ABSTRACT

A large battery of tests of peripheral and central nervous system function was administered to 205 former workers of a heavy industry (104 exposed to inorganic mercury and 101 not so exposed). These participants were recruited from two cohorts of workers studied using similar methods by the University of Michigan ten years prior to the current investigation. The mean age of the cohorts was 71 years. Exposed subjects had participated in a urine-mercury personal exposure monitoring program during the time of the industrial process requiring mercury and its subsequent clean-up. Mercury exposure had been high (mean peak urine mercury concentration was >600 μg/l) and had ended 30 years or more prior to neurologic and neurobehavioral testing. Peripheral nerve function outcomes that were statistically significantly associated with cumulative mercury exposure after controlling for covariates included a neurologic physical examination abnormality score, classification as having peripheral neuropathy, peroneal motor nerve conduction velocity, ulnar motor nerve conduction velocity, and peroneal motor nerve F-wave latency. Quantitative assessment of resting tremor was not significantly associated with cumulative mercury exposure. Results of the Handeye Coordination test were significantly associated with cumulative mercury exposure after controlling for covariates. Cumulative mercury exposure was not observed to be associated with a quantitative measure of dementia or with a number of cognitive neurobehavioral test outcomes. The associations with mercury exposure were observed in spite of (a) greater mortality among the exposed group than the unexposed group and (b) loss to follow-up of many of the most heavily mercury-exposed participants of the previous study.

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Final Report for
A Study of the Health Effects of Exposure to Elemental Mercury: A Follow-up of Mercury Exposed Workers at the Y-12 Plant in Oak Ridge, Tennessee

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1. Introduction

1.1 Background

Elemental or metallic mercury is liquid at room temperature and forms a vapor that is readily absorbed through the alveoli. In the occupational setting, inhalation is the primary route of absorption of elemental mercury. Excretion of mercury is handled mainly by the kidney. The primary target organs for mercury toxicity are the brain and kidney. Clinical manifestations of inorganic mercury exposure include personality changes, tremors, muscular weakness, gingivitis, and proteinuria (Goyer, 1991; Taylor, 1984). The purpose of the present study was to test whether occupational exposure to inorganic mercury continued to be associated with long-term adverse effects on the nervous system in a cohort of men who were tested and described earlier in the literature (University of Michigan, 1987). This cohort of workers from a nuclear facility in Oak Ridge, Tennessee, was found to exhibit mild clinical conditions (polyneuropathy or tremor) among some of the most heavily exposed workers. These exposed workers were examined again because: (1) of the findings in the University of Michigan report; and (2) this group of workers is documented to have received high exposures over a long period and have completed a long latency since first exposure.

The primary hypothesis to be tested was whether exposure to mercury in the distant past was associated with scores on neurologic and neurobehavioral tests.

1.2 Central Nervous System Effects

Occupational exposure to mercury vapor has long been known to cause neurobehavioral impairment. Subjective symptoms and mood changes related to sleep disturbance, fatigue, anxiety, and irritability are perhaps the most frequently reported findings (WHO, 1980). Mood differences between exposure groups have often been

150 nmol/L.

Bluhm et al. (1992) reported a patient case series of 26 construction workers acutely exposed to high levels of mercury vapor. These workers performed the Trail-Making and Stroop Color Word tests more poorly than would be expected from external normal values. However, this group's performance of two psychomotor tasks, finger tapping test and grooved pegboard test, was not worse than expected. Ngim et al. (1992) reported poorer performance on most neurobehavioral tests by a group of 98 dentists than by a group of 54 controls, including the finger tapping test, Trail-Making test, Symbol-Digit test, digit span test, and visual reproductions test. Because of substantial differences in exposure intensity, duration and latency experienced by subjects in these two studies and the retired Oak Ridge cohort, the results are of unclear relevance to the present inquiry into the persistent effects of mercury exposure in this population.

