intoxication does reduce the motor performance limits of individuals, then there could not be an occasional high performance from an individual on a given trial. This lack of capability in the high range would thus result in more consistent across trials performance but at a lower overall performance level. Thus, mean performance would be decreased and so also would the variation (standard deviation) of performance across trials; and this was the result found and reported above.

Inter-Tapping Time Analysis. A second approach to analyzing tapping is to take a more micro view of what is happening to the time between individual taps in a given trial. This time is called inter-tapping (I.T.). Such an approach seemed justified to check on possible cyclical patterns or for micro psychomotor difficulties in accomplishing the tapping tasks. Since all tapping was recorded on magnetic tape, it was possible to analyze these times between taps for all subjects and trials in Groups II and III. The primary dependent variables derived were the mean and standard deviation of inter-tapping times per subject, test, and trial. This variable was then utilized in conjunction with the previously noted seven independent factors in the stepwise linear regression analysis.

Since mean inter-tapping time is a reciprocal of mean tapping rate, it was expected that results shown in the previous Table X would be duplicated, and they were. The results for the standard deviations of inter-tapping times were disappointing. In no case was there a significant variation in inter-tapping times attributable to any of the seven independent factors tested. On the basis of the small sample size used the analysis of inter-tapping times did not appear to be fruitful as a sensitive measure of mercury intoxication. This in no way subtracts from the value of gross tapping rate performances previously noted as being a very good measure.

Retest of Group II. Psychomotor tests which were previously reported as showing positive correlations with body mercury levels show even stronger correlations when analyzed by individual subjects who were at considerably lower mercury levels in the retest.

The same psychomotor test battery as was administered in the first visit with Group II was repeated, as shown in Table IX. In this retest of Group II, data were collected on 11 of the same subjects who had either initially high body burdens or abnormal test results when initially tested six months earlier. Recall that these individuals had been away from mercury exposure for from four to six months.

A comparison of the test/retest of these 11 subjects is summarized in Table XI. In the left column of the Table are

TABLE XI
TEST/RETEST PSYCHOMOTOR PERFORMANCE DATA
Plant Group II

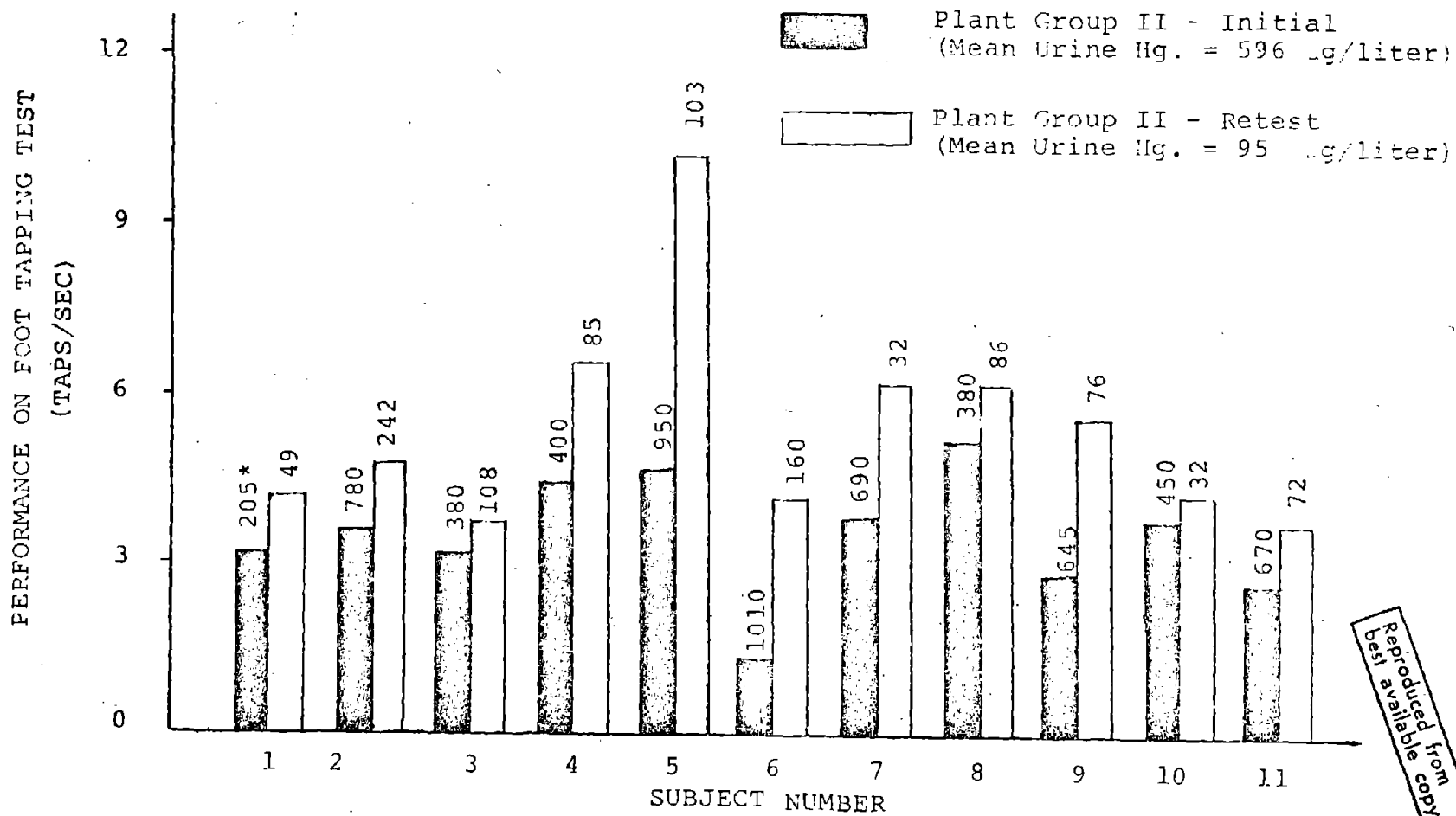
TEST	MEAN	STD. DEV.
<u>Four Choice Decision Time</u>		
First Test Mean	.622 sec	.125 sec
Second Test Mean	.621 sec	.104 sec
Significance Level		(.05)
<u>Two Choice Decision Time</u>		
First Test Mean	.449 sec	.084 sec
Second Test Mean	.470 sec	.087 sec
Significance Level		
<u>Simple Reaction Time</u>		
First Test Mean	.414 sec	.085 sec
Second Test Mean	.322 sec	.067 sec
Significance Level	(.08)	(.10)
<u>Finger Tapping Rate</u>		
First Test Mean	3.86/sec	.40/sec
Second Test Mean	5.38/sec	.65/sec
Significance Level	(.05)	
<u>Right Toe Tapping Rate</u>		
First Test Mean	3.52/sec	.50/sec
Second Test Mean	5.44/sec	.46/sec
Significance Level	(.002)	
<u>Left Toe Tapping Rate</u>		
First Test Mean	3.52/sec	.26/sec
Second Test Mean	4.12/sec	.34/sec
Significance Level	(.08)	
<u>Alternating Foot Tapping Rate</u>		
First Test Mean	4.26/sec	.42/sec
Second Test Mean	4.98/sec	.50/sec
Significance Level	(.10)	
<u>Pencil Flipping Test</u> (Time per 25 flips)		
First Test Mean	19.9 sec	1.8 sec
Second Test Mean	19.6 sec	1.4 sec
Significance Level		

the various tests with First vs. Second Test Means calculated only for the same 11 subjects. These two means were tested for their statistical difference using the student "t" distribution. The First Test blood mercury mean for 11 subjects was 11.8 $\mu\text{g}/100\text{ ml}$; the Second Test blood mercury mean was 1.0 $\mu\text{g}/100\text{ ml}$. The difference in blood mercury means is 10.8 μg ., which is significant at $\alpha=.1$. The First Test urine mercury mean for 11 subjects was 596 $\mu\text{g}/\text{liter}$ and the Second Test urine mercury mean was 95 $\mu\text{g}/\text{liter}$. The difference in urine mercury means is 501 μg ., which is also significant at $\alpha=.1$.

It is seen that the Right Toe Tapping mean time shows the strongest improvement with decreased mercury levels. A graph of the individual results is contained in Figure 12. Besides Right Toe Tapping improvement, all other tapping tasks and simple reaction time had significant improvement.

This reversal of tapping performance is in complete support of the earlier results with the combined data and strongly supports its use as an indicator of capability decrement with increased body mercury.

The improvement in simple response time was less expected. Recall that the combined data results of plant Groups II and III indicated a decrement in the two-choice decision time task; but it did not occur in the four-choice decision task. These results seem to suggest a possible decrement in the lower level psychomotor type tasks. Since the retest data results did not duplicate those of the initial Group II and



*Numbers along Bar Graph indicate Urine Hg. level (μ g/liter)

Figure 12 Test/Retest Comparison of Right Foot Tapping Rates

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III testing, this suggested decrement effect is not as strongly supported as those effects relative to tapping.

Summary and Discussion of Psychomotor Test Results

The results of the psychomotor testing conducted as a part of this research indicate that there are sensitive psychomotor tests which can be used in monitoring the effects of certain toxic elements on human performance. Among the various tests used in conjunction with mercury, it appears that finger and toe tapping type tasks should be prime candidates for consideration as one of these monitoring type measures of performance. A lower order decision task may also have merits for this purpose.

Support for the above conclusion concerning tapping comes from two statistically positive findings. First, there was a significant correlation between level of body mercury and tapping rate capability among a cross-section of some seventy-seven workers. As body mercury increased, tapping rate capability decreased. Second, a group of eleven workers initially with mild body mercury intoxication were retested after their body burden levels were considerably decreased. Tapping tasks showed a significant reversal in performance. The possibility that there may have been some artifact to have caused this was not ignored. But no such artifact in the experimental methodology or in the psycho-social physiological being of the subjects could be isolated.

The extent to which these psychomotor performance decrements are reversible cannot be determined by this study, only that there is a considerable degree of reversibility. The extent of this effect could, however, be determined by a longitudinal study of a population with cyclical intoxication levels.

Regarding neurological interpretation, the results for the tapping tasks may be indicative of some dysfunction in the pyramidal or extra-pyramidal paths. However, one could also implicate involvement of the cerebellar hemispheres. It has been suggested that foot tapping vs. individual foot performance may be used to diagnose a problem in information transfer between right and left cerebral hemispheres. Since alternating tapping was not less than individual foot tapping, it would seem that either such a problem did not exist, or else these tests were not sufficiently sensitive to detect such a problem if it did in fact exist. There was also no clear distinction between finger and toe tapping performance. Thus the particular tapping tests used did not indicate an involvement of the longer motor pathways to the feet as contributing to more decrement in performance. Other researchers (Vroom and Greer, 1972) have suggested temporal lobe involvement in their study involving relatively high levels of mercury intoxication. It was diagnosed by them on the basis of some irreversible short term memory effects. Our study included a qualitative clinical neurological exam which did

not reveal a short term memory loss in subjects. It is, however, recommended that a quantitative experimental memory measure be included in any future test battery being considered for potential monitoring purposes. The decision test reported herein probably did not include as much temporal involvement as a short term memory task, and no specific neurological interpretation of the decision task results will be attempted.

Finally, it is noted that the positive findings in this study which point favorably to the use of psychomotor performance testing are only a beginning of efforts to develop a sensitive test battery for mercury related performance decrement evaluation. Simple decision tasks and finger-foot tapping tasks showed promise as a result of this research effort. Short term memory tests are suggested as a further possibility for future testing. Additional longitudinal data on mercury exposed individuals would be particularly valuable in conclusively determining the reliability of these performance monitoring tests. It is also possible that there are other psychomotor types of tests which may eventually prove to be even better monitors of performance decrements and they should be searched for. The encouraging results of this study should be justification not only for additional mercury related research but also for future efforts involving even more sophisticated quantitative testing over populations having exposure to other types of toxic materials.

Section VI

Eye-hand Coordination

As depicted in the preceding sections, elevated blood and urine mercury levels due to chronic exposure to inorganic mercury correlate with deteriorations in specific neuromuscular and psychomotor capabilities. These specific dysfunctions strongly indicate that more general psychomotor skills may also be adversely effected at relatively low mercury body burdens. It, therefore, was the interest of the research described in this section to determine the nature of the potential mercury effects on a person's ability to repeatedly and accurately move their hand to specific locations in space. In other words, their general discrete positioning eye-hand coordination was evaluated as a function of the population parameters described in Section III, (i.e., blood and urine mercury levels, length of time of occupational exposure to mercury, height, weight, age and cigarette smoking rate).

Methods of Measurement

Equipment. The discrete positioning eye-hand coordination test chosen for the study was developed by Pooch (1968). It was chosen due to its test-retest repeatability ($r=.89$), its correlation with other motor functions ($r=.50$), and its correlation ($r=.35$) with the performance demonstrated by industrial people on various hand motions (i.e., reaches,

grasps, and moves) composing common industrial manual tasks (Poock, 1968).

The test is composed of a directionally varying maze of 119 holes ($1/8$ inch diameter) in an eight inch square steel plate. The subject is asked to repeatedly insert a stylus in each hole following a sequence dictated by a painted line connecting each hole. Figure 13 depicts a person performing the test.

The output from the test was recorded by two methods. An electrical stop clock (minimum reading 0.01 second) was used to measure the elapsed time from the withdrawal of the stylus from the first hole to insertion into the last hole. This measure produced the gross performance times on the test, which was the performance measure used by Poock (1968). A second performance measurement, which was developed for this study, greatly augmented the sensitivity of this test. This method utilized a second thin steel plate which was placed directly behind the first. A contact microphone attached to this plate, which was relatively acoustically isolated from the maze plate and frame, allowed the recording of the insertion of the stylus through the maze holes. To accomplish this a special signal conditioning amplifier was constructed to shape the "tapping" signals produced by the stylus hitting the second sounding plate into discrete changes in the signal level. These were then recorded on the same Hewlett Packard FM tape recorder used to record the EMG's and tremor signals described earlier.

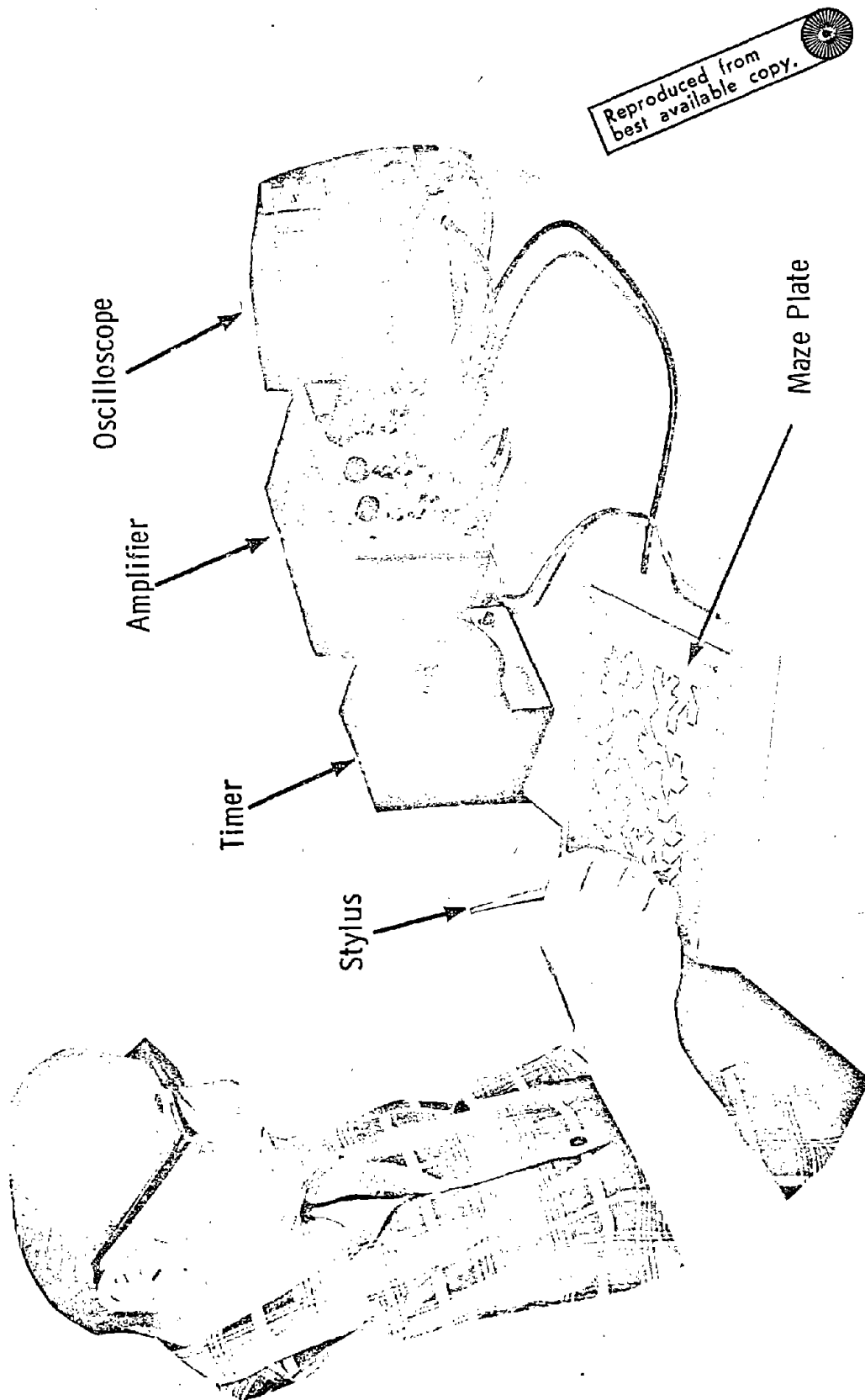


Figure 13. Eye Hand Coordination Test Setup

Test Procedures. The subject was acquainted with the test equipment. He then was asked to sit down and the maze plate was positioned directly in front of his body (i.e., in the mid-sagittal plane). If the subject was left handed the maze was rotated to provide the same motion pattern as for a right handed individual. He was asked to grasp the stylus about two inches from the contacting end, and, without allowing his hand to touch the maze, attempt several stylus insertions. He then was given an opportunity to move his chair forward or rearward to his own preference. Following this, he was given the test instructions:

1. Follow the painted line when moving between holes.
2. Perform the test as quickly as possible.
3. Do not skip any holes.
4. Completely insert the stylus into each hole.
5. Do not rest your hand or forearm on either the test, table or arm of the chair while performing the test.

The subject then attempted four trials. After the five minute weight holding exertions described in Section IV, he immediately performed a fifth trial. His performance on both the fourth trial before exertion and the fifth trial immediately after exertion were used for this study.

Analysis of Data. A special computer program was developed which timed (to 0.001 sec.) the intervals between successive insertions of the stylus into the holes. The out-

put of this program was a frequency histogram of hole-to-hole times.¹ As in the earlier tremor and EMG analyses, estimates of the following parameter values were developed for each trial recorded:

Average hole-to-hole times based on the mean, median, and modal values.

Variability in hole-to-hole times based on the standard deviation values.

Biasness of variability in hole-to-hole times based on the skewness values.

Each of the resulting parameter values was then regressed by multiple step-wise regression onto the population parameters described in Section III. This was done for both the combined group of 133 people and separately for only the exposed group of 75 people. Also, data from both the before and after exertion were evaluated independently.

Results of Eye-hand Coordination Test. The significant correlation coefficients are depicted for both combined populations and exposed, and for tests performed before and after the standard exertion in Tables IX, X, XI, and XII. From these the following general conclusions are drawn:

1. The age factor is the single most important variable in effecting the time to perform this test ($0.32 < r < 0.45$), with the older persons being slower. A plot of this effect is given in Figure 14.
2. After age, the level of body mercury burden becomes significantly important. It appears to decrease the

1. Figure 16 described in this Section illustrates the histogram output of the program.

TABLE IX

Significant Multiple Correlation Coefficients of
Eye-hand Coordination Test Data Administered
Before Exertion for Combined Group of
Exposed and Control

(Cases=133)

Dependent Variables	Independent Variables				
	Height	Weight	Age	Smoking Rate	Mercury Level
Blood Study					Blood
Median Performance Time	3(.48)-	--	1(.37)+	--	2(.45)-
Modal Performance Time	2(.40)-	--	1(.33)+	--	3(.44)-
Mean Performance Time	--	--	1(.32)+	--	2(.39)-
Std. Dev.	--	--	1(.17)+	--	--
Skewness	--	--	--	--	1(.19)+
Urine Study					Urine
Median Performance Time	3(.47)-	--	1(.37)+	--	2(.45)-
Modal Performance Time	3(.47)-	--	1(.35)+	--	2(.42)-
Mean Performance Time	--	--	1(.32)+	--	2(.37)-
Std. Dev.	--	--	--	--	--
Skewness	--	--	--	--	--

TABLE X

Significant Multiple Correlation Coefficients of
Eye-hand Coordination Test Data Administered
Before Exertion for Exposed Group

(Cases=75)

Dependent Variables	Independent Variables					
	Height	Weight	Age	Smoking Rate	Log Duration	Mercury Level
Blood Study						Blood
Median Performance Time	2(.48)-	--	1(.44)+	--	3(.52)+	4(.55)-
Modal Performance Time	2(.47)-	--	1(.37)+	--	--	--
Mean Performance Time	--	--	1(.35)+	--	--	--
Std. Dev.	--	--	--	--	--	--
Skewness	--	--	--	--	--	--
Urine Study						Urine
Median Performance Time	2(.50)-	--	1(.45)+	--	3(.53)+	4(.57)-
Modal Performance Time	2(.49)-	--	1(.39)+	--	4(.56)+	3(.53)-
Mean Performance Time	--	--	1(.38)+	--	--	--
Std. Dev.	--	--	--	--	--	1(.20)+
Skewness	--	--	--	--	--	1(.22)+

TABLE XI

Significant Multiple Correlation Coefficients of
Eye-hand Coordination Test Data Administered
After Exertion for Combined Group of
Exposed and Control

(Cases=133)