1.3 Tremor

Neuromuscular tremor, which commonly occurs at high levels of occupational exposure, is one of the most widely recognized adverse neurological consequences of exposure to mercury. At lower exposures more typical currently, clinically overt tremor has become less common. A variety of methodologies has been used to assess the occurrence and type of tremor among mercury-exposed workers. Ehrenberg et al. (1991), using standard clinical methods, observed static tremor more frequently among mercury-exposed thermometer workers than among unexposed comparison subjects; however, the difference was not statistically significant. In addition, they noted that among the exposed subjects, those with tremor had a higher mean urine mercury level and a much greater mean chronic exposure index. Several studies have used behavioral tests of hand steadiness to assess tremor among mercury-exposed workers.

Roels et al. (1982; 1989) using an orthokinesiometer and a hole tremormeter found significant differences between modestly mercury-exposed workers and unexposed comparison subjects on many parameters derived from measurements made with these devices.

Investigations utilizing accelerometer-based measurements have been used to evaluate tremor among mercury-exposed workers and have the advantage of providing information about the frequency and amplitude of tremor. Fawer et al. (1983) found that the highest peak frequency of tremor among exposed subjects was higher than that of unexposed comparison subjects. The amount of change was related to the duration of mercury exposure and to age. Chapman et al. (1990) also reported differences in tremor frequency between mercury-exposed and unexposed workers. Conversely, Roels et al. (1989) found no significant differences in tremor between mercury-exposed and unexposed groups as measured with an accelerometer-based method. Finally, in the original neurologic assessment of the Oak Ridge mercury-exposed workers, tremor was observed on clinical examination and identified using accelerometer-based measurements more frequently among subjects with remote past exposure to mercury resulting in urine mercury peak levels in excess of 600 µgHg/L than among subjects with less than 600 µgHg/L (Albers et al., 1988).

1.4 Peripheral Neurological Effects

Occupational exposure to elemental mercury has been shown to affect the peripheral nervous system. Slowing of nerve conduction velocity, prolongation of distal motor and sensory conduction latency, and diminution of sensory and compound motor amplitudes have been observed among mercury-exposed workers (Albers et al., 1982; Levine et al., 1982; Singer et al., 1987). In addition, abnormalities on neurological

physical examination including diminished sensation, diminished deep tendon reflexes, and impaired postural stability have been found more commonly among mercury-exposed workers (Albers et al., 1982; Albers et al., 1988; Ehrenberg et al., 1991).

1.5 Previous Studies of the Oak Ridge Cohort

At least four studies of the Oak Ridge Y-12 Plant mercury-exposed cohort have been reported. Cragle et al. (1984) reported the first and only mortality study of mercury workers. The University of Michigan (1987) presented the results of a medical survey of the same cohort that was investigated for adverse health outcomes on the renal, reproductive, central and peripheral nervous systems. Albers et al. (1988) reported specific neurological abnormalities associated with mercury exposure among the workers, and Alcser et al. (1989) reported the reproductive experiences of the cohort. An unpublished, follow-up clinical examination of a portion of the exposed members of the cohort was conducted in 1989.

The previous, most relevant investigation to the present investigation was that of peripheral and central nervous system effects of exposure performed by investigators from the University of Michigan (University of Michigan, 1987; Albers et al., 1988). In that study, all Oak Ridge mercury workers (N = 2,136) were rank-ordered by recorded cumulative mercury exposure and the most heavily exposed were invited to participate. A comparison group was selected from individuals who had worked in the same facility during the same era but not with elemental mercury. A total of 502 subjects were recruited as participants including 247 mercury workers and 255 unexposed.