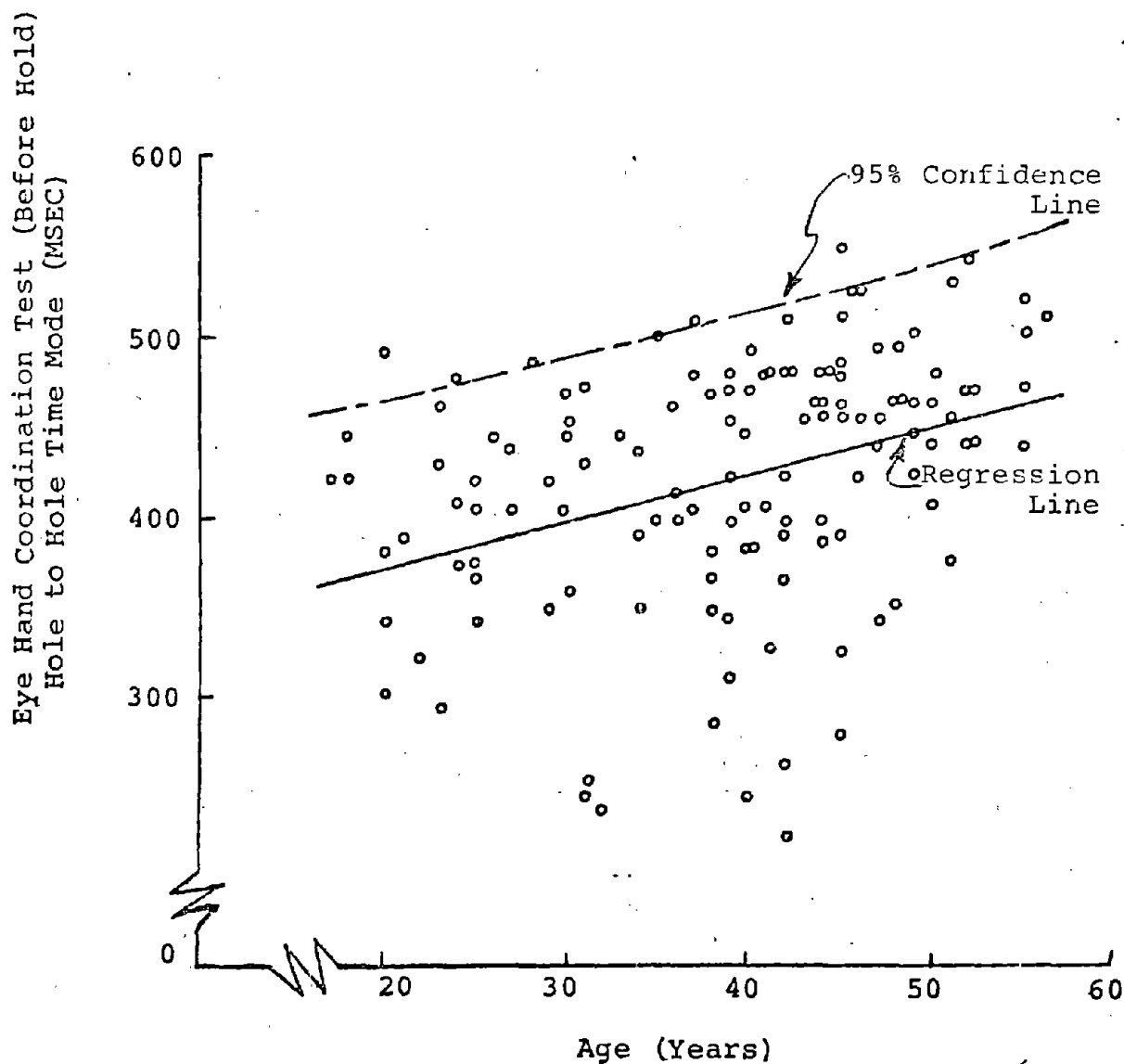
Dependent Variables	Independent Variables				
	Height	Weight	Age	Smoking Rate	Mercury Level
Blood Study					Blood
Median Performance Time	--	--	1(.40)+	--	2(.44)-
Modal Performance Time	--	--	1(.39)+	--	2(.42)-
Mean Performance Time	--	--	1(.41)+	3(.48)+	2(.45)-
Std. Dev.	--	--	--	1(.19)+	--
Skewness	--	--	--	--	--
Urine Study					Urine
Median Performance Time	--	--	1(.36)+	--	2(.41)-
Modal Performance Time	--	--	1(.39)+	--	2(.43)-
Mean Performance Time	--	--	1(.38)+	3(.46)+	2(.42)-
Std. Dev.	--	--	--	1(.26)+	2(.30)+
Skewness	--	--	--	--	1(.21)-

TABLE XII

Significant Multiple Correlation Coefficients of
Eye-hand Coordination Test Data Administered
After Exertion for Exposed Group

(Cases=75)

Dependent Variables	Independent Variables					
	Height	Weight	Age	Smoking Rate	Log Duration	Mercury Level
Blood Study						Blood
Median Performance Time	--	2(.45)-	1(.42)+	--	--	--
Modal Performance Time	--	--	1(.42)+	--	--	--
Mean Performance Time	2(.45)-	--	--	3(.48)+	--	--
Std. Dev.	--	--	--	--	--	1(.29)+
Skewness	--	--	1(.20)+	--	--	2(.28)-
Urine Study						Urine
Median Performance Time	--	--	1(.42)+	--	--	--
Modal Performance Time	--	--	1(.42)+	--	--	--
Mean Performance Time	2(.46)-	--	1(.42)+	--	--	--
Std. Dev.	--	--	--	2(.39)+	--	1(.33)+
Skewness	--	--	2(.30)+	--	--	1(.21)-



Prediction Equation for Regression Line:
 Eye Hand Coordination Test Mode (msec) = $289.55 + 2.46 \times \text{AGE}$
 Correlation Coefficient = 0.39
 Sample Size = 133

Figure 14

Eye-hand Coordination Test Modal Hole-to-Hole
 Test Times versus Subject Ages

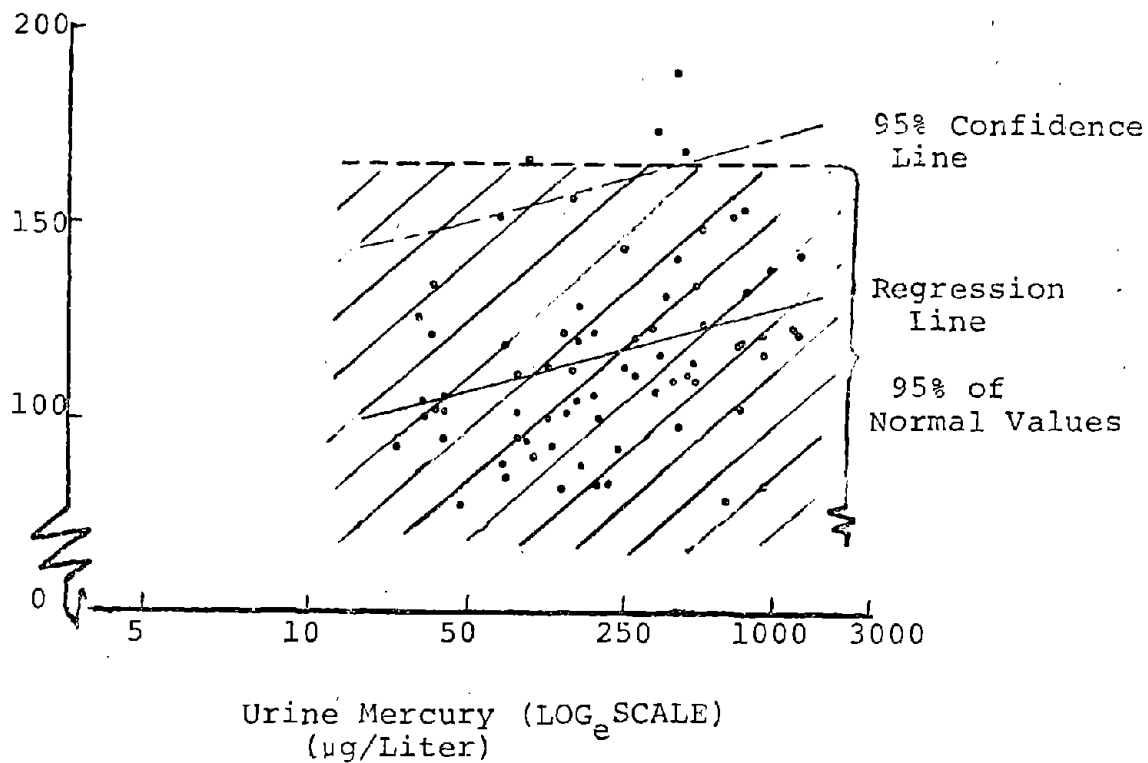
average time to complete the test (i.e., high mercury burden indicates faster average performance) when the combined (exposed and control groups) are evaluated (Tables IX and XI). This small effect, though consistent, is easily rationalized as a motivational effect (i.e., people with exposure to mercury "tried harder" than the volunteer controls). Evidence for it being motivational is gained by inspecting just the exposed groups' results, Tables X and XII. Here the effect of mercury is not nearly as great on the average performance times (as measured by mean, median and modal changes not being consistently correlated with blood or urine mercury levels). In fact, in Table XII there is no correlation of these parameters.

3. The elevated mercury effect on the test performance can be more directly evaluated when inspecting just the exposed groups' results. In particular, the variability of the hole-to-hole performance times (as measured primarily by the standard deviation and to a secondary degree by skewness) after the standardized exertion is significantly correlated with increased mercury burdens (Table XII and Figure 15). In other words, elevated mercury levels significantly correlate ($r=.33$) with more erratic performance in the successive 118 hole-to-hole movements required in each trial.

Because the performance on this type of a test can be motivational and age dependent, it becomes more difficult to set general population normal limits. The regression plotted in Figure 15 contains an estimate of the "normal limits" based on the controls obtained in plant visits III and IV.¹ This clearly depicts the large range of normal values associated with this test. This is not to indicate however, that this type of a test would not be useful in future studies of the

1. Appendix D summarizes the values for the control subjects in plant visits III and IV.

Variation in the Eye-hand Coordination
Test Administered After Exertion
(Hole-to-Hole Time Std. Dev.) (MSEC.)



Eye Hand Coordination Test STD. DEV. (msec) = $77.32 + 7.18 * \text{LOG}_e(\text{Urine})$
Correlation Coefficient = 0.33
Sample Size = 74

Figure 15

Regression of Eye-hand Coordination Test-
Variability in Performance and Urine Mercury
Levels in Exposed Population

effects of various potential neural toxins. It only indicates that population norms will probably not be useful, due to such individual intervening factors as motivation and age.

To further illustrate the statistical effects of mercury, the data from an age matched group of five exposed and five controls were selected. Figure 16 depicts the average hole-to-hole time distributions for each of these two groups. The result can be visualized in the proportionally larger number of slower movements (i.e., those taking greater than 480 msec) incurred by those people having elevated blood and urine mercury levels, though their mean times are not significantly changed. Based on the preceding analyses it would appear that the variability in performance of the test is the single most sensitive parameter to potential mercury intoxication, with increased mercury burdens significantly correlated with more erratic performances.

Results of Retest Analysis. As was the case with the preceding evaluations, 32 people were restudied after a period of four to six months. During this period they had either no exposure due to job changes, or were exposed to far less mercury through seasonal effects in ventilation and improved industrial hygiene controls. The means of the four major performance parameters for these 32 people are presented in Table XIII, along with the changes in blood and urine mercury levels corresponding to when each test was given.

What is evident is that the workers' average hole-to-

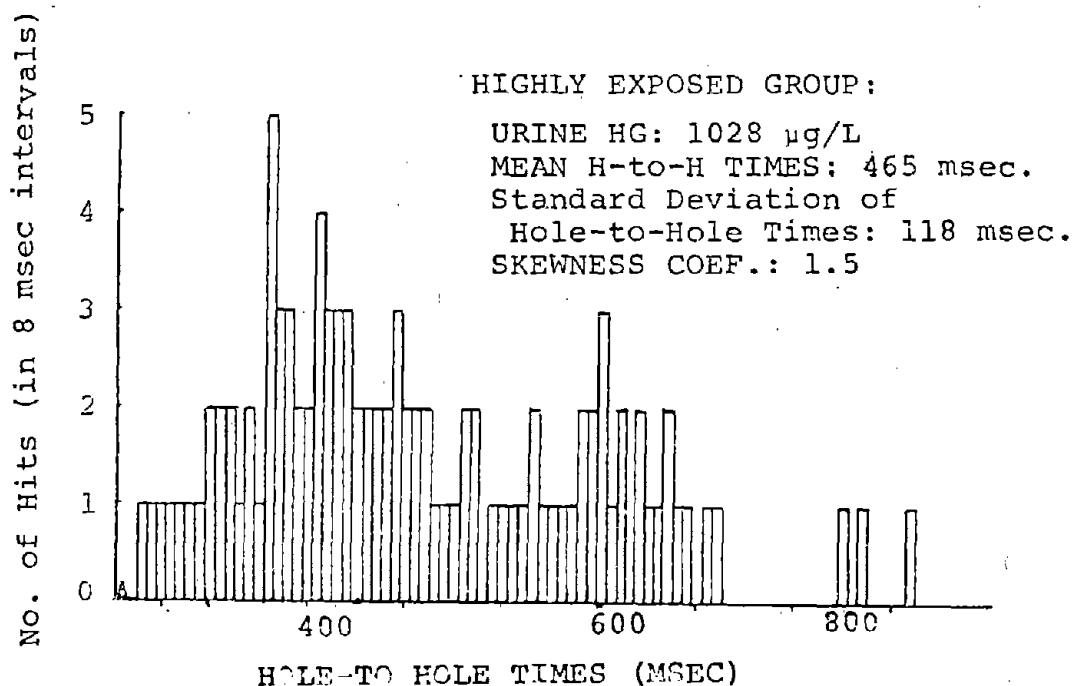
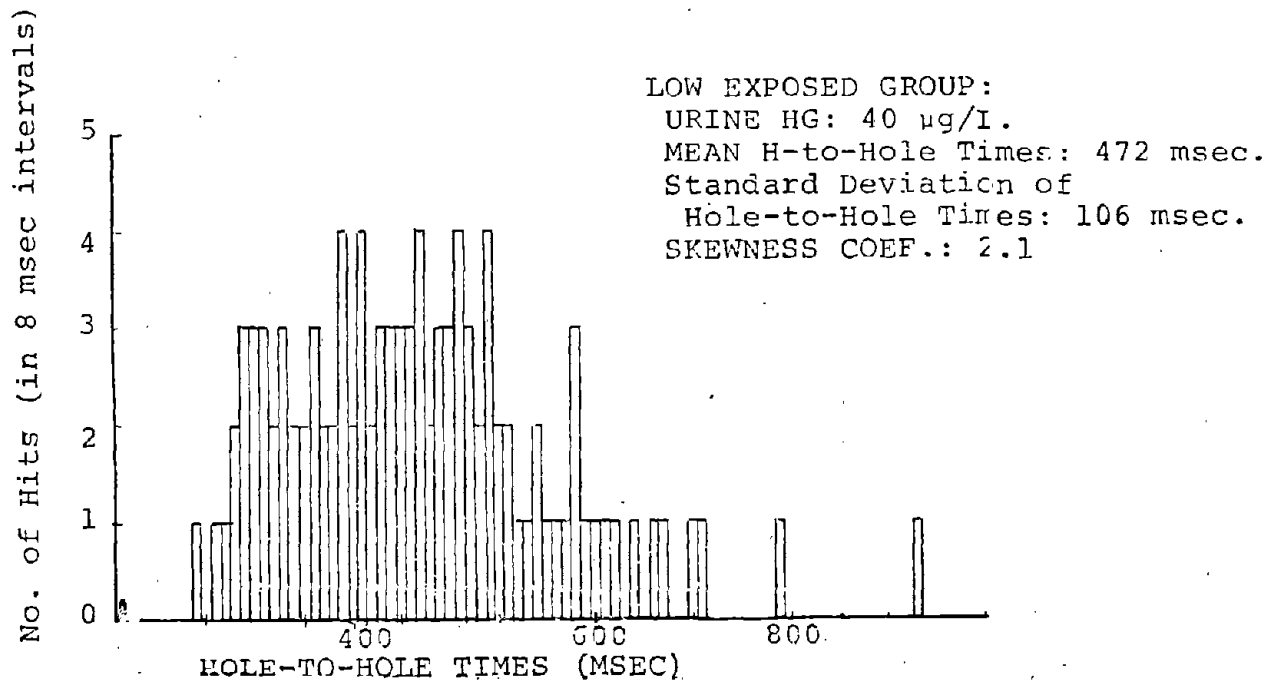


Figure 16

TYPICAL EYE-HAND COORDINATION HOLE-TO-HOLE TIME
 DISTRIBUTIONS (AFTER CONTROLLED EXERTION) FOR FIVE
 LOW AND FIVE HIGHLY EXPOSED SUBJECTS MATCHED ON AGE

Table XIII

Comparison of Test/Retest Results for
Eye-hand Coordination Test of 32 People

Fatigue Condition	Test Sequence	Mean Eye-hand Coordination Test Parameters (msec.)			
		Mode	Mean	Standard Deviation	Skewness
Before Exertion	First Test**	387	469	137	1.51
	Second Test***	366*	455*	124*	1.64*
After Exertion	First Test	383	459	118	1.96
	Second Test	371	438*	121	1.90

* Denotes second test mean is different than first at $\alpha \leq .1$ level.

** First Test Blood Mercury Mean = 11.4 $\mu\text{gm}/100 \text{ ml}$.
 First Test Urine Mercury Mean = 599 $\mu\text{gm}/\text{L}$.

*** Second Test Blood Mercury Mean = 6.7 $\mu\text{gm}/100 \text{ ml}$.

*** Second Test Urine Mercury Mean = 292 $\mu\text{gm}/\text{L}$.

hole movement times (mode and mean times) did improve when retested after a four to six month period had elapsed during which a reduction in mercury blood and urine levels also occurred. Thus the retesting evaluation indicates that mercury may slow a person's average time to make discrete hand motions, as well as increase the variability in repeated hand motions. Furthermore, the adverse effects on these two functional capabilities are reversible within the range of mercury levels included in this retest study (i.e., up to the group mean of 599 $\mu\text{gm/liter}$ urine mercury).

Summary, Discussion and Recommendations
Regarding Eye-hand Coordination Test Findings

Summary. The discrete positioning eye-hand coordination test employed in this study has been found to be sensitive to age and potential motivational effects which increase the variation in the population's average performance results. Thus the correlations with body mercury burdens were not well documented on a cross-sectional basis, with the exception of the variability in the hole-to-hole movement times, which were particularly affected after a moderate arm exertion. In this instance an increase in the variability (i.e., standard deviation) in hole-to-hole motion times was significantly correlated with increased blood and urine mercury levels (.29 and .33, respectively). The duration of occupational

exposure to mercury did not correlate with any of the test parameters. This could have been due to the age effect blocking out the duration of exposure factor since these two independent factors were in effect reasonably correlated ($r = .34$).

The retesting of 32 people who were known to have reduced exposures over a period of from four to six months disclosed that the average performance times may indeed be adversely affected (prolonged) by elevated mercury burdens. It must be speculated at this time, therefore, that the reason the cross-sectional population study did not also develop a significant effect of elevated mercury burdens on average test performances, is due to the motivational and age related intervening variables causing a high individual variability in the data, thus confounding any statistical relationships with mercury body burdens. At least the disparity between the cross-sectional study and the retest results clearly indicates the need for further research.

Discussion of Findings. The adverse effect of elevated mercury burdens on the variability in hole-to-hole motion times after a moderate arm exertion is of note. The fatigue effect, which is known to itself induce muscle tremor (Chaffin, 1969 and 1973 and Eagles, et al, 1953), apparently made performance of the test for those people who had elevated mercury burdens (and based on preceding analyses showing existence of initial tremors and impaired motor responses)

multiplicatively more difficult. In other words, there was a compounding stress effect wherein the exertion made the adverse effects of elevated mercury on the test performance worse for those people having the higher burden levels than for those with lower levels.

The effect on the test performance can also be characterized as a type of ataxia, wherein the consistent skill necessary to make 118 small motions of the hand is not maintained for the approximate 45 seconds necessary to complete the maze. When viewed in this way perhaps the ability to concentrate on the task is adversely effected, as suggested by Hook, 1954 and Neal, 1941.

The general recovery in retest performances corresponding to reduced mercury body burdens after four to six months appears to be one of the most significant findings, though not conclusive. It does indicate that for an individual longitudinal study (i.e., when the effect of mercury is evaluated over time on the same person) the eye-hand coordination test may become a very good indicator of intoxication and recovery states.

Recommendations. It is recommended that the eye-hand coordination test be administered to persons having exposures to mercury which vary on a controlled basis (i.e., varying with job rotations, seasonal ventilation changes, and by other industrial hygiene control measures). It is proposed that there is a strong enough statistical effect of elevated mercury burdens in this study to warrant this recommendation.

By such research, data could be gathered concerning the long-term effects (and their reversibility) due to exposures to mercury which would be useful in estimating the deterioration in a basic function capability necessary for precision industrial work.

Additional studies should be undertaken in conjunction with the use of the above test to ascertain whether defects in concentration are correlated with chronic exposures to mercury. These should be quantitative (interval scaled) in nature to allow regression analysis to be used. Also, other quantitative eye-hand coordination tests should be developed and tested in similar studies.

Section VII

Clinical Neurological Correlations
with Mercury Body BurdensIntroduction

The data reported in this section are the result of the standard clinical neurological examination and patient interview as outlined in Appendix E. The examinations were performed with no prior knowledge of the patient's exposure or past history. The objectives of this phase of the Mercury Project, broadly stated, are:

1. The detection of any clinical impairment of neurologic function due to mercury exposure.
2. A comparison between these results and the classical findings from the literature, in an effort to substantiate or re-evaluate the latter.
3. The determination of the most sensitive indicator in the neurologic examination which might be used in future diagnostic efforts.
4. The development of additional evidence to the present theories relating mercury concentrations in the central nervous system and corresponding impaired neurologic function.
5. A determination of the possible reversibility of any

of the abnormal clinical findings following removal from exposure for a period of eight months.

6. An examination of the relationship between clinical evaluation and sub-clinical psychomotor testing.

Objectives 1, 3, 5 and 6 will be approached from a statistical point of view as it is conceivable that this procedure will offer the most convincing evidence. The remaining two objectives will be left to a subjective evaluation.

The group examined was 32 chloralkali workers, 14 of whom were not directly exposed to mercury but whose blood and urine mercury levels were of sufficient average concentration so as to eliminate them as a valid control group. Mean blood mercury level was 7.8 $\mu\text{g}/100\text{ ml.}$ for the whole group and 10 $\mu\text{g}/100\text{ ml.}$ for the exposed group. Mean urine mercury level for the entire group was 360 $\mu\text{g}/\text{liter}$ and 500 $\mu\text{g}/\text{liter}$ for the directly exposed group. Arbitrarily a blood level above 1 $\mu\text{g}/100\text{ ml.}$ and a urine level above 300 $\mu\text{g}/\text{liter}$ were considered to reflect toxic exposure realizing full well that there are no universally agreed standards. The duration of exposure ranged from 6 months to 20 years for those workers directly exposed to mercury vapor, the mean being 111 months or approximately 9 years. The 12 subjects chosen for re-examination, 8 months after removal from exposure, were selected on the basis of the highest blood and/or urine mercury levels found at the

initial assessment. Mean urine and blood mercury levels at the time of retesting were 95 µg/liter and 1.03 µg/100 ml. respectively. (This is actually based on only 11 subjects, as one man had not been removed from exposure and his levels were considerably greater than the rest of the group.)

Results of Neurological Examination

A. Initial Examination of 32 Subjects

The positive clinical findings in the initial examination are found in Table XVI along with each subject's blood and urine mercury levels. In the mental status interview, 24 of the 32 subjects were noted to have impairments in judgment, calculation ability, and abstraction, which would be clinically most consistent with some degree of amentia. One patient was thought to be depressed. Twelve of the original 32 subjects were noted to have eyelid fasciculations. Generalized fasciculations, myokymic movements, or other evidence of neuromuscular irritability were not encountered. As was to be expected, there was a striking lack of any abnormalities in the sensory examination. Two subjects were noted to have minimal diminution of vibratory sensation, and a third subject had a generalized polyneuropathy, but had an ongoing metabolic problem which could quite clearly account for this. Eleven of the subjects were noted to have hyperactive deep-tendon reflexes and eight subjects were noted to have prominent facial reflexes such as jaw jerk or snout responses. Two sub-

TABLE XVI

POSITIVE CLINICAL NEUROLOGICAL TEST RESULTS


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SUB. NO.	URINE HG. ug/liter	BLOOD HG. uc/100ml.	MENTAL STATUS	NEURO- MUSCULAR	SENSORY MODALITIES	DEEP TENDON REFLEX	CERE- BELLAR FUNCTION	DERMAT- OGRAPHIA	VISUAL ACUITY
1	890	13.0		Eyelid Fascicu.		Left 3+ Snout & Jaw Jerk		Neg.	20/10 20/35
2	60	0.8	Mild Amentia	Eyelid Fascicu.			Perioral Tremors	Not Tested	20/35 20/20
3	645	18.6	Impaired Calcula- tion					Slight	20/100 20/40
4	1010	9.8		Eyelid Fascicu.				Not Tested	20/200 20/100
5	220	13.5				1+		Neg	20/20 20/35
6	230	7.3	Depression					Neg	20/20 20/50
7	20	3.0				Trace Jaw Jerk	Ataxia Int. Tremor	Neg	20/30 20/40
8	40	2.7	Impaired Judgement	Eyelid Fascicu.	Decreased Vibration	3+ Snout		Neg	20/10 20/100
9	20	2.0	Amentia Depression			Snout Jaw Jerk	Sustention & Slight Inten. Tremor	Neg	20/200 20/200
10	5	2.0	Amentia Impaired Judgement	Eyelid Fascicu.		3+ Jaw Jerk	Bilateral Int. & Sust. Tremor	Pos.	20/30 20/35
11	400	11.1				3+		Not Tested	20/20 20/20
12	60	4.9	Slight Amentia	Eyelid Fascicu.				Not Tested	20/20 20/20
13	250	6.8	Slight Impaired Calculation	Eyelid Fascicu.		3+		Not Tested	20/20 20/20
14	380	8.6	Impaired Judgement				Slight DDK	Not Tested	20/50 20/50
15	690	7.2	Slight Abstraction Impairment					Not Tested	20, 20 20/20
16	790	12.7	Amentia Flat Effect					Neg.	20/20 20/20
17	670	10.4	Impaired Judgement					Neg	20/20 20/30

(continued)

TABLE XVI (continued)

SUBJ. NO.	URINE HC. ug/liter	BLOOD HC. ug/100ml.	MENTAL STATUS	NEURO MUSCULAR	SENSORY MODALITIES	DEEP TENDON REFLEX	CEREB. BELLER. FUNCTION	DERMAT. SENSIBILITY	VISUAL ACUITY
18	435	10.3	Amentia			3+		Not Tested	20/20 20/20
19	380	7.3	Amentia					Not Tested	20/20 20/20
20	950	16.8	Amentia	Eyelid Fascicu.				Pos.	20/20 20/20
21	280	4.3	Slight Amentia	Eyelid Fascicu.		1+		Neg	20/20 20/20
22	205	15.8	Slight Amentia				Min. Bi-lateral Inten. Tremor	Slight	20/20 20/20
23	160	2.7					Slight Int. Tremor	Pos.	20/35 20/25
24	450	12.0				Absent Jaw Jerk	Mod. Int. Tremor Sust.	Neg	20/70 20/20
25	84	3.7		Eyelid Fascicu.		3+ Jaw Jerk	Slight Int. Tremor Sust.	Neg.	20/70 20/30
26	790	18.7	Slight Amentia Schizoid			3-1/2+ Jaw Jerk	Head & Perioral Tremors	Neg	20/100 20/70
27	1030	9.1	Slight Amentia	Eyelid Fascicu.				Pos.	20/40 20/40
28	310	6.0	Slight Amentia			3+Symm		Pos.	20/30 20/25
29	30	2.1	Impaired Judgement						20/20 20/20
30	40	2.7	Impaired Memory		Decreased Vibration			Neg.	20/20 20/70
31	30	1.6	Slight Remote Memory Imp.	Eyelid Fascicu.	Neuro-pathy	3+Symm. Jaw Jerk	Int. Tremor	Not Tested	20/100 20/20
32	5	1.7	Amentia			3+Symm.		Not Tested	20/35 20/50

jects were noted to have slightly diminished reflexes. Under the heading of cerebellar function is also included perioral tremors as well as postural or sustentation tremors, although these do not necessarily have to be of cerebellar origin. Twelve subjects were found to have abnormalities in this area. Seven of 20 subjects tested for dermatographia were noted to either have the classical triple response or an erythema and flare response. Visual acuity measurements were initially done although this was not pursued further because of the lack of facilities for determining corrected visual acuity. Table XVII is an example of the data form used and as well indicates the specific frequencies of each symptom and sign. (The script numerals indicate frequencies in the retest group.) Among the symptoms that were listed, those most frequently encountered included headache in 7 subjects, vertigo in 4, tinnitus in 5, sleep disturbances in 8, and extremity numbness in 5. These were graded by the examiner arbitrarily as mild, moderate and severe, and for the most part the symptomatic complaints were in the mild category.

B. Retest Examination of 12 Subjects

The 12 subjects who were found to have the highest levels of blood and urine mercury were re-evaluated 8 months later. These subjects were examined without reference to their initial neurologic examination or their initial urine or blood mercury level. A summary of the findings in this retest group can be found in Table XVIII. Blood and urine

TABLE XVII

History and Neurological Examination Data Summary

Examiner: _____ Date: _____

Patient's Name _____

UMH Reg. # _____ Age _____ Sex _____ Handedness _____

<u>Symptoms</u>	<u>Incidence of Described Symptoms</u>		
	<u>Mild</u>	<u>Moderate</u>	<u>Severe</u>
Headache	4 2	2 1	1
Vertigo	4 3		
Tinnitus	3	2	
Visual acuity loss			
Anosmia			1
Diplopia			
Ageusia			
Facial numbness		1	
Nausea	1		
Vomiting	1		
Convulsions			1
Loss of consciousness		1	
Extremity numbness	1	3	1
Extremity tingling		1	
Extremity burning			
Extremity pain			
Weakness		1	
Atrophy			
Dysarthria			
Gait disturbances		1	
Lethargy			
Irritability			
Tremor	3 1		
Sleep disturbances	8 1	1	
Lack of libido		1	
Abdominal pain			
Diarrhea	1		
Constipation			
Dyspnea			

Blood Pressure:

Pulse:

Note; script numerals indicate retest frequencies

TABLE XVII (continued)

<u>Signs</u>	Mild		Moderate		Severe	
Consciousness defect						
Disorientation	4		1			
Acalculia	5	1	4	1		1
Memory defect	1					
Remote	6		1			
Immediate			1		1	
Abstraction defect	6	2	5	5	7	1
Judgment defect	4	2	3	1	1	1
Hallucinations						
Illusions						
Delusions						
Affect disorder			1			
Depression	2					
Mania						
Flat affect	1					
Pseudobulbar affect						
Aphasia						
Dysarthria						
Apraxia						
Ideational						
Dressing						
Constructional						
Anosmia	3					
Visual acuity by Jaeger	3		3			
Central scotoma						
Visual field narrowing						
Hemianopsia						
Papilledema						
Optic atrophy						
Retinal vessel abnormalities						
Gaze palsy						
EOM palsy					1	
Nystagmus						
Pupillary abnormalities						
Corneal reflex loss						
Facial sensory loss						
Mastication muscle weakness						
Facial weakness						
Loss of taste (anterior 2/3)						
Hearing loss					1	
Gag reflex loss						
Dysphonia						
Weakness of trapezius, etc.						
Tongue weakness or atrophy						
Ocular Dysmetria	1					

TABLE XVII (continued)

Sensation	By Chart		
Vibration	3		
Position			
Touch	1		
Pin			
Deep pain	1		
Stereognosis			
Two-point			
	Mild	Moderate	Severe
Gait ataxia			
Unstable station			
Romberg test	Neg	Pos	
Limb ataxia			
Upper			
Right		1	
Left		1	
Lower			
Right			
Left			
Weakness			
Hemiparesis			
Right			
Left			
Monoparesis			
Right			
Left			
Spasticity			
Arm			
Right			
Left			
Leg			
Right			
Left			
Tremor			
Dysdiadokokinesia	1	1	
Perioral Tremors		2	
Intention	3	5	
Sustention		4	
Head		1	1
Postural	1	2	3
Atrophy-fasciculations			
Arm			
Right			
Left			
Leg			
Right			
Left			
Eyelid Fasciculation		12	5

TABLE XVII (continued)

	Mild	Moderate	Severe
Chorea			
Ballismus			
Myoclonus			
Athetosis			
Focal motor seizure			

Reflexes (0 through 4 or Positive vs. Negative)

None	Mild	Moderate	Severe
2+	Diminished	3+Symm	3+, Snout or Jaw Jerk
16	4	5	7
7	1	1	3

Summary

	Mild	Moderate	Severe
Mental deficit	13 11	11	
Speech deficit			
Sensory deficit	2	1	
Cerebellar deficit	4 3	12 1	3
Cranial nerve signs (Vis. Acuity)	3	3	
Reflex abnormalities	3 1	7 1	15 3
Dermatographia	2 5	4 1	2

TABLE XVIII

SUMMARY OF CHANGES IN NEUROLOGIC FUNCTION
 FOUND IN RE-EXAMINATION OF 12 SUBJECTS (DATA FROM FIRST AND SECOND TESTS)

SUB. NO.	BLOOD HG (ug/100ml)		URINE HG (ug/liter)		MENTAL STATUS		DEEP TENDON REFLEX		CEREBELLAR FUNCTION		DERMATOGRAPHIA		NEUROMUSCULAR	
	FIRST	SECOND	FIRST	SECOND	FIRST	SECOND	FIRST	SECOND	FIRST	SECOND	FIRST	SECOND	FIRST	SECOND
1	15.8	0.8	205	49	Slight Amentia	Abstraction			Min. Bil. Int. Trem.		Slight	Neg.		
2	12.7	1.2	780	242	Amentia Flat Eff.	Abstraction					Neg.	Neg.		Eyelid Fascic.
3	8.6	1.4	380	108	Judgement	Abstraction Judgement			Slight DDK		NT	Slight		
4	11.1	1.0	400	85		Abstraction	3+	Jaw Jerk			NT	Slight		
5	16.8	1.1	950	103	Amentia	Affect Dis. -Hostile		3+ Symm.	Mild Post. Tremor		Slight	Severe	Eyelid Fascic.	Eyelid Fascic.
6	9.8	1.3	1010	160		Abstraction Acalculia Imm. Memory		3+ Jaw Jerk	Mild Post. Tremor		NT	Neg.	Eyelid Fascic.	Eyelid Fascic.
7	18.7	20.4	790	412	Slight Amentia, Schizoid	Judgement	3 1/2+ Jaw Jerk	3 1/2+ Jaw Jerk	Perioral & Post. Int. Head Int. Head Tremor Tremor		Neg.	Slight		
8	7.2	0.8	690	32	Slight Abstraction	Abstraction Judgement					NT	Trace		
9	7.3	0.8	380	86	Amentia	Acalculia Judgement					NT	Moderate		
10	18.6	1.1	645	76	Acalculia	Acalculia Abstraction					Slight	Slight		
11	12.0	1.0	450	32			Absent Jaw Jerk	Absent Jaw Jerk	Mod. Int. & Sust. Tremor		Neg.	Severe		
12	10.4	0.8	670	72	Judgement	Abstraction Flat Effect			DDK	Slight Post. Tremor	Neg.	Neg.		

mercury levels are recorded for comparison of the initial and follow-up determinations. The neurologic abnormalities are also listed for comparison of test to retest. Nine of the 12 subjects were noted to have abnormalities on the initial test evaluation and 11 of the 12 were noted to have abnormalities in the mental status evaluation on the retest. In addition, more quantitative descriptive deficits are noted in the retest situation. Deep-tendon reflexes were identical for 10 of the 12 subjects from test to retest, while in 2 subjects the deep-tendon reflexes were noted to increase from 2+ to 3+. In the area of cerebellar function, 3 subjects were noted to have abnormalities on the initial exam were found to be normal in the follow-up. One subject was found to improve from a deficit of dysdiadokokinesia to a slight postural tremor and 2 subjects were noted to have mild postural tremors on the retest evaluation who were thought to be normal during the initial exam. These are the same 2 subjects whose reflexes increased from 2+ to 3+. Seven subjects on the retest examination were noted to have dermatographia. Four of these subjects were not tested for this during the initial evaluation. At least one subject was noted to have a marked response in the retest situation who was tested previously and thought to be negative. In the neuromuscular evaluation, 3 subjects were found to have eyelid fasciculations in the retest group who had also been noted to have eyelid fasciculations in the

initial examination. One additional subject was noted to have eyelid fasciculations in the retest group although they were not observed during his initial evaluation.

Statistical Tests for Determination of Significant Symptoms or Signs

The use of statistical arguments for presenting significance of clinical data is usually seen only in cases of large study populations (Smith, et al, 1970). Previous studies based upon percentages and case studies might acquire support in their relationship of particular symptoms to mercury exposure by the use of statistical proof, it is thought. It is also hoped a sensitive indicator might become apparent. The analysis was complicated by the qualitative nature of the clinical data and the reliance upon blood and urine mercury levels as a basis for relative degree of poisoning, for although they are sensitive indicators of absorption of mercury, they are unreliable as a guide to the onset or severity of symptoms (Section II and Bistrup, 1964). The quantifying of the data was aided by a classification system devised according to the relative severity of different symptoms (Table XIX). From this basis a neurologic index was devised, based upon mental status having a relative severity of one and cerebellar function, deep-tendon reflexes and dermatographia as a relative severity of two. This index was used in determination of group relationships with blood and urine mercury levels, significance of change for the group and individual

TABLE XIX

SIGNIFICANT NEUROLOGICAL SYMPTOMS

MENTAL STATUS

3. Impaired Judgement, Memory, Abstraction, Calculation
2. Amentia
1. Normal

CEREBELLAR FUNCTION

4. Perioral and/or Head Tremors
3. Sustention and/or Intention Tremors
2. Slight Intention Tremor or Disdiadokokinesia
1. Normal

DEEP TENDON REFLEXES

4. +3, Snout or Jaw Jerk
3. +3 Symmetrical
2. Diminished (+1) or Absent Reflexes
1. Normal (+2)

DERMATOGRAPHIA

4. Profound (i.e. raised red weal occurs)
3. Present (i.e. reddening of localized area)
2. Slight (i.e. slight reddening)
1. Normal

EXAMPLE OF NEUROLOGIC INDEX DETERMINATION

SUBJ. #5 (AUG.)

NI = MENTAL STATUS + CEREBELLAR + REFLEXES + DERMATOGRAPHIA

$$20 = (1 * 2) + (2 * 2) + (2 * 3) + (2 * 4)$$

(i.e. relative severity of classification multiplied
by relative severity within classification)

symptoms and rank correlations with the psychomotor data produced in conjunction with this study.

I. Mann-Whitney Non-Parametric Test

This test is used for ordinally measured variables to determine whether two independent groups have been drawn from the same population. In this case our two groups consist of those whose performance on a given neurologic test (e.g., judgment) was judged normal and those whose reaction was considered abnormal. The hypothesis tested in each case is that the abnormal reaction group and the normal reaction group are evenly distributed among the blood and urine mercury levels. The alternate one-sided hypothesis is that the abnormal reaction group has a stochastically higher distribution of high mercury levels. This test is regarded as a useful alternative to the parametric T-test but is not restricted by the assumption of that test (Siegel, 1956). The power of this test is probably the greatest for a non-parametric test. This statistic was computed using the Scientific Subroutine Package (SSP) provided on the Michigan Terminal System. The results for this test are given in Table XX for the 32 subjects tested initially and for the retest group of 11 subjects. A comparison of the significance of each symptom for the retest study (Table XXI) exhibits a change in significance for most symptoms which will be discussed further. The choice of a significance level for rejection of the null hypothesis is difficult due to a lack

TABLE XX

SUMMARY OF STATISTICS CONCERNING SIGNIFICANCE
OF PARTICULAR SYMPTOMS AND SIGNS

SYMPTOM/SIGN		NO. IN GROUP		MEAN HG BLOOD LEVEL ug/100ml.		MEAN HG URINE LEVEL ug/liter		NON-PARAM. SIGNIF.w/ BLOOD URINE	
		POS.RXN	NORM.RXN	POS.GP.	NORM.GP.	POS.GP.	NORM.GP.	BLOOD	URINE
DERMOGRAPHIA	12/71	7	13	10.14	8.15	472	384	.10	.10
	8/72	7	4	1.03	1.03	75	75	.11	-.18
DEEP TENDON	12/71	16	16	7.03	8.55	264	458	-.10	-.10
REFLEX	8/72	4	7	1.12	.91	95	95	.21	-.47
CEREBELLAR	12/71	12	20	6.78	8.39	240	434	-.13	-.05
FUNCTION	8/72	3	8	1.07	1.01	112	89	.18	.11
MENTAL	12/71	11	21	6.30	8.57	272	408	-.08	-.05
STATUS,	8/72	9	2	1.03	1.05	101	68	-.05	.01
includes:									
ABSTRACTION	12/71	1	31	7.20	7.83	690	351	-.20	.37
	8/72	7	4	1.05	1.00	107	74	.24	.19
JUDGEMENT	12/71	5	27	5.16	8.30	225	387	-.11	-.11
	8/72	3	8	1.00	1.04	75	102	-.404	-.310
ACALCULIA	12/71	2	30	12.70	7.48	448	355	.14	.06
	8/72	3	8	1.07	1.01	107	90	.05	.05
EYELID	12/71	12	20	7.25	8.69	385	345	-.06	.33
FASCICULATIONS	8/72	4	7	1.15	.91	134	73	.003	.011
SUBJECT'S RESPONSE TO HISTORY EXAMINATION-FIRST PLANT VISIT ONLY									
HEADACHE		7	25	9.36	7.35	443	338	.18	.22
VERTIGO		4	28	8.65	7.66	379	358	.33	.50
TINNITUS		5	27	4.82	8.34	146	401	.09	-.06
SLEEP DISTUBANCES		8	24	7.26	7.96	298	382	.38	-.27
EXTREMITY NUMBNESS		5	27	7.66	7.81	317	369	.45	-.38

TABLE XXI

COMPARISON OF STATISTICS FOR 11 SUBJECTS
EXAMINED IN DECEMBER AND AUGUST

SYMPTOM/SIGN	NO. IN GROUP		MEAN HG BLOOD LEVEL ug/100ml.		MEAN HG URINE LEVEL ug/liter		NON-PARAM** SIGNIF.w/ BLOOD URINE		TEST-RETEST SIGNIFICANCE OF CHANGE			
	POS.RXN	NORM.RXN	POS.GP.	NORM.GP.	POS.GP.	NORM.GP.	BLOOD	URINE	GOT WORSE	IMPROVED	SIGN.	
DERMOGRAPHIA	12/71	3	4	17.1	13.5	600	673	.13	-.61			
	8/72	7	4	1.0	1.0	75	75	.11	-.18	3	1	None
MENTAL	12/71	5	7	12.7	11.9	659	566	.47	.29	3	0	None
STATUS	8/72	9	2	1.0	1.1	101	68	-.05	.01			
excluding Amentia)												
DEEP TENDON	12/71	4	8	13.6	11.8	605	616	.14	-.40			
REFLEX	8/72	4	7	1.1	.9	95	95	.21	-.47	3	0	None
CEREBELLAR	12/71	5	7	11.7	12.8	426	706	-.53	-.53			
FUNCTION	8/72	3	8	1.1	1.0	112	89	.18	.11	2	4	.344
EYELID	12/71	4	8	12.8	12.2	797	520	.34	.04			
FASCICULATIONS	8/72	4	7	1.2	.9	134	73	.003	.011	2	0	None

** MANN-WHITNEY NON-PARAMETRIC TEST

H₀: Particular symptom/sign is evenly distributed
among low and high blood/urine Hg values

of precedence for rigorous statistics applied to clinical data, but a level of 0.10 is considered adequate for this type of data, although significance levels less than this are noted.

II. Sign Test for Significance of Change

In an effort to determine whether the change for each particular symptom and for the group as a whole was significant as the literature would imply it would be, this test was used to establish the difference between two sets of conditions. The two sets examined here are exposure to a mercury environment and the conditions that exist eight months after removal from this exposure. This test is useful as it does not require quantifying the data and requires only subjective evaluation of "worse" or "better". The null hypothesis is that the median difference is zero (i.e., the number of patients improving is the same as those who appear worse). The null hypothesis is rejected if too few differences of one kind, in this case "improved", occur. If no difference occurs the pair is dropped from the analysis. Table XXI exhibits the significance levels for each symptom or sign. The power-efficiency of this test is 95% for $N=6$ but declines as the size of the sample increases.

III. Spearman Rank Correlation Coefficient

This measure of association between two ordinally measured variables is used to determine possible relationships between the neurologic index previously described in

Table XIX and the psychomotor tasks described in the preceding Section V which were performed simultaneously with the clinical neurologic examination. The eye-hand coordination test described in Section VI was also included in this analysis. The purpose of trying to develop these relationships is to gain consensual validity thus further substantiating these tests as useful tools in determining mercury poisoning. It is believed that if a good correlation with any one particular test can be shown, this test could conceivably be used in ascertaining degree of impairment at a sub-clinical level, as proposed in earlier studies (Neal et al, 1941, Hanley, 1972).

This statistic is obtained by a ranking of the two variables (e.g., neurologic index and blood) which is deemed preferable to regression analysis due to the subjective nature in which the neurologic index was arrived at and to account for analysis error in blood and urine samples. The null hypothesis in each case is that the two variables in question are not associated in the population and that the observed value of r_s (correlation coefficient) differs from zero only by chance. All the significance levels indicated are for a one-tailed probability for the desired direction of the relationship (i.e., positive correlation means direct relationship and negative implies inverse relationship). The efficiency of the Spearman rank correlation compared to the most powerful parametric correlation is about 91% (Hotelling and Pabst, 1960). That is, if there is a corre-

lation r_s for 100 cases, it will reveal the same significance as the Pearson for 91 cases.

Discussion of Statistical Results

In the initial study it is seen from Table XVII that there are no significant symptoms among the 32 subjects examined. Dermatographia comes the closest to being significant in relation to blood and urine mercury levels. If the people tested in the second trip are included, this sign is significant at .01 for urine and .001 for blood. (Not all subjects were tested for dermatographia as it was not a part of the initial exam protocol until it was found incidentally in one subject.) The only other significant symptom is acalculia (.06), but with only two patients exhibiting this impairment, this is not considered an important sign.

Upon re-examination, it can be seen that certain symptoms do become significant, such as dermatographia with blood mercury, mental status impairment with urine mercury, eyelid fasciculations with both blood and urine, and possibly impaired cerebellar function with urine mercury. As was noted previously, the tremor found on retesting was only mild postural tremor and not necessarily related to cerebellar dysfunction. Eyelid fasciculations appear to be significant with both blood and urine mercury and this appears to be consistent for these 11 subjects in both the initial and retest examinations (Table XXI). The generally increased significance

levels are most likely due to the smaller sample size and in the case of the retest group, a relatively low standard deviation among the mercury levels found (.22 $\mu\text{g}/100\text{ ml.}$ for blood and 60 $\mu\text{g}/\text{liter}$ for urine).

There was no significant change found for any of the symptoms or signs found. The group change was not at all significant either. This lack of change would appear significant in relation to previous studies which found most abnormalities disappearing within eight months of removal from mercury exposure.

Rank correlations between blood mercury and neurologic index for the initial group is actually negative (-.35 for urine level and -.23 for blood level), but became strongly correlated for the retest group (.54 for blood and .68 for urine, both significant at .05). This rather confusing result is attributed somewhat to the small sample size. Correlations with the psychomotor tasks (Table XXII) were not extremely significant and gave some confusing results when compared between test groups. It appears that decision times and mean alternating toe tapping rate are significant for the larger test group. The decision task correlations could be associated with the mental status impairment noted and may or may not be related to the mercury exposure. Correlations with the eye-hand coordination maze test (Table XXIII) again offer a confusing result with comparison from the larger test group to the smaller group. The indications from the correlation with the larger group are as would be expected, with

TABLE XXII

COMPARISON OF PSYCHOMOTOR-
NEUROLOGIC CORRELATIONS

Test	Parameter	PLANT 2 FIRST TEST Corr. w/32 subjects	PLANT 2 FIRST TEST Corr. w/11 subjects	PLANT 2 SECOND TEST Corr. w/11 subjects
Two Choice Decision msec/response	Mean	.51*	.09	.17
	Std Dev	.29	-.28	-.01
Four Choice Decision msec/response	Mean	.60**	.72**	.16
	Std Dev	.43*	.48*	.03
Simple Reaction msec/response	Mean	.57**	.33	-.12
	Std Dev	.44*	.56**	-.69**
Finger Tapping taps/5 secs	Mean	-.40	.36	.02
	Std Dev	.32	-.06	.07
Toe Tap- Right taps/5 secs	Mean	-.03	.06	.44*
	Std Dev	-.21	-.03	.44*
Toe Tap- Left taps/5 secs	Mean	-.03	-.02	-.12
	Std Dev	-.14	-.47*	-.35
Toe Tap- Alt. taps/5 secs	Mean	-.57**	-.28	.50*
	Std Dev	-.20	-.32	.18
Pencil Flipping secs/25 flips	Mean	.48*	.29	-.01
	Std Dev	-.14	.08	-.48*

* Significant @ .10

** Significant @ .05

TABLE XXIII
COMPARISON OF MAZE -
NEUROLOGIC CORRELATIONS

	Parameter	Data II-2 Corr. w/31 subjs.	Data II-3 Corr. w/11 subjs.
MAZE	Median	.47*	-.26
TEST	Mode	.48*	-.22
BEFORE	Mean	.43	-.48
#15	Std Dev	.06	-.57**
HOLD	Skewness	.32	.54**
		<u>w/26 subjs.</u>	
	Median	.42*	-.19
MAZE	Mode	.39	-.08
TEST	Mean	.46*	-.39
AFTER	Std Dev	.66**	-.52**
#15	Skewness	-.72**	.45*
HOLD			

* Significant @ .10

** Significant @ .05

the central tendencies being significantly related to increased neurological abnormality, and the skewness or presence of multi-modal distribution indicating an unusual pattern of behavior (possibly fumbling) being negatively correlated.

Discussion of Clinical Findings

It should be noted first of all that none of the patients in the test group had spontaneously complained of any of the classical symptoms of acute or chronic mercurial poisoning. There was no functional impairment with regard to work responsibilities, or habits of daily living. Among the list of symptoms found in Table XVII of the History and Neurologic Examination special attention was directed to those of irritability, sleep disturbances, anorexia and weight loss, because significant correlations had been found in a previous study (Smith, 1970) with regard to these particular symptoms. We could not substantiate these findings in this report. Additionally, all of the patients' medical records were reviewed with regard to weight determinations on their annual physical examinations, going back periods from 3-10 years, and no significant weight changes had occurred in any of the patients. If anything, there was a slight tendency to gain in body weight. What positive symptoms could be elicited could not be correlated with urine or mercury levels although it should be remembered throughout the discussion that there are no good identifiable controls among the subject group.

Correlation of positive symptoms with dose exposure must be guarded as well as the symptoms are intermittent and the urine and blood mercury levels vary a great deal from month to month. While it can be said that no definite trend to the development of the classical symptoms of inorganic mercurialism could be found in this test group, whether or not the incidence of positive symptoms found here would exceed that of normal population would be a matter of conjecture. Blood pressure determinations were made on all the patients as well as a review of their previous medical record with regard to this factor. There are conflicting reports in the literature as to the effect of chronic mercury exposure on the diastolic and systolic blood pressure. One report (Smith, 1970) suggests that there may be an overall lowering of the diastolic blood pressure and this is explained as perhaps due to a diuretic effect of the mercury, although mercurial diuretics are all organic mercurial compounds. In a small series of nine cases (Vroom and Greer, 1972), five patients were found to be hypertensive. In our series, 29% were found to be mildly hypertensive but again no specific correlation could be made with present blood and urine mercury levels.

Mental Status Evaluation

This was carried out as outlined in Appendix E. The mood, affect and personality changes normally associated with mercury poisoning, such as irritability, timidity, anxiety or depression, were difficult to assess in the brief interview session.

It would have been perhaps more informative to discuss the patient's behavior with his friends and relatives who have had the opportunity to observe any mood or personality changes over a much longer period of time. An important variable with regard to judgment or emotional status was the pending loss of job security resulting from the announced closure of the chlorine plant. There were few instances of recent memory impairment and no specific instances of difficulties with concentration. There were a number of patients who showed impaired ability with regard to judgment, calculation and abstraction, however, taken in comparison to their verbal skills this was considered most likely an amentia or reflection of the life long low-normal intelligence. Formal psychological testing would be required to be more certain of this. In the retest group more time was available for the mental status interview. As a result, a greater variety of test questions could be put to the subject. In what appears to be a slight increase quantitatively in their deficiencies is perhaps just a reflection of a more critical analysis of capabilities in this area. As an example, their abstraction ability was judged on the basis of their interpretation of a single proverb in the initial test situation, whereas they may have been presented with three or four proverb interpretations in the retest analysis. Significantly they did not change qualitatively, as our deficits reflected again amentia and not impairment of recent memory, comprehension, or affect and mood changes.

Neuromuscular System

The only observed abnormality in this area was the presence of eyelid fasciculations which were observed in 12 of the subjects of the initial test group and one additional subject in the retest group. Eyelid fasciculations are not necessarily abnormal findings and perhaps have been experienced by most people from time to time. However, the casual observation of this phenomenon in 13 subjects is probably significant. Again, this could not be correlated with the level of blood or urine mercury at the time of observation. However, in only one subject was this phenomenon noted who had both normal urine and blood mercury levels. Additionally it should be noted that the retest group was examined without reference to their previous neurologic abnormalities. The same three subjects in which eyelid fasciculations were noted on the initial evaluation were again noted to have them on retest evaluation eight months later. Additionally, one subject was found to have eyelid fasciculations in the retest group whereas these were not noted in his initial exam.

Sensory Modalities

Those tested included pinprick, touch, position, vibration and cortical sensation, and there were no significant abnormalities found. Two patients had minimally diminished vibratory sensation and the third patient had a peripheral neuropathy which was clearly related to an ongoing metabolic problem.

Deep-Tendon Reflexes

Deep-tendon reflexes are classically graded from 0 to 4+, 0 indicating an absence of stretch response and 4+ indicating repetitive responses after the introduction of only a single stimulus. Either extreme is clearly more objective. The grades in between the extremes reflect the judgment of the examiner. It should be noted that there seems to be a fair amount of internal consistency reflected in the retest subjects. Ten of the 12 retest subjects were graded exactly the same as on their initial evaluation without reference to the initial examination at retest. Two subjects were noted to have 2+ or normal reflexes on the initial examination and were noted to have 3+ deep-tendon reflexes on the retest examination. The significance of this will be dealt with later. In all, roughly a third of the test subjects showed evidence of hyperactive deep-tendon reflexes. This is somewhat lower than previously published reports (Neal, 1941) of subjects with similar mercury exposure. This would seem to be significantly more frequent than one would expect from the casual observation of a "normal control population". Again no statistical relationship could be found with the level of urine or blood mercury, though only two subjects could be considered to have both urine and mercury levels which were both below standards for significant exposure.

Cerebellar Function and Involuntary Movements

Specific tests of cerebellar function included the ob-

servation of intention tremors, dysmetria, and dysdiadokinesia (DDK). The presence or absence of sustension (postural) tremors were also noted although these are much less specific for implicating involvement of the cerebellum and are frequently seen in a variety of metabolic conditions as well as in tense, anxious individuals. The presence or absence of perioral, tongue, or other facial or head tremors which are the more classical findings in mercurialism were also noted. Twelve of the original 32 test subjects were noted to have one or another of these abnormalities. Again no significant relationship could be determined to specific levels of blood and urine mercury but in only two subjects were these abnormalities noted in which both the blood and urine mercury were below accepted standards for exposure. In the retest group, five individuals were initially noted to have specific deficits of cerebellar function on their initial examination. In the follow-up examination after they had been removed from exposure, four of the five individuals showed complete clearing of the cerebellar deficits. The fifth individual was still working in the plant and his urine and blood mercury levels reflected continued significant exposure. One of the above four subjects showed perhaps a slight postural tremor and was previously noted to have dysdiadokinesia. Two subjects whose initial examinations were normal were noted to have mild postural tremors on retest, in the face of a dramatic return to normal levels of mercury in

their blood and urine. These were the same two subjects whose deep-tendon reflexes were noted to increase from a normal 2+ to a 3+ on the retest examination. If there are any two features of the neurologic exam which are going to reflect anxiety, it will be tremulousness of the outstretched hands and an increase in the activity of the deep-tendon reflexes. It is proposed that this apparent worsening might merely be a reflection of the stress of having been singled out for recall. Subject #5 did in fact express very conscious and hostile concern over the possibility that he may have been "poisoned" by exposure.

Dermatographia

It should be noted that the term in this text includes erythema and flair response as well as the classical triple response. Several subjects were not tested for this peculiar abnormality because it had not occurred to the examiner to include this in the initial protocol until one subject was noted to develop a marked weal and flair skin response after the application of the blood pressure cuff. The test consists of scratching the skin and observing over a period of three minutes the development of an erythematous flair reaction and/or a raised weal. The classical triple response has been estimated to occur in fewer than 0.1% of the general population, however, the incidence of erythematous flare response which is much likely higher and which is included here is not known. This particular phenomenon was found to have the highest

significant statistical correlation with blood and urine mercury levels. Fifty-two of the subjects in our study were found to exhibit some measure of dermatographism. There were some inconsistencies noted such as the development of the rather marked response in one subject in the retest group whose initial test was negative and whose blood and urine mercury levels had dramatically fallen off by the time of the re-examination.

Conclusions

Inorganic mercury classically produces a triad of 1) oral cavity disorders- gingivitis, stomatis, 2) involuntary movement disorders- perioral, head and intention tremors, 3) psychological disturbances- irritability, timidity, confusion, impaired comprehension (Joselow, et al, 1972) as well as rigidity and specific memory defects (Vroom and Greer, 1972). Unlike organic mercurial poisoning there has been little in the way of pathological correlation in humans. It can be said that none of the subjects in this study exhibited any signs of acute inorganic mercurial poisoning, with perhaps one exception (Subject 26 who was apparently still exposed on the retest examination). Few showed any overt classical signs of chronic mercurialism. The abnormalities that were found in the mental status interview indicated primarily a life-long limited intelligence though, as has been stated before, this may not have been a fair judgment in the sense that mood, affect and personality changes are probably best

judged by interviewing the patient's relatives and friends. Additionally, more formal psychological testing may have indicated abnormal behavior that was not clinically recognized in the interview session. The only clear-cut improvements that were found in the retest group occurred in the sphere of cerebellar function. This might be expected in keeping with the previous literature on the subject. The most significant findings of this study would appear to be the observations of eyelid fasciculations and dermatographia. The physiology of eyelid fasciculations is not known and it would be sheer conjecture to speculate on the pathophysiology with regard to mercury exposure. Dermatographia was initially reported as a complication of chronic mercurialism by Neal (1941) but in subsequent studies little attention has been directed toward this phenomenon. The phenomenon of dermatographia is mediated by the so-called axon reflexes. Fine sensory fibers in the peripheral nervous system are thought to transmit antidromic impulses (in the opposite direction of their normal afferent course) in response to mechanical stimulation. At the peripheral nerve terminals histamine or some other vasodilatory substance is released which produces the local edema and vasodilatation. The exaggeration of this response is seen frequently with proximal involvement of sympathetic fibers both within and without the central nervous system. It might be speculated that inorganic mercury produces some central imbalance of the autonomic nervous system,

however, the possibility of local direct toxic action in the skin cannot be ruled out. In evaluating any of these minor neurologic abnormalities, consideration must be given to the incidence of herditive familial neurologic disorders in this particular geographic area. There is certainly an increased incidence of epilepsy, cerebral dysfunction syndromes, and a lower than average intelligence level. Against this background it might be difficult to assess minor disturbances in coordination and pathologically brisk reflexes. Any real control population will have to come from an adjoining community. As we might have expected from the results of previous studies (Bahigelli, 1960) there was a great deal of variation in the individual sensitivity or tolerance to inorganic mercury exposure as reflected by urine or blood mercury levels and these indices do not necessarily reflect the concentration within the central nervous system.

Recommendations

1. It is recommended that special attention be directed by clinical observers to the phenomena of eyelid fasciculation and dermatographia in the evaluation of subjects suspected of exposure to inorganic mercury. It should be emphasized that the presence of these minor abnormalities would seem to reflect either present or past exposure, and do not necessarily remit following removal of the subject to a safe environment.

2. It is recommended that subjects exposed to other

heavy metal toxins such as arsenic, lead, antimony, zinc, as well as organic mercurial compounds be investigated in the future with regard to the above phenomena to ascertain whether these minor neurologic abnormalities are peculiar to inorganic mercury.

3. It is recommended that there be continued reservation with regard to correlations between specific blood and urine mercury levels and the clinical neurological expressions of mercurialism.

4. It is recommended that in the future perhaps more attention should be focused on other areas of possible autonomic nervous system dysfunction such as postural changes in blood pressure, pilomotor responses, impotence, abnormal sweat patterns, dermatographia, as well as studies of skin temperature and skin resistance.

Section VIII

Conclusions and Recommendations

The following conclusions and associated recommendations have resulted from this investigation:

Conclusion 1

The following neuromuscular and psychomotor functions are significantly correlated with varying levels of blood and urine mercury burdens:

- A. The frequency of forearm tremor increases with elevated blood and urine mercury levels (Sec. IV, p. 41).
- B. The bandwidth of the surface EMG increases with elevated blood and urine mercury levels (Sec. IV, p. 48).
- C. The speed of hand and foot tapping and simple response time decreases with elevated blood and urine mercury levels (Sec. V., p. 79).
- D. The ability to repeatedly move the hand to discrete positions (eye-hand coordination) becomes more varied with elevated blood and urine mercury levels (Sec. VI, p. 106).

Recommendation 1. The above functional measures should be utilized as components of routine assessments of health status for individuals repeatedly exposed to inorganic mercury.

Conclusion 2

The retesting of the above measures of tremor, EMG, tapping ability, eye-hand coordination, and simple response time tests was performed after a four to six month period of reduced exposure. This resulted in the conclusion that these decrements in functional capabilities were reversible wherein the chronic exposure to mercury resulted in a mercury body burden of about 600 µgm/liter of urine or an equivalent mercury burden of about 11 µgm/liter of blood (Sections IV, p. 58, V., p. 85, and VI, p. 105).

Recommendation 2. This conclusion further substantiates

the feasibility of these subclinical functional measures as being useful in assuring the health status of a person who is occupationally exposed to inorganic mercury. It is therefore proposed that a longitudinal demonstration project be established to assess the utility of these tests in controlling industrial mercury intoxication.

Conclusion 3

Based on Conclusion 1 above, it is postulated that the cerebellum is probably the neurological structure most associated with chronic inorganic mercury loading. This is consistent with tissue differential distribution studies of others (Sec. II, p. 20). The clinical evidence of an increased prevalence of eyelid fasciculation and dermatographia among workers demonstrating relatively high mercury body burdens (averaging 787 µg/liter of urine) suggests a more diffuse neurological involvement (Sec. VII, p. 140). This same group of workers failed to demonstrate remission of these findings after four to six months removal from exposure. (N.B.-- The decrease in burden reached 95 µg/liter in urine.)

Recommendation 3. Development and evaluation of additional quantitative neurological tests should be promoted to better establish the pathology of long term chronic exposures to inorganic mercury.

Conclusion 4

It is concluded that the simple variable, "length of time exposed to occupational mercury", is not a good predictor of the effects on a person's health, even when combined with knowledge of the person's current urine and blood mercury burdens.

Recommendation 4. Future studies of this type should include either routine atmosphere or biological sampling records to provide detailed information regarding the history of exposure.

Conclusion 5

It would appear that functionally based routine health status testing would be warranted for any person whose mercury concentrations exceed approximately 100 µgm/liter in urine. In other words, this could become the Health Evaluation Action Level for mercury. It was at this level that the population studied disclosed changes in the neuromuscular

indices of tremor and EMG (Sec. IV, p.47 and p.55). It should also be noted that the psychomotor tests were shown to be affected at higher levels; this could be due to the higher variability in the population's responses on these tests (Sec. V, p. 79, Sec. VI, p. 100).

Recommendation 5. The large individual variations in response to given levels of urine and blood mercury burdens (documented in this and other studies) suggests that routine health evaluations be instigated to develop better future alternatives to protect the individual's health. Based on the data of this study, a biologically based action level of 100 μ gm of mercury per liter of urine is recommended. On exceeding this level a person must be routinely examined to determine if any deterioration in his health status has taken place. The outcome of these functionally based health evaluations would determine if the individual should be removed from exposure, or simply be retested at frequent intervals. The basis for this latter more important decision requires further investigations.

Conclusion 6

It is concluded from the standardized five-minute weight holding test that localized muscle fatigue per se is probably not associated with increased mercury body burdens, as determined by mean EMG frequency changes (Sec. IV, p.56). It must be noted, however, that the performance on the eye-hand coordination test was more adversely affected by mercury when the test was performed after the standard exertion (Sec. VI, p. 101).

Recommendation 6. A standardized exertion may be helpful in differentiating the effects of mercury on certain psychomotor test parameters, and therefore its use in future testing should be pursued. Furthermore, additional evaluations of muscle fatigue as effected by elevated mercury body burdens should be undertaken using measures other than the EMG mean frequency shift. For example, abnormal strength decrements may be found after a submaximal exertion by those people having elevated body burdens if a denervation or decreased muscle fiber contractility has occurred.

Conclusion 7

It is concluded at present that neither blood nor urinary mercury level is better correlated with a person's functional changes, especially in the tremor and EMG. The fact that blood and urinary mercury burdens were correlated

with $r=.79$ (which is similar to other reports in the literature) indicates a potential for one or the other to become the dominant correlator with health status measures. This did not happen, however, and hence this conclusion.

Recommendation 7. In performing this study, it was not possible to control the sampling times during the day or week, thus they were reasonably random in time. Hence, it is recommended that future studies of this type attempt to be more specific as to when the samples are taken. This could possibly increase the correlations with the health status indicators and help determine whether one or the other should be favored for biological controls.

In general, it is believed by these investigators that this study has greatly contributed to the knowledge required to define the mercury control procedures which are both necessary and reasonable. The challenge now is to further develop and implement health evaluation tests which can be routinely administered when mercury intoxication is suspected as a result of atmospheric and biological assessments. With such future tests, it is proposed that the effects due to other toxic materials as well as mercury could be controlled in a manner that would provide the maximum protection of the worker's health and well-being.

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Appendix A

Subject Information and
Consent Forms

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
Health Services and Mental Health Administration
National Institute for Occupational Safety and Health
Cincinnati, Ohio 45202

MERCURY BEHAVIORAL STUDY/EMPLOYEE FORM

This study is being conducted by the University of Michigan under Contract HSM 099-71-62 "An Evaluation of Chronic Mercury Exposures on EMG and Psychomotor Function." The sponsor and monitor of this project is the Behavioral Studies Laboratory, Behavioral and Motivational Factors Branch, Division of Laboratories and Criteria Development, National Institute for Occupational Safety and Health.

CONSENT

I hereby voluntarily agree to participate in the Mercury Behavioral Study which is being conducted by the University of Michigan and sponsored by the National Institute for Occupational Safety and Health.

The study has been discussed with me and I understand:

- A. Purpose of study and confidentiality of information:
 - (1) This study is meant to assess whether long-term low levels of exposure to metallic mercury are harmful to health, and
 - (2) all information collected will be kept in strict confidence;
- B. Questionnaire and study tests:
 - (1) a questionnaire must be answered,
 - (2) the study tests are not hazardous to my health and pose a minimum of discomfort,
 - (3) samples, such as blood, urine, hair will be required for monitoring purposes and for special clinical tests, and
 - (4) tests will be given to measure hand-eye coordination, muscle function and strength and balance;
- C. Medical records and release of test results:
 - (1) my medical records will be required and separate written consent for release of records will be requested, and
 - (2) I may request, by separate written consent, a report of my test results or any significant behavioral findings from this study be sent to physicians of my choice;
- D. Employment protection and withdrawal from study:
 - (1) my participation in this study or my test results will not be used in any way to jeopardize my employment, and
 - (2) I may withdraw from the study at any time.

(Signature of Volunteer)

Date: _____

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
National Institute for Occupational Safety and Health
Cincinnati, Ohio 45202

MERCURY BEHAVIORAL STUDY

CONDUCTED BY: University of Michigan

Plant Code: _____

SPONSORED BY: National Institute for
Occupational Safety and
Health

Employee Code: _____

Test No: _____

CONTRACT NO: HSM 099-71-62

Date: _____

EMPLOYEE QUESTIONNAIRE

(To be completed by subject volunteer)

1. Name (please print): _____
(Last) (First) (Middle)
 2. Age: _____ (years)
 3. Height: _____ (inches)
 4. Weight: _____ (pounds)
 5. Sex: M F
 6. Circle highest grade completed:

1	2	3	4	5	6	7	8
<u>Pre-high school</u>							

1	2	3	4
<u>High school</u>			

1	2	3	4
<u>College</u>			
 7. Name of plant where you work: _____
 8. Job title: _____
 9. How long have you worked for this company? _____ (years)
 10. How long have you worked in your present job? _____ (years)
 11. For what other companies have you worked during the last 10 years?
- | <u>Name of Company</u> | <u>Job Title</u> | <u>How long
(years)</u> | <u>Years
Worked</u> |
|------------------------|------------------|-----------------------------|--------------------------|
| 1) _____ | _____ | _____ | From: _____
To: _____ |
| 2) _____ | _____ | _____ | From: _____
To: _____ |
| 3) _____ | _____ | _____ | From: _____
To: _____ |

- | | <u>YES</u> | <u>NO</u> |
|---|------------|-----------|
| 12. Did you work with mercury or was mercury used at all in the companies you listed under question 11? | () | () |
| 13. Describe the location within the plant of your present job: _____ | | |
| 14. How often do you change into freshly cleaned work clothes?
_____ | | |
| 15. Do you have separate lockers for work and street clothing? | () | () |
| 16. Do you shower at the plant when your shift is over? | () | () |
| 17. Does your job require that you wear a respirator while you are working? | () | () |
| 18. Have you been involved in a work accident at this plant? | () | () |
| 1) If yes, how many? _____ | | |
| 2) If yes, causes: _____ | | |
| 3) If yes, how many total days work did you lose? _____ (days) | | |
| 19. Were you hospitalized in the last two years? | () | () |
| 20. Any sickness in past 30 days? | () | () |
| 1) Type of illness: _____ | | |
| 2) Duration of sickness(days): _____ | | |
| 3) Medicine taken, if known: _____ | | |
| 21. Did you take any medicine in past 24 hours? | () | () |
| 1) Give name of medicine: _____ | | |
| 2) Amount taken/day: _____ | | |
| 22. Did you take any salt tablets in past 24 hours? | () | () |
| 23. Have you experienced any of the following: | | |
| 1) Weight loss in last 6 months(exclude dieting)? | () | () |
| 2) Night sweats? | () | () |
| 3) Tire easily? | () | () |
| 4) Lose temper easily? | () | () |
| 5) Noticeable change in your personality recently? | () | () |
| 6) Wake-up from sleep often? | () | () |
| 7) Can't go to sleep easily? | () | () |

- | | <u>YES</u> | <u>NO</u> |
|--|------------|-----------|
| 8) Feel depressed? | () | () |
| 9) Blush easily? | () | () |
| 10) Have difficulty concentrating? | () | () |
| 24. Have you ever had a tremor (shakiness) of: | | |
| (1) hands? | () | () |
| (2) lips? | () | () |
| (3) face? | () | () |
| (4) arms? | () | () |
| (5) legs? | () | () |
| (6) tongue? | () | () |
| (7) whole body? | () | () |
| 25. Do you presently have any tremor? | () | () |
| 26. Which ones (list by above number)? _____ | | |
| 27. Has your handwriting become shakier? | () | () |
| 28. Have you developed any difficulty in talking? | () | () |
| 29. Do you have any numbness of your tongue or lips? | () | () |
| 30. Do you have any numbness of your arms or legs? | () | () |
| 31. Do you feel unsteady when you walk? | () | () |
| 32. Do you get frequent headaches? | () | () |
| 33. Have you ever had any disease of the nervous system
(e.g., meningitis, neuritis, etc.)? <u>Exclude nervousness.</u> | () | () |
| 34. Have you ever been treated for loss of consciousness? | () | () |
| 35. Do you wear glasses or contact lenses? | () | () |
| 36. Do you have frequent itching or tearing of your eyes? | () | () |
| 37. Has your eyesight worsened recently? | () | () |
| 38. Do you think you have normal hearing? | () | () |
| 39. Have you ever smoked cigarettes regularly? | () | () |
| 40. Do you smoke cigarettes presently? | () | () |
| 41. Circle how many cigarettes/day you smoke | | |
| 1) less than 5? | | |
| 2) 1/2 pack? | | |
| 3) 1 pack? | | |
| 4) 1 1/2 packs? | | |
| 5) more than 2 packs? | | |

42. Do you inhale? YES () NO ()
43. How many years did you smoke cigarettes before stopping? _____ (years)
44. How many years since you stopped smoking cigarettes? _____ (years)
45. Have you ever been allergic to anything? () ()
- | <u>Item</u> | <u>Type of Reaction</u> |
|-------------|-------------------------|
| 1) _____ | _____ |
| 2) _____ | _____ |
| 3) _____ | _____ |
46. Have you ever had any kidney problems? () ()
47. Do your legs or feet swell up? () ()
48. Do you participate in any sport or hobbies? () ()
- | <u>Name</u> | <u>Hours per week</u> |
|-------------|-----------------------|
| 1) _____ | Hours/week _____ |
| 2) _____ | Hours/week _____ |
| 3) _____ | Hours/week _____ |
| 4) _____ | Hours/week _____ |
49. Have you lifted weights recently? () ()
- 1) Range of weights lifted (pounds): _____
 - 2) Duration of work-out (minutes): _____
 - 3) Date of last work-out: _____
50. Write the following sentence in quotation marks in the bracket provided:
 "This is a specimen of my handwriting."



51. Which hand did you use to write the above sentence?
 (circle answer)

Right

Left

52. If there is anything we did not cover regarding your work, your health and physical condition that you think is important, please comment below in your own words.

Comment: _____

(Signature of Employee)

Date: _____

Appendix B

Description of Equipment and
Procedures developed for
Determination of Mercury
in Blood and Urine

The analysis of mercury in biological samples is of the utmost importance in monitoring the exposure of workers to industrial sources of mercury. This importance has generated a need for a method of analysis of total mercury content of blood, urine, and flesh that is quick, economical, precise, sensitive, and which has a detection limit in the neighborhood of 10 parts per billion (ppb). To satisfy this need, flameless atomic absorption has been adapted and refined as the primary method of choice first by Hermann, Butler, and Smith (1970), and later by Hecker (1972). The system described in this paper incorporated refinements which were developed at Environmental Health Labs, Inc., Farmington, Michigan.

Theory of Operation

This system consists of three essential parts with the following functions: 1) the furnace, which burns the sample to liberate free mercury vapor from the various mercury compounds within the sample matrix; 2) a series of traps for separating free mercury from the combustion products of the sample matrix; 3) a mercury vapor meter to quantify the amount of mercury vapor liberated from the sample. (See Figure 1) These three components are connected with glass joints and tygon tubing in the order shown. A vacuum pump is connected to the distal end of the apparatus to generate an airflow through the entire system so that a sample may be injected into the furnace and free mercury vapor from

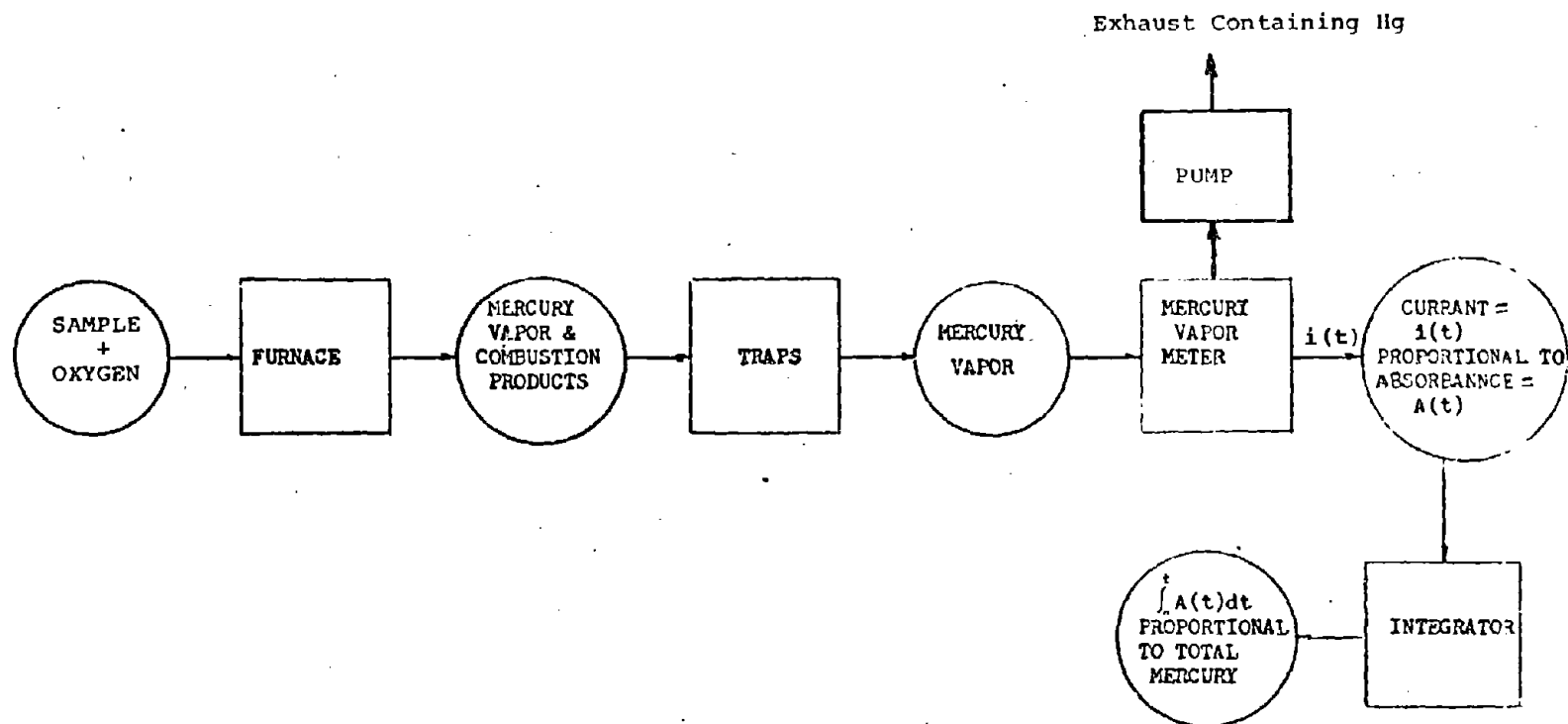


Figure No. 1 - General Schematic of Flameless Atomic Absorption Device Used to Analyze Biological Samples for Mercury Content

the sample will ultimately be drawn through the mercury vapor meter for quantification.

The actual size, shape, and mechanism of the furnace may vary greatly from one device to another. All that is of crucial importance is that the sample be heated long enough at sufficiently high temperatures to liberate free mercury vapor from the various sample matrices. The type of furnace system selected for this particular system is shown in Figure No. 2. The system consists of four Hoskins furnaces which heat two ceramic tubes. To enhance the transfer of heat from the furnaces to sample and to provide a burning surface, the ceramic tubes were filled with berl saddles. The two tubes were mounted at right angles in the vertical and horizontal planes so that the sample could be dropped directly into the furnace and so that the furnaces would be more compact.

It has generally been found desirable to operate the furnaces at approximately 1000°C ; but since the Hoskins furnace has a design temperature limit of 1000°C , the last three quarters of the combustion tubes were heated to only 950°C . in order to provide a safety factor to prevent burn out. The first quarter of the combustion tubes were heated to only 550°C .

The temperature of this first section of the combustion tube is the most critical parameter of the system. If this section is too hot, the blood mercury results will be erroneously high, and if the temperature is too low,

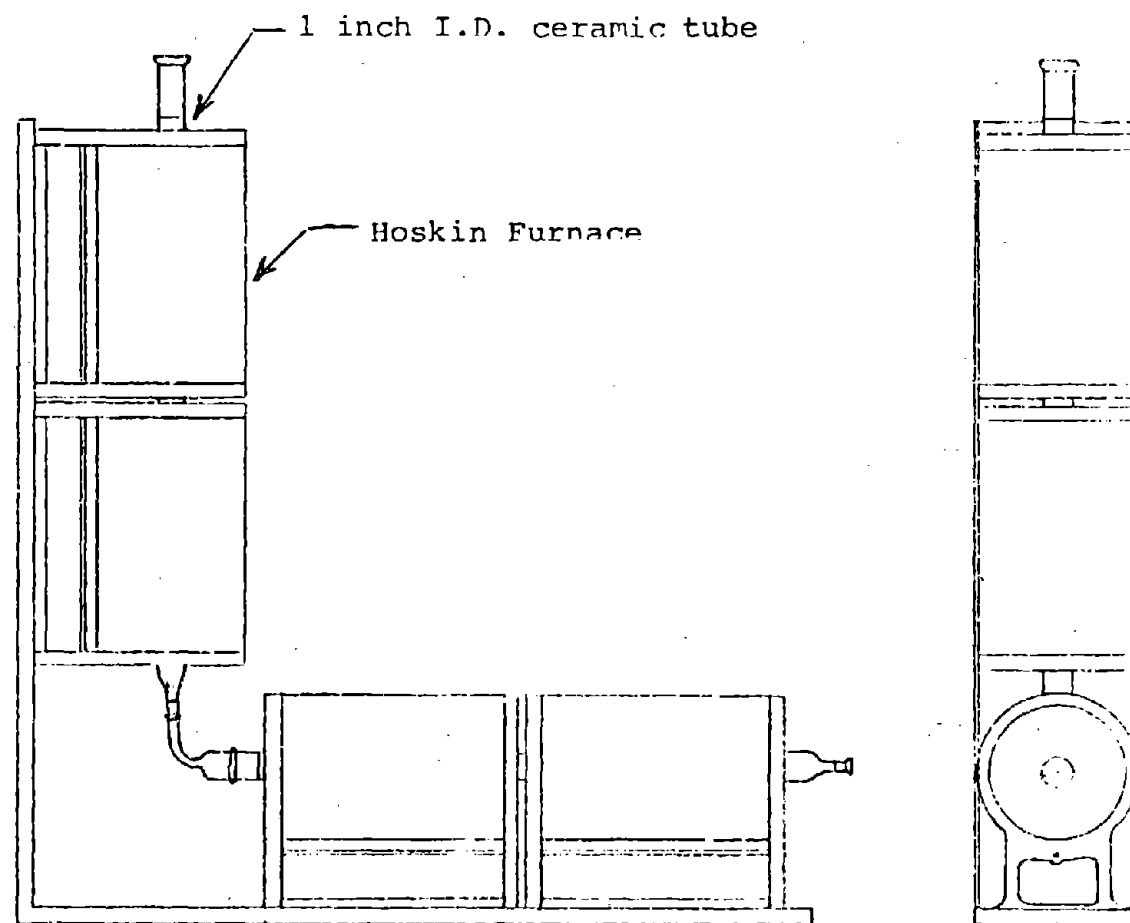


Figure No. 2 - Arrangement of Combustion Furnaces

(1/10 scale)

the levels will be found to be lower than the actual value. The final temperature setting for this section is determined empirically in the following manner: water and blood standards of the same mercury concentrations are injected alternately until they each produce the same standard curve. There are some indications that when the first tube is maintained at too high a temperature, large quantities of NO_x may be generated; such an occurrence will bias the results.

The furnace design must reflect some consideration of the sample size to be injected into it at one time. Generally speaking, for a sample of fixed mercury concentration, the amount of mercury vapor liberated and consequently the amount of electrical signal should be proportional to the sample size. However, if the sample is too large, the system will produce a much larger signal than expected. This may be due to incomplete combustion of the sample in the furnace, which causes an excess of combustion products to overwhelm the series of traps between the furnaces and mercury vapor meter. The exact limit of the sample size depends upon the properties of the sample matrix, and can be determined empirically before the system is used simply by injecting a series of increasingly larger standard sample volumes and plotting the results, absorbance vs. sample volume. Sample volumes may be used which are in the linear range of the resulting curve. It has been found desirable to keep the sample size for blood at less than

one hundred microliters. Although the maximum sample size can vary somewhat, a much larger blood sample would be expected to create problems.

The system should be periodically checked for false signals by injecting a sample of distilled water into the furnace and making sure that no signal results. False signals may be due to some residue of mercury or other interfering materials in the furnace. This problem is generally encountered when breaking in a new system or after excessively large amounts of mercury have been injected into the furnace. For this reason, it is recommended that the furnaces be left "on" between use when scheduled for daily use, and left at partial heat when used less frequently. It is also advisable to turn the furnace on and allow air and oxygen to flow through well in advance of any use.

The primary purpose of the trap system is to remove the combustion products from the mercury vapor so that the vapor can be quantified with no interferences. Interfering materials which are commonly encountered include NO_x , H_2O , CO_2 , acids, and particulates. Each of these materials may absorb some ultraviolet light and would be interpreted as mercury in the mercury vapor meter. The traps consist of components in the following order and with the following functions: A Friedrich condenser which removes water and acid vapors; a glass fiber filter which removes suspended particulate materials; a fritted bubbler with 0.1NN sodium

hydroxides which absorbs carbon dioxide and other acidic gases; and finally, a cold trap to remove additional water vapor. (Fig. 3)

The mercury vapor meter selected for this system is shown in Figure No. 4. It consists of two essential parts -- an optical system and an electrical system.

The optical system consists of a mercury germicidal lamp and two RCA 935 photo tubes. Between one of photo tubes and the light source is placed a quartz gas cell. Between the second photo tube and the light source is a variable width slit which allows adjustment of the intensity of light reaching the second photo tube. When the light reaching each tube is equal the system is said to be optically balanced. The gas cell is connected in series with the trap and furnace systems so that all air and samples drawn into the furnace must ultimately pass through it. As free mercury vapor passes through the cell, it will absorb light produced by the mercury lamp. This absorption will cause less energy to be transmitted to one of the photo tubes and will result in an optical imbalance causing a difference in the output of the photo tubes, which is measured by the electronic portion of the system.

The electronic portion of the system utilizes a wheatstone bridge circuit to measure differences in the output of the photo tubes. (See Figure 4). The bridge consists of an 80v battery, an ammeter, two photo tubes and two variable resistors. The variable resistors are

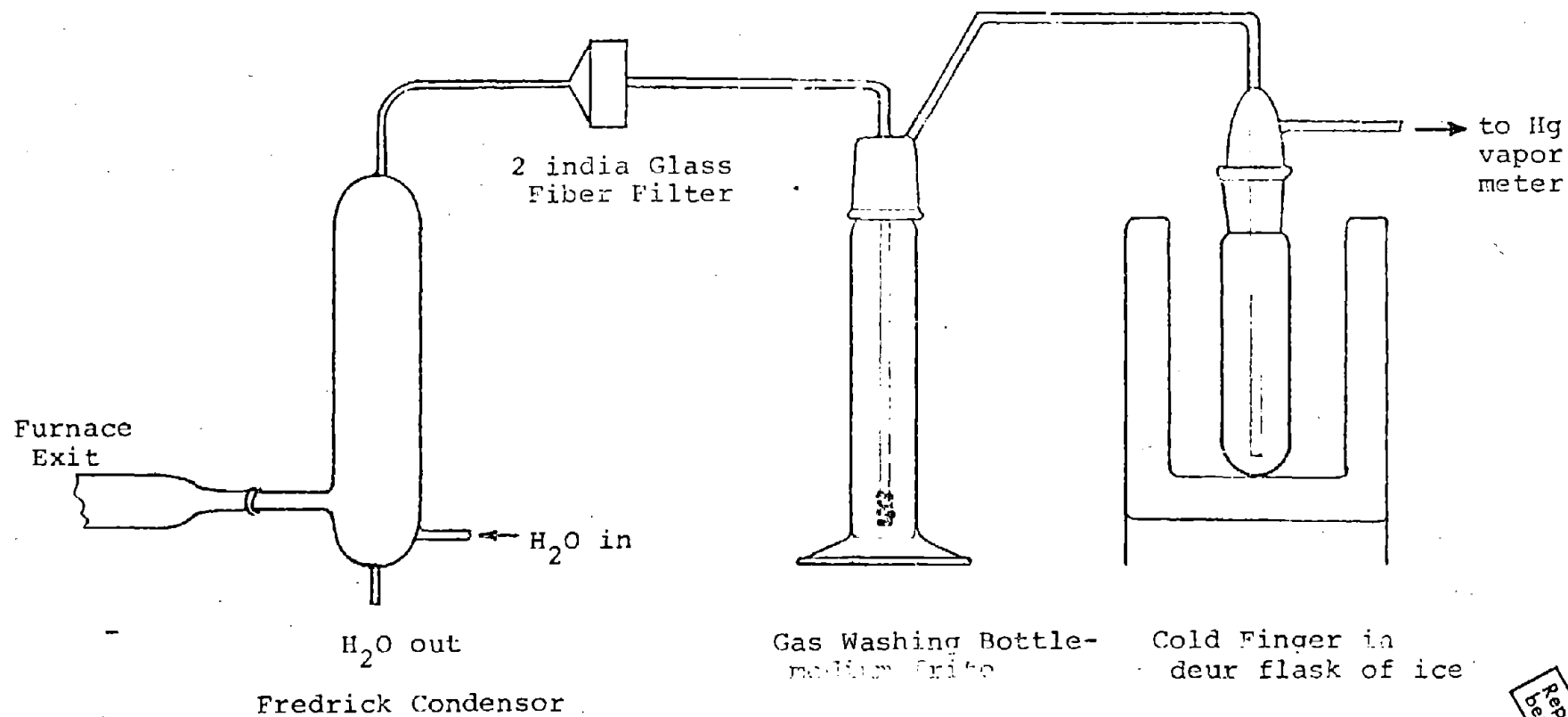


Figure No. 3 - Trap System Used to Separate Mercury from
Combustion Products of Sample (1/4 scale)

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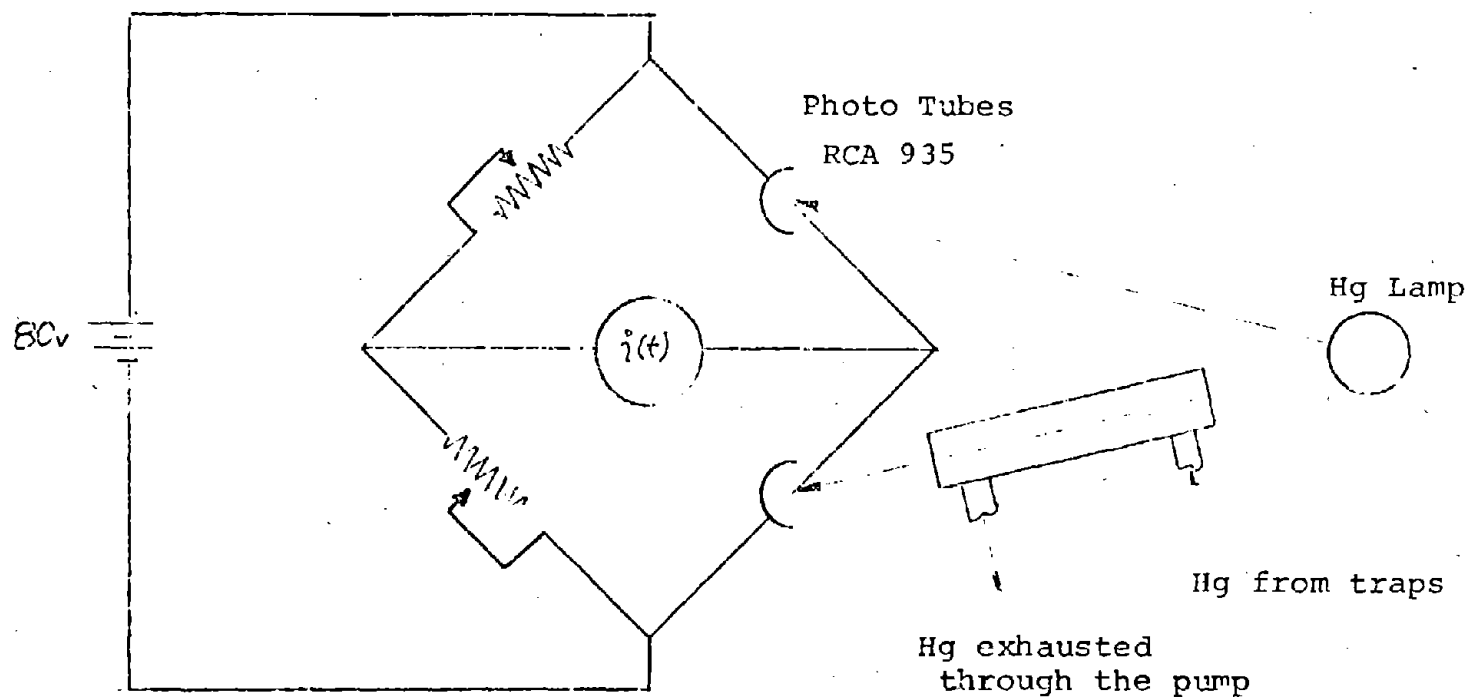


Figure No. 4 - General Layout of Electrical-Optical Bridge Circuit

used to electrically balance the system. As the output of one photo tube changes, the bridge becomes electrically imbalanced and a potential difference will be established across the center of the bridge, leading to an imbalance current $i(t)$.

Because typical mercury analysis involves very low concentrations of mercury, the current across the center of the bridge will generally range from 10^{-7} to 10^{-8} amps. This current, $i(t)$, is a first order linear function of absorbance, $a(t)$. Absorbance is a first order linear function of the total mass of mercury vapor passing through the cell--which is a function of time, $m_{\text{Hg}}(t)$. These relations are summarized as:

$$i(t) = k_1 \times a(t)$$

$$a(t) = k_2 \times m_{\text{Hg}}(t)$$

hences: $i(t) = k_3 \times m_{\text{Hg}}(t)$

where k_1 , k_2 , and k_3 are constants. We are interested in the total amount of mercury in a sample, M_{Hg} , which is the first time integral of $m_{\text{Hg}}(t)$. By the same logic as shown above we can write:

$$\int_{t_1}^{t_2} i(t) dt = K_1 \int_{t_1}^{t_2} a(t) dt = K_3 \int_{t_1}^{t_2} m_{\text{Hg}}(t) dt$$

For convenience, we will write:

$$I = K_1 \times A + K'_1 = K_3 \times M_{\text{Hg}} + K'_3$$

where I is the total current, A is the total absorbance, and M_{Hg} is the total mass of mercury, and where current is integrated electronically. These relations are shown graphically in Figure No. 5. In practice, the constants K_3 and K'_3 are determined experimentally by analyzing several samples of known mercury content, and then plotting a standard curve of I vs. M_{Hg} . Such a curve is shown in Figure No. 6. Mercury concentration of unknown samples is determined by injecting the sample into the furnace and recording I .

In this system, two types of electrometer and integrator systems were used. The more successful system consisted of a Keithly 615 Digital Electrometer and an Autolab 6300-02 Digital Integrator. This system provided automatic base line display and correction, a signal discriminator, automatic on-off switching, and a digital print-out. The second system seemed to provide a smaller detection limit, it was more sensitive to electronic noise which interfered with interpretation of the results. It was also a manually switched system -- a feature that resulted in more operating errors.

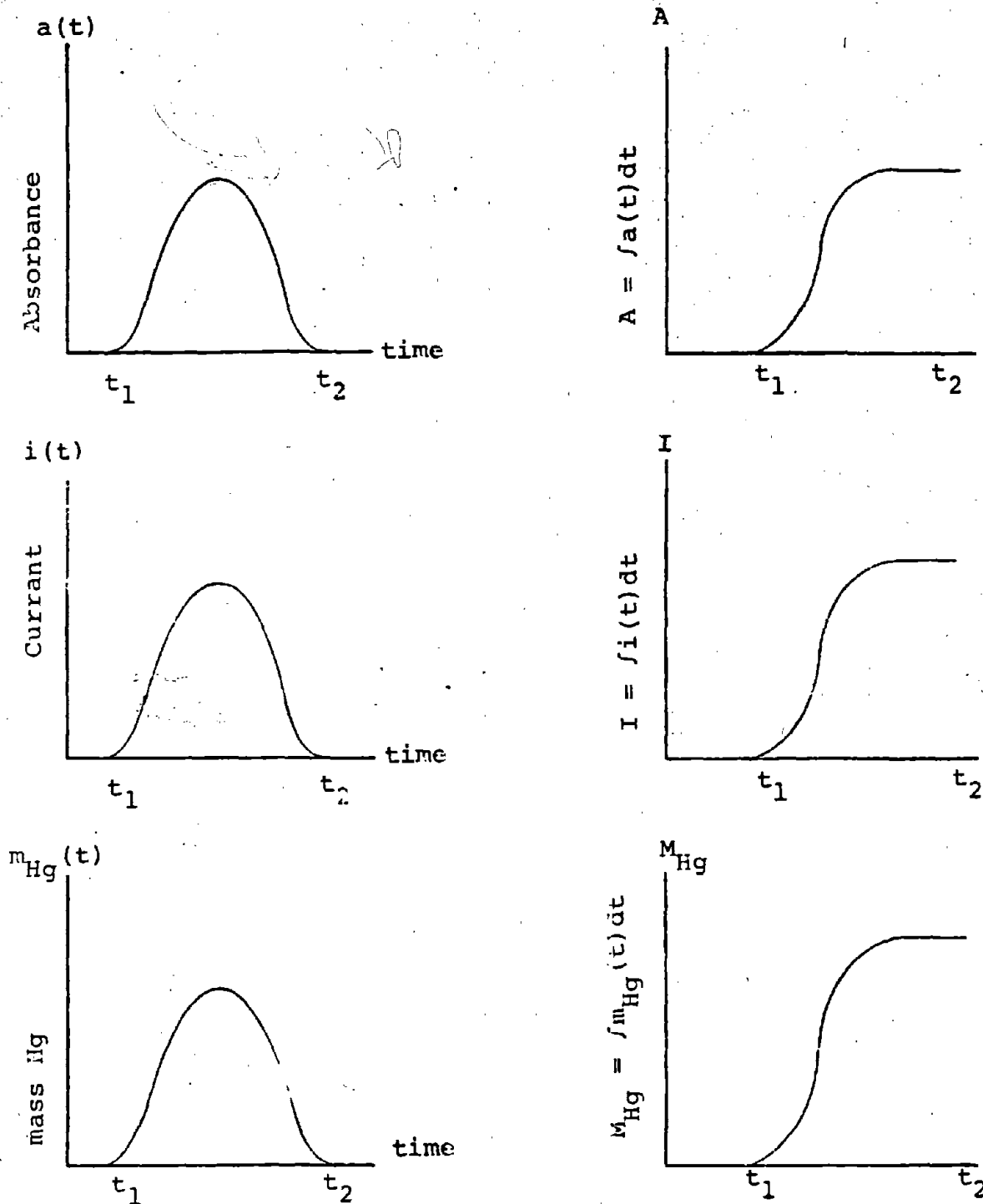


Figure No. 5 - Relation Between Absorption, Current, Mercury Concentration and Their Respective Integrals

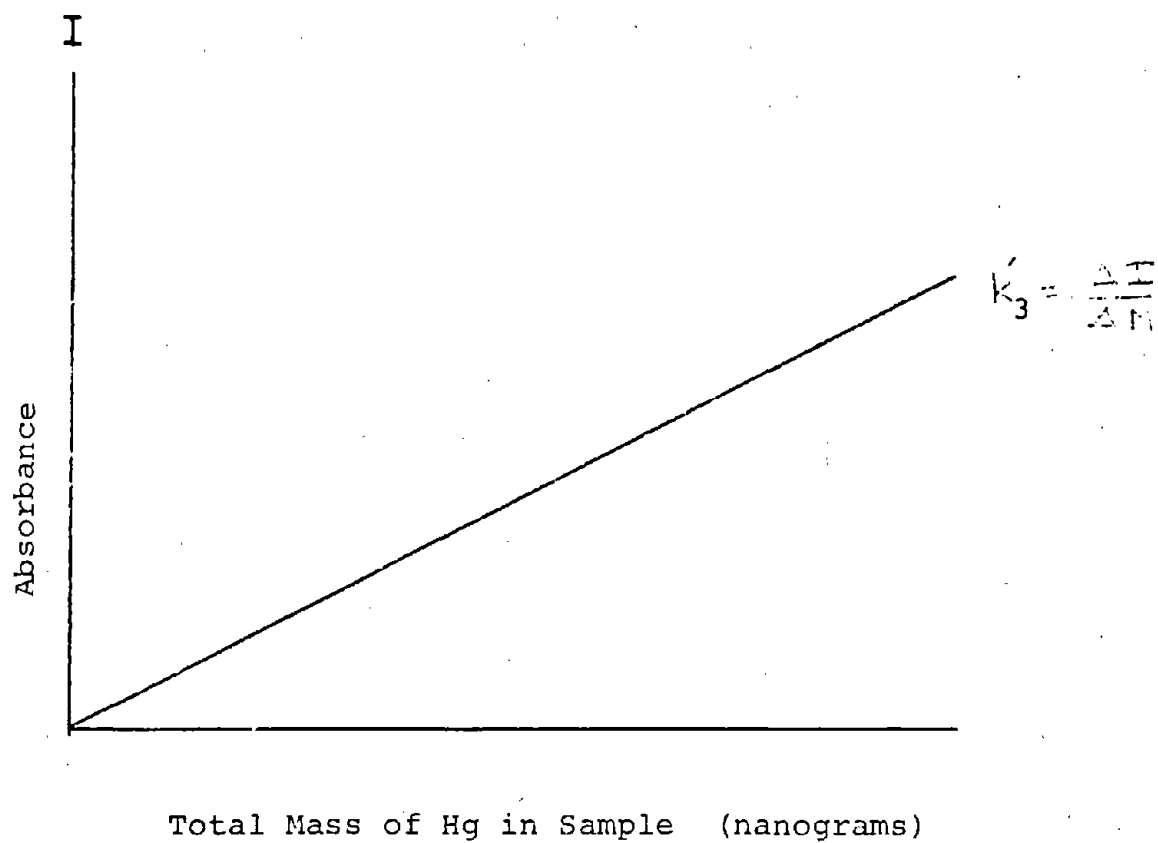


Figure No. 6 - Typical Standard Curve for Hg Analysis

Appendix C

Prediction Equations resulting from
Stepwise Regressions of
Sections IV and VI

Abbreviations for the Variables
used in the following Prediction Equations

ABBREVIATION	DESCRIPTION	ABBREVIATION	DESCRIPTION
	<u>INDEPENDENT POPULATION VARIABLES</u>		
HT	Height (inches)	EFMD	First Spectra Median Frequency
WT	Weight (pounds)	EFSD	First Spectra Standard Deviation
AGE	Age (years)	EF SX	First Spectra Skewness Coefficient
CIG	Cigarettes Smoked (packs/day)	EF3	First Spectra Percent Power in 0-30Hz Band
DUR	Duration of Exposure to Mercury (months)	EF47	First Spectra Percent Power in 40-70Hz Band
LDUR	Log _e (Duration in months of Exposure to Mercury)	EF69	First Spectra Percent Power in 60-90Hz Band
BL	Blood Mercury Concentration (µgm/100 ml)	EF12	First Spectra Percent Power in 100-200Hz Band
LBL	Log _e (Blood Mercury Concentration in µgm/100 ml)	EFMD	First Spectra Median Frequency
UR	Urine Mercury Concentration (µgm/L.)	EFR	First Spectra RMS Voltage
LUR	Log _e (Urine Mercury Concentration in µgm/L.)	EBMN	Rate of Change of Mean Frequency with Time
PL	Plant (I, II, III, and IV)		<u>Eye-hand Coordination Test Parameters</u>
	<u>DEPENDENT POPULATION VARIABLES</u>		
	<u>Tremor Spectra Parameters</u>	MBMN	Before Fatigue Hole-to-Hole Mean Time
TFMO	First Spectra Modal Frequency	MBMD	Before Fatigue Hole-to-Hole Median Time
TFMN	First Spectra Mean Frequency	MBMO	Before Fatigue Hole-to-Hole Modal Time
TFSD	First Spectra Standard Deviation	MBSD	Before Fatigue Hole-to-Hole Standard Deviation
TF SK	First Spectra Skewness Coefficient	MBSK	Before Fatigue Hole-to-Hole Skewness Coefficient
TFR	First Spectra RMS Voltage	MAMN	After Fatigue Hole-to-Hole Mean Time
	<u>EMG Spectra Parameters</u>	MAMD	After Fatigue Hole-to-Hole Median Time
EFMN	First Spectra Mean Frequency	MAMO	After Fatigue Hole-to-Hole Modal Time
		MASD	After Fatigue Hole-to-Hole Standard Deviation
		MASK	After Fatigue Hole-to-Hole Skewness Coefficient

Prediction Equations for EMG

<u>COMBINED GROUP</u>	<u>MULTIPLE CORRELATION COEFFICIENT</u>
EFMD = 53.59 - 1.563*LBL	0.21
EFSD = 24.24 + 0.11*AGE + 1.132*LBL	0.36
EFSD = 20.48 + 0.106*AGE + 1.14*LUR	0.42
EFSE = 1.674 - 0.009*AGE + 0.051*LBL	0.27
EF3 = 11.487 + 3.535 + 1.591*LBL	0.42
EF3 = 10.272 + 0.72*LUR + 3.7*CIG	0.37
EF47 = 50.64 - 0.147*AGE - 1.165*LBL - 1.938*CIG	0.39
EF47 = 53.29 - 0.134*AGE - 0.969*LUR - 1.879*CIG	0.38
EF69 = 29.63 - 1.727*LBL - 2.665*CIG	0.34
EF12 = 2.054 + 0.098*AGE + 0.637*LUR	0.26
<u>EXPOSED GROUP</u>	
EFMD = 47.94 + 0.233*AGE - 1.844*LBL - 2.657*CIG	0.41
EFSD = -7.845 + 0.495*HT + 1.683*LBL	0.38
EFSD = -9.949 + 0.44*HT + 1.69*LUR	0.42
EF47 = 47.45 - 2.306*LBL	0.31
EF47 = 53.19 - 1.849*LUR	0.30
EF69 = 31.91 - 2.355*LBL - 3.036*CIG	0.40
EPR = 218 + 251*LDUR	0.43

Prediction Equations for Eye-hand Coordination Test

<u>COMBINED GROUP</u> <u>(Before Hold)</u>	<u>MULTIPLE CORRELATION</u> <u>COEFFICIENT</u>
MBMD = $587 - 3.744*HT + 2.68*AGE - 15.09*LBL$	0.48
MBMD = $587 - 3.366*HT + 2.68*AGE - 10.246*LUR$	0.47
MBMO = $716 - 5.945*HT + 2.574*AGE - 11.716*LBL$	0.44
MBMO = $705 - 5.464*HT + 2.765*AGE - 9.682*LUR$	0.47
MBMN = $391 + 2.189*AGE - 12.106*LBL$	0.39
MBMN = $407 + 2.23*AGE - 7.648*LUR$	0.37
MBSK = $1.564 + 0.096*LBL$	0.19
(After Hold)	
MAMD = $327 + 2.771*AGE - 11.385*LBL$	0.44
MAMD = $358 + 2.548*AGE - 8.275*LUR$	0.41
MAMO = $293 + 2.686*AGE - 8.988*LBL$	0.42
MAMO = $312 + 2.774*AGE - 7.462*LUR$	0.43
MAMN = $374 + 2.662*AGE - 12.888*LBL + 21.253*CIG$	0.48
MAMN = $404 + 2.405*AGE - 8.466*LUR + 20.356*CIG$	0.46
MASD = $99.7 + 2.587*LUR + 10.132*CIG$	0.30
MASK = $1.827 - 0.058*LUR$	0.21
<u>EXPOSED GROUP</u> <u>(Before Hold)</u>	
MBMO = $675 - 6.06*HT + 3.161*AGE - 11.947*LBL + 14.171*LDUR$	0.55
MBMO = $697 - 5.77*HT + 3.222*AGE - 12.277*LUR + 13.995*LDUR$	0.57
MBMO = $915 - 9.076*HT + 3.478*AGE - 14.812*LUR + 13.477*LDUR$	0.56
MBSD = $85.2 + 4.334*LUR$	0.20
MBSK = $1.18 + 0.119*LUR$	0.22
(After Hold)	
MASD = $102 + 7.212*LBL$	0.29
MASD = $80 + 5.974*LUR + 8.76*CIG$	0.39
MASK = $1.377 + 0.01*AGE - 0.09*LBL$	0.28
MASK = $1.708 + 0.01*AGE - 0.093*LUR$	0.30

Prediction Equations for TremorCOMBINED GROUPMULTIPLE CORRELATION
COEFFICIENT

TFMD = $-5.016 + 0.165*HT + 0.458*AGE + 0.824*LBL$	0.55
TFMD = $-5.845 + 0.147*HT + 0.059*AGE + 0.579*LUR$	0.55
TFMO = $-5.154 + 0.134*HT + 0.571*AGE + 0.825*LBL$	0.50
TFMO = $-6.521 + 0.122*HT + 0.065*AGE + 0.676*CIG + 0.601*LUR$	0.54
TFMN = $-2.527 + 0.151*HT + 0.034*AGE + 0.731*LBL$	0.55
TFMN = $-2.539 + 0.126*HT + 0.048*AGE + 0.485*LUR$	0.53
TFSD = $3.503 + 0.244*LBL$	0.29
TFSD = $3.163 + 0.146*LUR$	0.23
TFSK = $2.486 - 0.003*WT - 0.012*AGE - 0.176*LBL$	0.43
TFSK = $2.284 - 0.015*AGE - 0.108*LUR$	0.39

EXPOSED GROUP

TFMO = $-10.738 + 0.257*HT + 1.162*LBL$	0.56
TFMO = $-9.873 + 0.206*HT + 0.919*LUR$	0.52
TFMO = $-10.909 + 0.228*HT + 1.239*LBL$	0.52
TFMO = $-2.889 + 0.014*WT + 0.957*LUR + 1.066*CIG + 0.574*LDUR$	0.61
TFMN = $-6.709 + 0.22*HT + 0.949*LBL$	0.53
TFMN = $-6.097 + 0.18*HT + 0.74*LUR$	0.49
TFSD = $3.61 + 0.318*LBL - 0.377*CIG$	0.29
TFSK = $2.544 - 0.005*WT - 0.222*LBL$	0.39
TFSK = $2.744 - 0.004*WT - 0.156*LUR$	0.33

Appendix D

Normal Parameter Values
presented in Sections III, IV and VI

Normal Value for Parameters Discussed in
Sections III, IV and VI based on
Control Group (Plant III and IV)

(Sample Size = 36)

	<u>Mean</u>	<u>Standard Deviation</u>
<u>Independent Variables</u>		
Height (inches)	69.64	2.475
Weight (pounds)	177.2	23.17
Age (years)	34.67	8.737
Cigarettes smoked (packs/day)	0.444	0.583
Blood mercury ($\mu\text{g}/100\text{ml}$)	0.797	0.409
Urine Mercury ($\mu\text{g}/\text{liter}$)	16.91	19.58
<u>Tremor Spectra Parameters</u>		
Median Frequency (Hertz)	8.073	1.159
Modal Frequency (Hertz)	6.058	0.619
Mean Frequency (Hertz)	9.171	1.078
Standard Deviation (Hertz)	3.521	0.754
Skewness Coefficient	1.485	0.516
RMS Voltage (10^{-5} volts)	12.13	6.190
<u>Eye Hand Coordination Test</u> <u>(Before 15# Hold)</u>		
Median time (msec.)	416.3	64.52
Modal time (msec.)	385.6	65.35
Mean time (msec.)	462.1	67.21
Standard Deviation (msec.)	105.6	31.91
Skewness Coefficient	1.630	0.544
<u>(After 15# Hold)</u>		
Median Time (msec)	428.6	67.74
Modal time (msec)	392.7	63.38
Mean time (msec)	472.8	64.50
Standard Deviation (msec)	112.4	27.62
Skewness Coefficient	1.589	0.466
<u>EMG Spectra Parameters</u>		
Median Frequency (Hertz)	53.47	8.855
Modal Frequency (Hertz)	46.89	12.42
Mean Frequency (Hertz)	54.45	8.434
Rate of change of mean frequency (Hertz/minute)	-2.284	0.946
Standard Deviation (Hertz)	27.34	4.047
Skewness Coefficient	1.349	0.423
% Power in 0-30 Hertz Band	12.55	5.090
% Power in 40-70 Hertz Band	44.87	5.846
% Power in 60-90 Hertz Band	28.37	8.618
% Power in 100-200 Hertz Band	7.834	5.072
RMS Voltage (10^{-7} volts)	1256.6	586.72

APPENDIX E

Description of Neurologic Examination

Description of Neurologic Examination

The 32 subjects in this study were examined according to the history and neurologic examination form, Table IX. At no time was the examiner aware of the subject's job responsibilities, risk of exposure, or previous blood or urine mercury levels.

Patient History: The patients were quizzed with regard to the list of prepared neurologic symptoms. If any of the symptoms were present, a judgment was made with regard to their severity.

Mental Status Evaluation: This consisted of determining a patient's level of alertness, his orientation, any defects in both recent and remote memory, and his ability to abstract and make appropriate judgments. There was also an opinion made of his emotional well-being. The character of the patient's speech, articulation and phonation was determined, as well as his ability to follow simple commands.

Visual Acuity: Corrected and uncorrected visual acuities were measured.

Cranial Nerve Examination: Cranial nerve 1, or the olfactory nerve was tested individually with coffee and tobacco odors. Cranial nerve 2, the optic nerve, was tested with the aforementioned visual acuity as well as the examination of the patient's visual fields to confrontation and a fundiscopic examination. Cranial nerves 3, 4, and 6 were tested by eval-

uating pupillary size in reaction to light and accomodation as well as extraocular movements, and the presence or absence of abnormal movements such as nystagmus. Cranial nerve 5 was examined by testing sensation over all three divisions, testing corneal reflexes and testing the power of masseter and pterygoid muscles. Cranial nerve 7 was tested by examining the patient's facial muscles and the symmetry of their movements. The 8th cranial nerve was examined by gross testing of the patient's hearing. Cranial nerves 9 and 10 were tested with regard to the patient's ability to respond to the gag reflex and voluntary elevation of the palate. Cranial nerve 11 was tested by evaluating the power and symmetry of sternocleidomastoid and trapezius muscles. Cranial nerve 12 was tested by evaluating the symmetry, power, and bulk of the tongue.

Sensory Modalities: These included vibration, position, touch, pinprick, deep pain, stereognosis and two point discrimination.

Gait and Station: The patient's gait was then tested according to his ability to heelwalk, toewalk and tandem walk.

Motor Examination: This was carried out by testing of the bulk, power and tone of all major muscle groups in both the upper and lower extremities, as well as observations of any involuntray motor activity.

Cerebellar Function: Tests of cerebellar functions in the upper extremities included finger to nose testing, rapid

repeated movements, rapid alternating movements and in the lower extremities, heel to shin testing. Observations were noted with regard to any involuntary movement such as resting tremors, chorea, athetosis, myoclonic jerks, or fasciculations. Special attention was directed to the presence or absence of perioral, head, or jaw mouth tremors.

Deep-Tendon Reflexes: The patient's deep-tendon reflexes were examined in grades 0 through 4.

Dermatographia: A spot check of the integrity of the autonomic nervous system was done by testing for dermatographia. This was accomplished by scratching the subject's skin and observing for the development of a wheal and erythema.

Appendix F

Eye Hand Coordination Test

Data Analysis Procedure

This appendix supplements the information pertaining to the Eye Hand Coordination Test in Section VI.

The following decision rules were used for analyzing the recorded signal to obtain hole-to-hole times:

- a. The signal spikes resulting in hole-to-hole times of 200 milliseconds or less were ignored. Such signal spikes could be attributed to the following causes:
 - i. 60 hertz noise
 - ii. Re-hit in the same hole
 - iii. Hard hit on the top plate.
- b. Should the number of recorded spikes result in more than 116 hole-to-hole times, the data was strip charted and only 117 most prominent spikes were considered for calculating 116 hole-to-hole times.
- c. Whenever gross time was not recorded, the mean hole-to-hole time was calculated by dividing the cumulative hole-to-hole time by 116.

The hardware used for recording the data was not designed to identify a hole-to-hole time with a specific move on the maze pattern. In view of this shortcoming, it was not possible to distinguish between a prolonged hole-to-hole time and a "convoluted" time resulting from one or more inadequate stylus insertions. It was decided, therefore, to calculate the desired parameters by excluding those hole-to-hole times which were greater than 2 times the mean time. The decision to use this cut-off level was based on the following reasons:

- a. The hole-to-hole time distribution is right skewed, with 70% of the hole-to-hole times being less than the mean time.
- b. Since the mean hole-to-hole time varies appreciably

from person to person, it was decided to choose a cut-off level related to the subject's own mean performance time rather than setting a fixed cut-off level for all subjects.

- c. The number of recorded hits in various bands (based on mean hole-to-hole time) was independent of blood or urine mercury concentration.

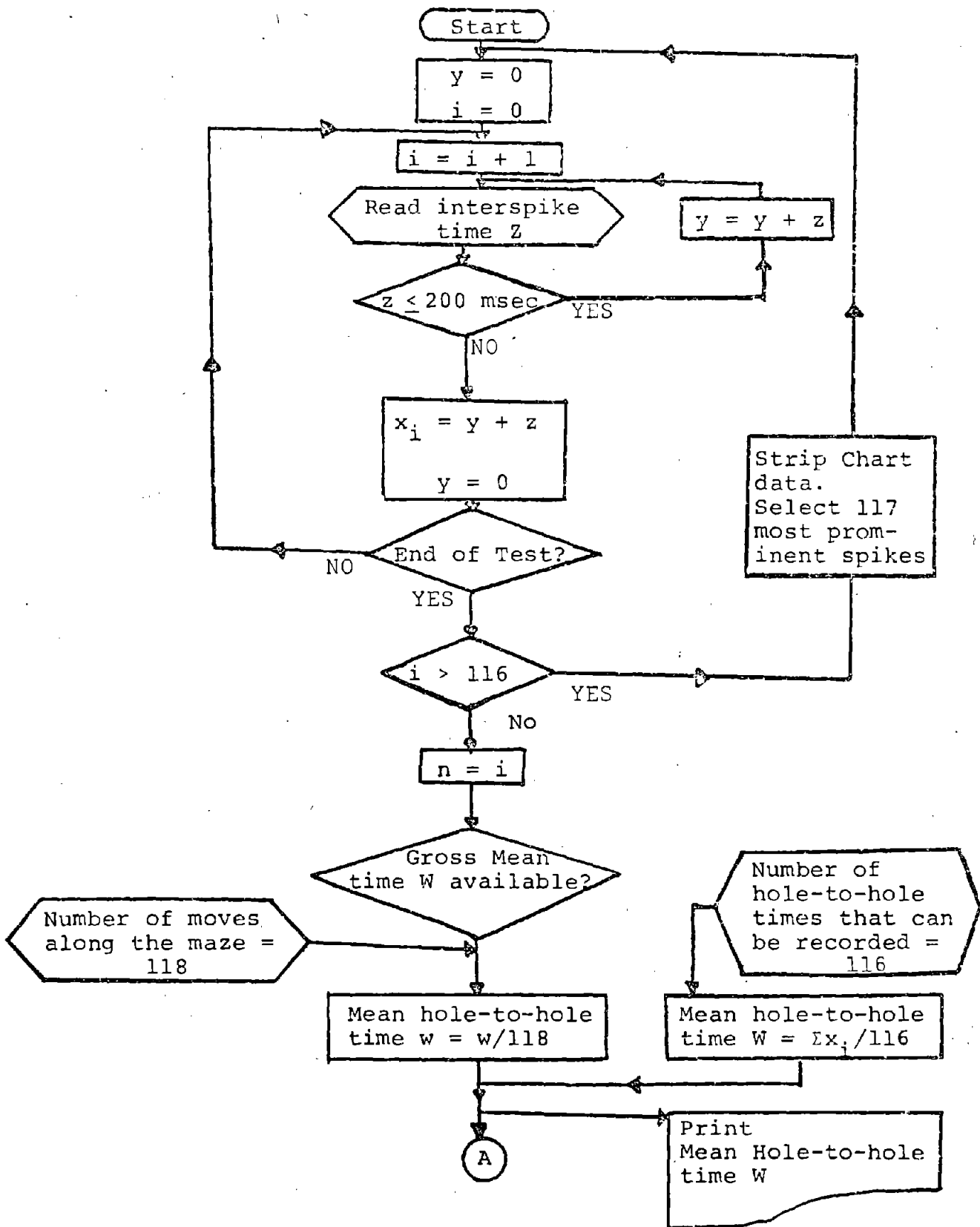
Note that the modal time, used in the calculation shown in Section VI, is independent of the cut-off level.

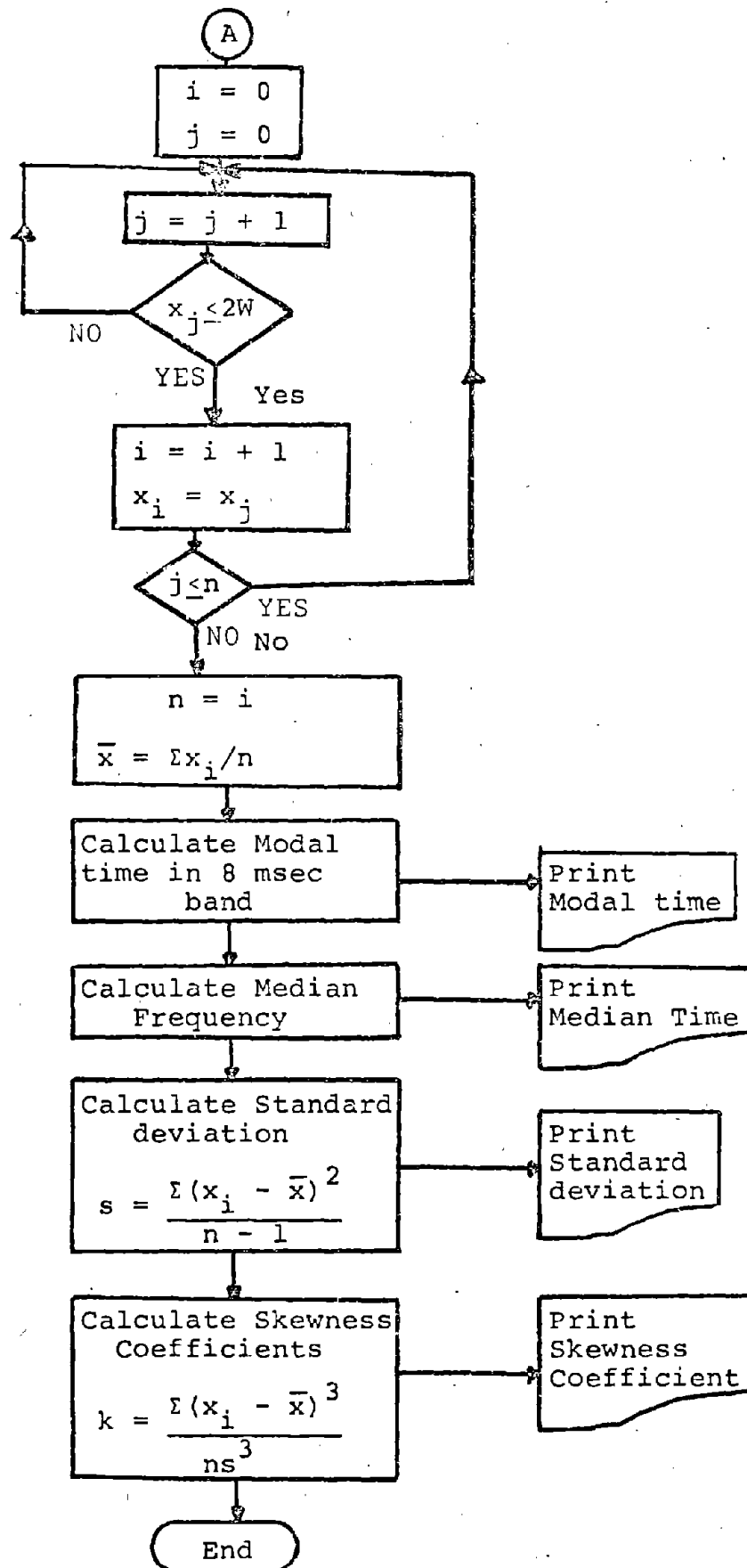
It is appropriate to point out at this stage that although there are 118 moves along the maze, in view of the microswitches inserted under the first and last holes, only 116 hole-to-hole times are recorded.

The mean hole-to-hole time value, used for the calculations in Section VI, was derived from the gross time recorded with the timer for the following reasons:

- a. Enable comparison with Poock's data, if so desired.
- b. Eliminate the need for recording the data and subsequent access to computer, in case these facilities are not available.

A flow chart showing the analysis procedure accompanies this write-up, along with a listing of program instructions.





```

C *****
C *
C * S.A.KELKAR.
C * EYE HAND COORDINATION TEST PROGRAM *
C * HOLE-TO-HOLE TIME PLOT, HISTOGRAM, *
C * REGRESSION AND MOMENTS *
C * (CUT OFF :- 2*MCAN) *
C *
C *****
C
      DIMENSION X(118),Z(118),L(118),K(7)
      5 READ(5,10)N,K,TM
      10 FORMAT(14,2X,7A1,F8.2)
      READ(5,15)LL(J),J=1,N)
      15 FORMAT(20I4)
      WRITE(6,20)
      20 FORMAT('1')
      WRITE(6,125)K
      CALL TPLT(N,L)
      WRITE(6,30)
      30 FORMAT(50X,'SUCCESSIVE HITS ')
      TM=TM*100.0/118.0
      XX=0
      DO 40 J=1,N
      Z(J)=L(J)
      X(J)=J
      40 XX=XX+Z(J)
      XA=X/118.0
      IF(TM=0.1)50,50,45
      45 XX=TM
      50 MCHUS=XX
      XA=XA+2.0
      MN=N
      CALL CUT(MN,Z,X,XX)
      CALL REG(MN,Z,X,F,C,AA,BB)
      MN=MN-2
      WRITE(6,55)MN,F,C,AA,BB
      55 FORMAT(10X,'F RATIO( 1.,14,' ) =',F8.1,5X,'CORR.=',F8.4,5X,
      1'A - INTERCEPT =',F8.3,5X,' B - SLOPE =',F8.5,' (2*M)')
      CALL MHIST(N,L)
      WRITE(6,90)
      90 FORMAT(50X,'TIME IN MILLISECONDS')
      CALL YHMT(MN,Z,A,B,C,E,M1,M2)
      MEAN=A
      MSTD=B
      WRITE(6,105)M2,M1,MCHUS,MEAN,MSTD,C,D
      105 FORMAT(10X,'MCHUS=',15,' MEDN=',15,' MEAN=',15,' (',15,')', STDV=',
      15,' SKEW=',F8.3,' KLMT=',F8.3,' (2*M)')
      WRITE(6,125)K
      125 FORMAT(' TEST NO.:-',2X,7A1)
      GO TO 5
      END

```

```

SUBROUTINE REGR(N,S,G,F,C,AA,BB)
  DIMENSION S(200),G(200)
  Z=N
  X=0
  Y=0
  YY=0
  XX=0
  XY=0
  DO 10 I=1,N
    XXX=C(I)
    YYY=S(I)
    X=X+XXX
    Y=Y+YYY
    XX=XX+XXX*XXX
    YY=YY+YYY*YYY
    XY=XY+XXX*YYY
  10 XY=XY+XXX*YYY
  XM=X/Z
  YM=Y/Z
  XC=XX-(X*X)/Z
  YC=YY-(Y*Y)/Z
  XYL=XY-(X*Y)/Z
  RM=XYC/XC
  AM=YM-XM
  REG=RM*XYC
  RES=(YC-REG)/(Z-2.0)
  F=REG/RES
  CO=(XYC*XYC)/(XC*YC)
  IF(CO)20,20,30
  20 C=0
  GO TO 50
  30 C=SQRT(CO)
  IF(AB)40,50,50
  40 C=-C
  50 CONTINUE
  RETURN
  END

```

```

SUBROUTINE YMYT(N,Y,A,B,C,D,M2,M1)
  DIMENSION Y(115),LL(200)
  A=0
  DO 10 I=1,N
  10 A=A+Y(I)
  AN=Y
  A=A/AN
  B=0
  C=0
  D=0
  DO 15 I=1,N
  15 B=B+(C3-A)**2
  C=C+(C2-A)**3
  D=D+(C3-A)**4
  B=B/AN
  C=C/AN
  D=D/AN
  B=SQRT(B)
  C=C/B**3
  D=D/B**4
  DO 25 I=1,200
  25 LL(I)=0
  DO 30 I=1,N
  30 X=X+Y(I)/B.0
  MX=XM
  IF(MX-200)28,28,26
  26 MX=200
  28 CONTINUE
  30 LL(MX)=LL(MX)+1
  LG=0
  MI=0
  DO 35 I=1,200
  35 IF(LL(I)-LG)35,35,32
  32 LG=LL(I)
  MI=I
  35 CONTINUE
  MI=MI*3-4
  MN=M/2
  IF(MN-M*2)60,60,38
  38 MN=MN+1
  I=0
  LG=0
  40 I=I+1
  LG=LG+LL(I)
  IF(MN-LG)42,50,40
  42 M2=I*B-(LG-MN)*3/LL(I)
  GO TO 90
  50 M2=I*B
  GO TO 90
  60 SN=MN
  SN=SN*0.5
  I=0
  G=0
  65 I=I+1

```

```

GG=LL(I)
G=G+GG
IF(SN-G)72,80,65
72 GG=(G-SN)*9.0/CG
M2=GG
M2=I*B-M2
GO TO 90
80 M2=I*B
90 CONTINUE
RETURN
END

```

```

SUBROUTINE CUT(MN,Y,X,G)
  DIMENSION Y(200),X(200)
  J=0
  DO 20 I=1,MN
  20 IF(Y(I)-G)10,10,20
  10 J=J+1
  X(J)=X(I)
  Y(J)=Y(I)
  20 CONTINUE
  MN=J
  RETURN
END

```

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```

SUBROUTINE TMPLT(N,L)
  DIMENSION K(23,119),L(200),KY(23),KX(13)
  LSHFT=2**24
  KM=122*LSHFT
  IF(N-119)20,20,10
10  NY=119
   GO TO 30
20  KM=N
30  CONTINUE
   DO 40 I=1,23
40  KY(I)=(23-I)*40+200
   DO 50 J=1,13
50  KX(I)=(I-1)*10
   DO 60 J=1,23
60  K(J,I)=4*LSHFT
   DO 70 I=1,N
   J=L(I)/40-4
   IF(J-23)58,68,65
65  J=23
68  J=24-J
70  K(J,I)=212*LSHFT
   WRITE(6,75)
75  FORMAT(6X,'+',24(5H----+))
   DO 90 I=1,23
90  WRITE(6,85)KY(I),KM,(K(I,J),J=1,119),KM
   WRITE(6,75)
   WRITE(6,90)(KX(I),I=1,13)
90  FORMAT(6X,12,12(7X,13))
   RETURN
   END

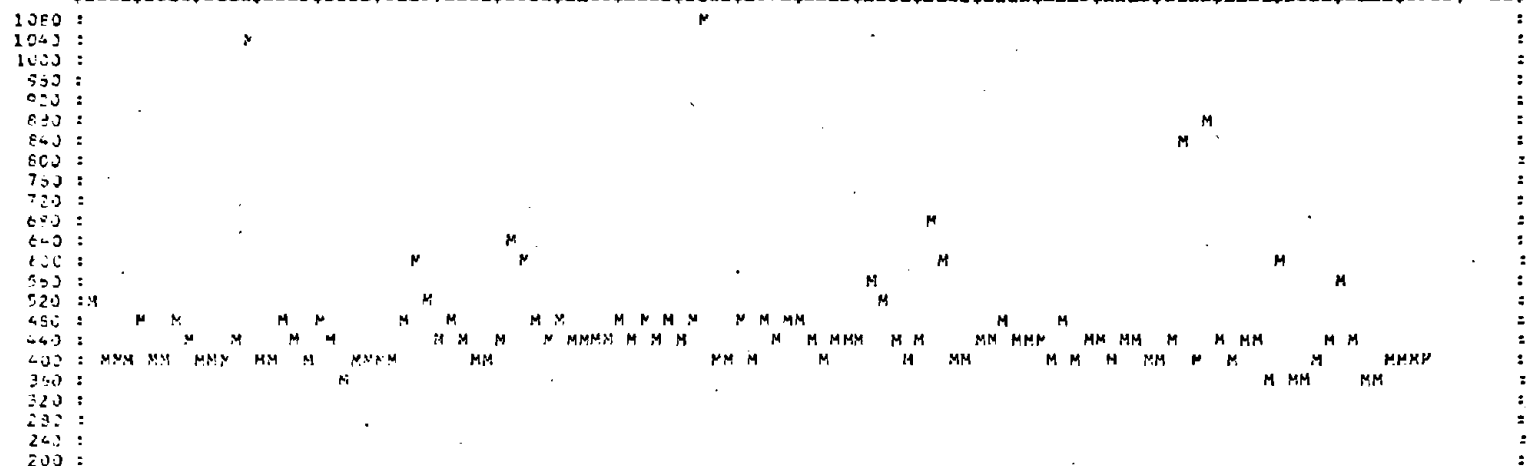
```

```

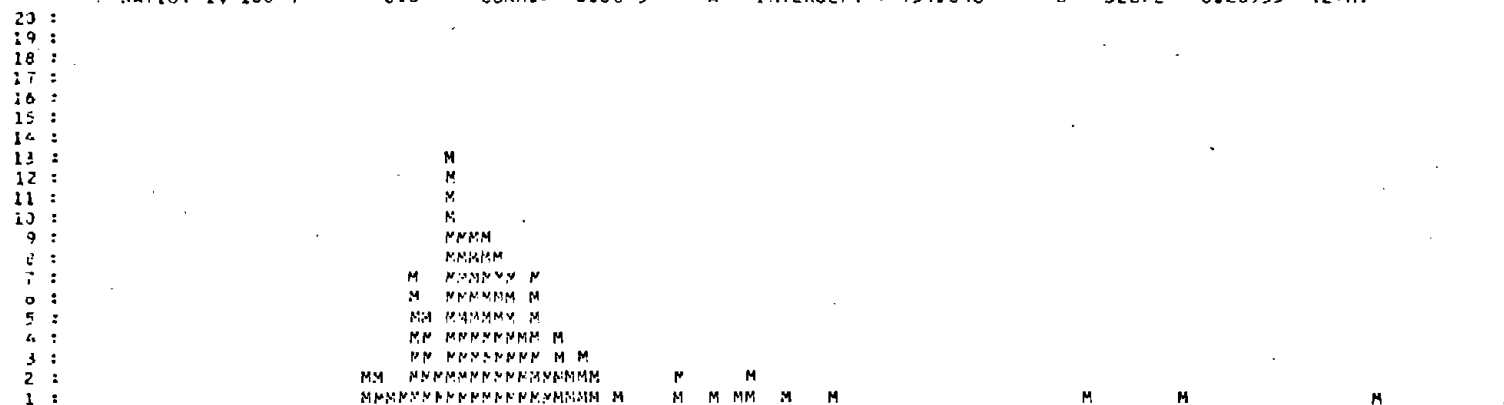
SUBROUTINE MHIST(N,L)
  DIMENSION L(200),K(121),M(121),KY(20),KX(12)
  LSHFT=2**24
  KM=122*LSHFT
  DO 10 I=1,20
10  KY(I)=21-I
   DO 15 J=1,12
15  KX(I)=(I-1)*80+200
   DO 20 J=1,121
20  M(J)=0
   DO 40 I=1,N
   MM=L(I)/8-20
   IF(MM)40,40,25
25  IF(MM-120)30,30,35
30  M(MM)=M(MM)+1
   GO TO 40
35  K(121)=K(121)+1
40  CONTINUE
   DO 60 J=1,20
   DO 45 J=1,121
45  K(J)=64*LSHFT
   DO 55 J=1,121
   IF(K(J)-21+1)55,50,50
50  K(J)=212*LSHFT
55  CONTINUE
60  WRITE(6,55)KY(I),KM,(K(J),J=1,121)
65  FORMAT(15,1X,122A1)
   WRITE(6,70)
70  FORMAT(6X,'+',24(5H----+),'*')
   WRITE(6,75)(KX(J),J=1,12)
75  FORMAT(9X,12(14,6X))
   RETURN
   END

```

TEST NO.:- 710825B



SUCCESSIVE HITS
 F SAT(01 1, 108) = 0.8 CORP. = 0.0845 A - INTERCEPT = 454.046 B - SLOPE = 0.20935 (2*H)



MODE= 420 MEDN= 444 MEAN= 454(465) STOV= 40 SKEW= 2.976 KURT= 14.760 (2*H)

TEST NO.:- 710825B

84591

192

Appendix G

EMG MEAN FREQUENCY CHANGES IN CATS
EXPOSED TO INORGANIC MERCURY

In a preliminary study in July and August, three cats were chronically exposed to mercury by daily injection of 0.3 mg. Hg./Kg. body weight mercuric chloride solution, (see Figure G1 for review of animal preparation). A gradual mercury blood burden was realized, as measured by repeated samples during the day, (see Figure G2). EMG power spectra were obtained from the gastrocnemius muscle each time a blood sample was taken during the day. Typical specie comparison spectra are displayed in Figure G3.

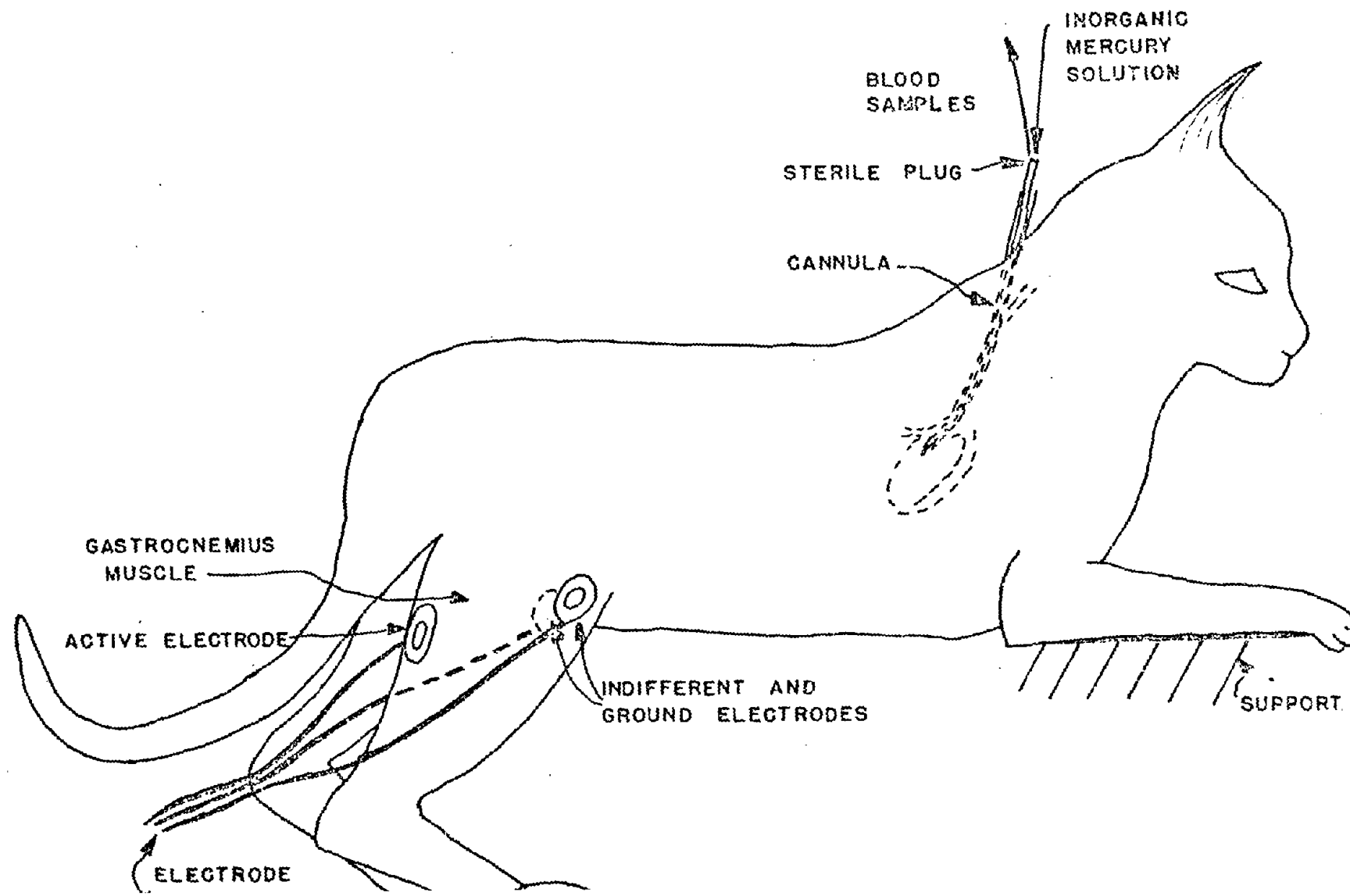
Two of the three cats were exposed for 27 days, while a third cat was continued through 39 days of exposure and 16 days of recovery. The first two cats required antibiotic treatments for reoccurring infections associated with the cannula. The third cat did not require any medication.

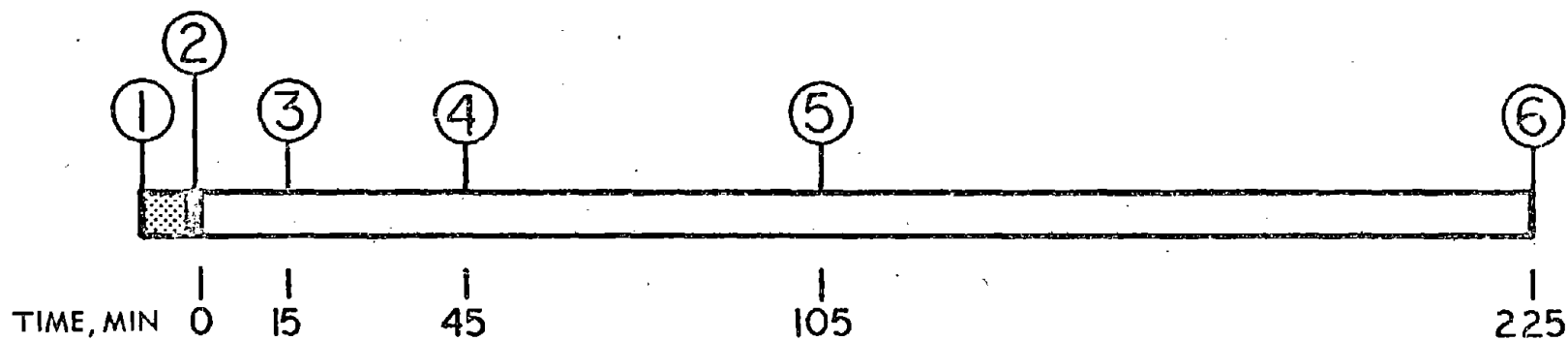
Results of Cat Experiments

The blood mercury burden and tissue burdens were described earlier in the Second Quarter Progress Report to NIOSH.

Briefly, the following general results were noted:

1. Blood mercury levels remain high for a period of about 15 minutes and then rapidly decrease in a basically exponential manner until about 3-4 hours, whereupon the levels stabilize for the day.
2. The ability to quickly (within the first hour) remove mercury from the blood appears to become more efficient with repeated exposures.





① 24-HR TEST

④ 45-MIN TEST

② MERCURY DOSE

⑤ 1 HR 45-MIN TEST

③ 15-MIN TEST

⑥ 3 HR 45-MIN TEST

Figure G2

DAILY MERCURY EXPOSURE SCHEDULE

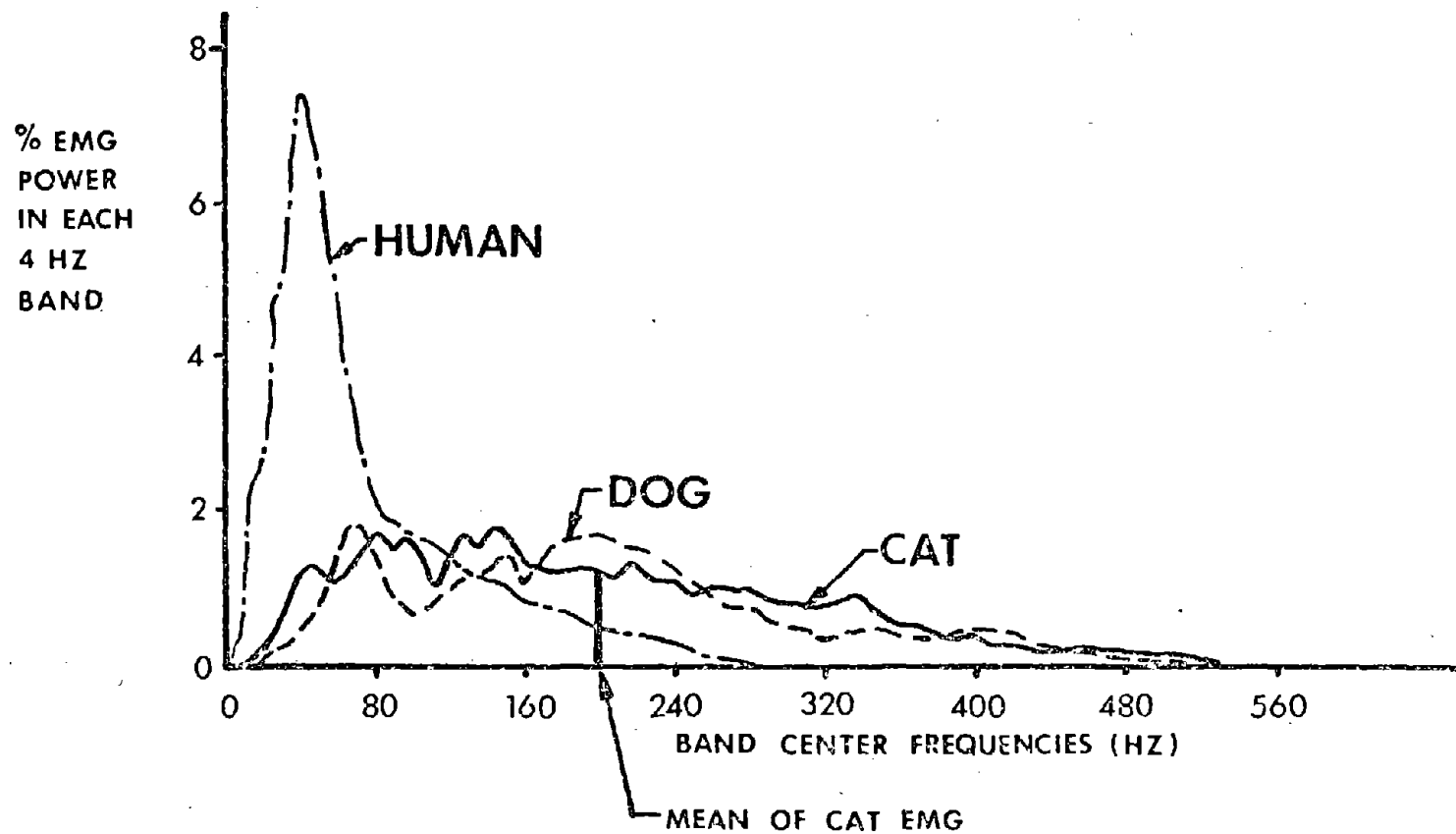


Figure G3

EMG POWER SPECTRA-NORMAL GASTROCNEMIUS MUSCLES

3. With the exposure schedule described, a gradual increase in the daily blood burden was achieved, as displayed in all of the samples taken each day. The rate of increase each day was higher with the first injections than with the later injections (this will be shown later in Figure G7).
4. Tissue samples taken immediately after the death of each cat showed the relative distributions displayed in Figure G4. The increase in the spinal cord levels was primarily attributed to excessively high uptakes in Cat 2, the long term cat. The relative distributions in the spinal cord showed the lateral tracts to have relatively more mercury uptake than the dorsal and ventral portions.

The EMG frequency shifts were used to demonstrate neuromuscular changes. EMG changes appeared to occur in two phases, based on length of exposure. During the early exposure phase (days 1-13), the EMG means increased significantly in all three cats immediately after the injection. This effect is illustrated in Figure G5 wherein the 15 minute post-injection EMG spectra means are higher than the 24 hour pre-injection means. Though a gradual increase is noted in the EMG mean frequencies in the subsequent 3 hours and 45 minutes, an apparent reversal of the effect takes place over the remaining 20 hours, 15 minutes. Cat 2, the long term cat, continued this pattern for another two weeks.

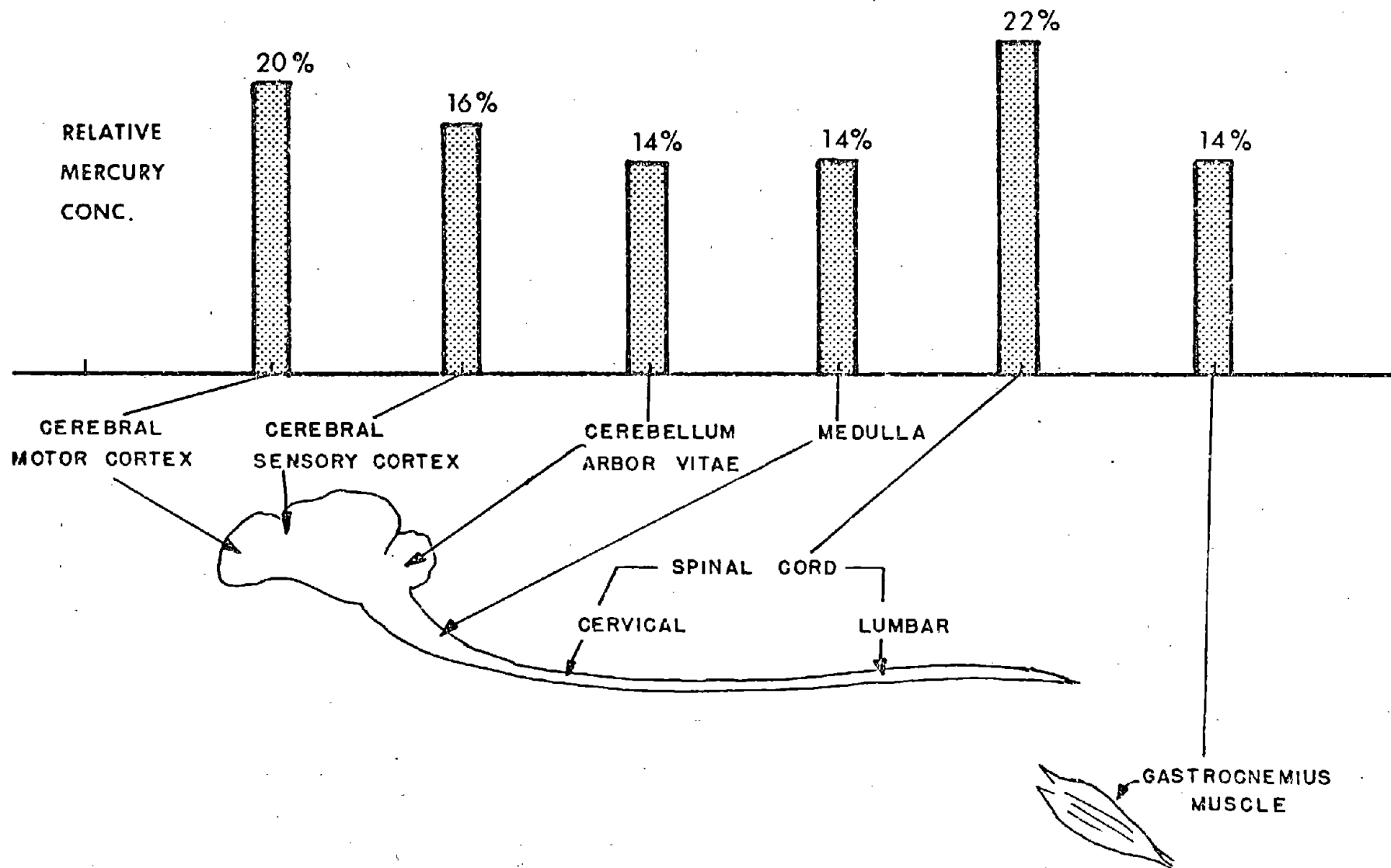


Figure G4
MERCURY CONCENTRATIONS IN CAT TISSUE

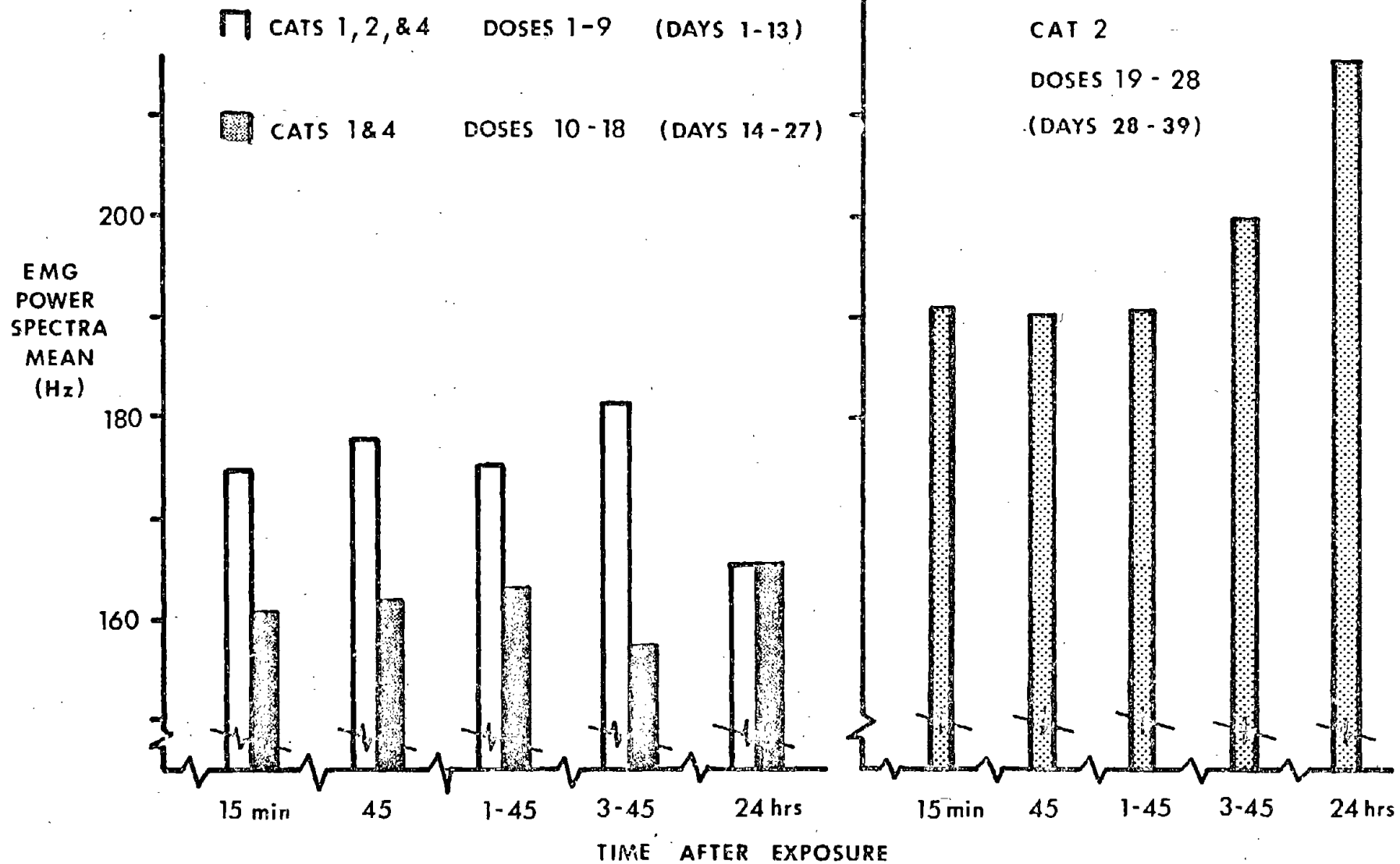


Figure G5

DAILY EXPOSURE EFFECTS

The second phase of EMG changes appeared in Cats 1 and 4 during the next two weeks (days 14-27). These changes were essentially a reversal of the earlier effects. In this case, both cats displayed a relatively constant mean EMG frequency following injection with a slight increase 24 hours after injection. This second phase was even more pronounced in Cat 2 with an extended exposure period. What was consistently demonstrated with this cat was a reduction in the EMG mean frequency immediately after injection of mercury, and then an increase in the mean frequency after a few hours duration. The 24 hour pre-injection mean EMG frequency was higher than the 15 minute post-injection result in 9 of 10 cases (as displayed in Figure G6). Also, a long term average effect of mercury is evident in the EMG mean frequencies shifting towards higher frequencies with subsequent exposures (as displayed in Figure 11).

Since Cat 2 did not receive any medication, and was carried through the greatest number of exposures, its 24 hour EMG and blood mercury level data are plotted for inspection in Figure G7. What is evident is the average increase in both the 24 hour blood mercury levels with each injection, and the EMG mean frequency towards the latter stages of exposure. Also, a rapid shift back to lower frequencies was observed when the injections were stopped.

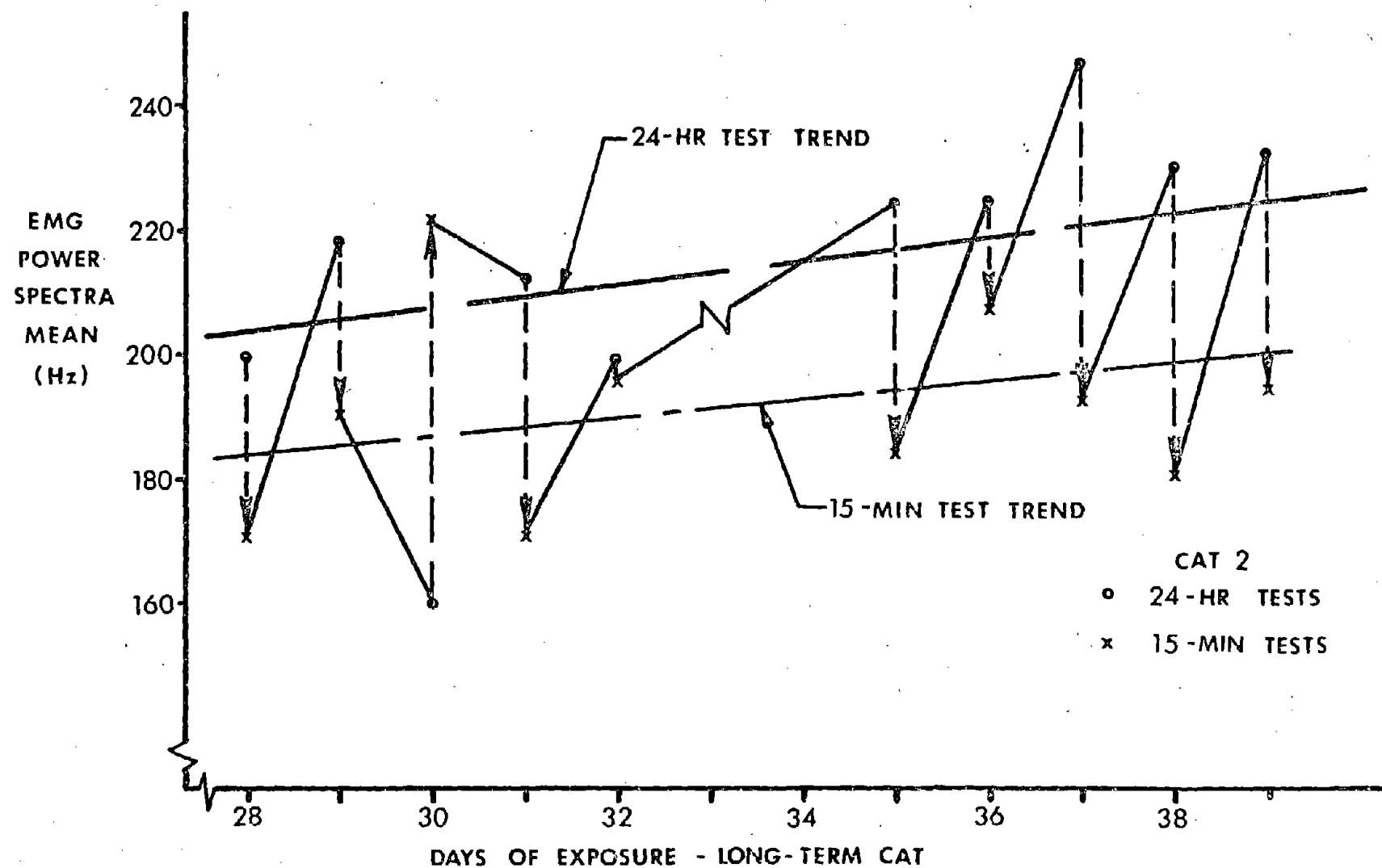


Figure G6

LONG-TERM EXPOSURE EFFECTS

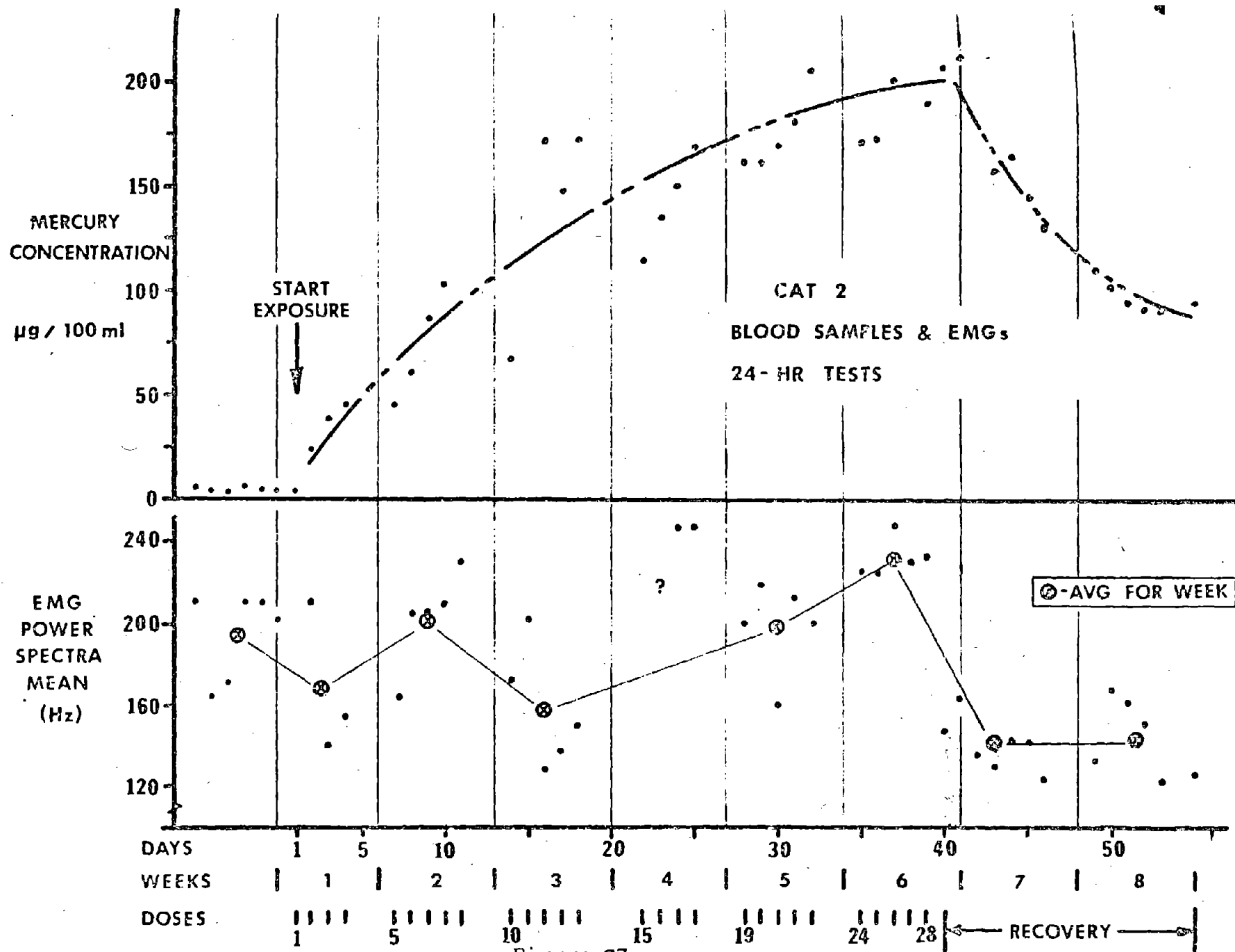


Figure G7
EFFECTS OF MERCURY ON BLOOD & EMG

Preliminary Interpretation

Mercury exposure of the type described does show a complicated but consistent effect on the EMG mean frequency. In the early stage, the mercury appears to cause a higher frequency EMG, which has been reported by others and these investigators to be correlated in humans having various myopathies (with polyphasic motor units), and certain neuropathies of the peripheral nerves and/or spinal cord. This initial change in EMG appears to persist since the EMG mean frequency continued to gradually increase with later exposures. However, a secondary and more transient effect was found later, and this is to cause EMG shifts towards lower frequencies immediately following the mercury injections. One cause for EMG shifts to low frequency is to have temporal grouping of the motor units as discussed in the text. This also results in increased tremor, which is a classic characteristic of mercurialism. Thus the mercury tremor so often referred to may be a short duration transient effect of exposure to relatively low levels of mercury, and would only be present after a period of repeated exposures. The long term effects would cause more subtle myopathic and/or neuropathic effects, which might be evident in a lack of complex coordination, weakness, EMG shifts towards higher frequencies, and reduced mental capacity.