Besides administration of a health and demographics questionnaire, all participants

were asked to take quantitative tests of tremor amplitude and frequency, motor skills (one-hole test, simple reaction time, and hand-eye coordination) and cognitive function (short-term memory span test, verbal ability, symbol-digit substitution, Benton visual retention test, and profile of mood scale). All participants were offered a clinical neurological examination (motor strength evaluation, deep tendon reflex function, presence of pathologic reflexes, acuity of sensation to touch, pain, vibration and two point contact, and characterization of upper extremity sustension tremor). An "arbitrarily selected" (Albers et al., 1988) subset of participants was administered electrophysiologic tests of nerve conductivity and evoked response amplitude (ulnar and tibial compound motor action potential amplitude, motor conduction velocity, distal motor latency, ulnar, median, and sural sensory action potential amplitude, sensory conduction velocity, and distal sensory latency).

Estimates of past mercury exposure were based on records of urine mercury measures required quarterly by plant management. Multiple estimates of mercury exposure were constructed from the historical urine mercury concentration data. These estimates included mercury exposure status (exposed versus unexposed), duration of mercury exposure, average urinary mercury concentration, total cumulative urine mercury concentration, peak urine mercury concentration, number of quarters with average urine mercury concentration more than 300 μgHg/L (the "plant action value"), number of quarters with average urine mercury concentration greater than 600 μgHg/L (twice the plant action value), a dichotomized variable for ever exceeding a urine mercury concentration of 300 μgHg/L, a dichotomized variable for ever exceeding a urine mercury concentration of 600 μgHg/L, and the average urine mercury concentration for the highest exposure period of 1955-1956. Not all measures of outcome were explored for associations with all measures of exposure. The most commonly used exposure

measures were mercury exposure status, total cumulative urine mercury concentration, ever exceeding urine concentration of 600 μgHg/L, and peak urine mercury concentration. Associations between exposures and outcomes were investigated using regression analyses with appropriate covariates and potential confounders included in the models.

A total of 502 subjects were recruited for examination. All 502 underwent a standard battery of neurologic exams and a subset of 386 were additionally administered an electrophysiologic examination. A total of 52 disorders that could account for abnormal neurologic function were identified. Of the 502 subjects, 108 had one or more of these disorders, thus requiring their deletion from some analyses or creation of a dummy variable to adjust for potential confounding in others. The p-values of associations of selected neurologic outcomes with five of the exposure measures are presented in Table 1 for outcomes where at least one exposure measure showed a significant or near significant association at the 0.05 significance level.

Among the neurobehavioral measures, significant or near significant associations with at least one exposure measure were observed for the one-hole test, simple reaction time test and the hand-eye coordination test. No single exposure variable was significantly associated with all three outcome measures. For the one-hole test, significant associations were reported to be due mainly to extreme results from few heavily-exposed subjects.

On neurologic physical examination, sustension tremor score was significantly associated with two of the four measures of exposure reported (peak urine mercury concentration, ever exceeding urine mercury of 600 μgHg/L). A normal examination

was significantly associated with ever having a peak urine mercury concentration greater than 600 µgHg/L but not with mercury exposure status. No association was observed between a neurologic examination demonstrating polyneuropathy on any of the conventional exposure measures. An additional analysis was performed in which polyneuropathy status was compared between subjects with greater than 850 µgHg/L peak exposure and all other subjects. In this analysis, a significant association was observed, although only 51 workers ever exceeded this level, thereby, severely restricting the exposed group. Among the workers who exceeded 850 µgHg/L, 27.45% (N=14) exhibited peripheral neuropathy compared with 10.2% in exposed workers not exceeding this limit and with 16.47% in the control group.

Displacement tremor measures were not associated with any of the exposure variables. Like the results obtained for the one-hole test, significant associations between tremor results and exposure measures were reported to be due mainly to extreme results from a few heavily exposed subjects.

Among the electrophysiologic tests, significant associations with at least one exposure measure were observed only for median sensory nerve distal latency and median sensory nerve amplitude. A near significant association was observed for ulnar motor nerve conduction velocity and two of the exposure measures. No electrophysiologic tests of nerves in the lower extremity were significantly associated with any of the mercury exposure measures.

Only results of the neurologic physical examination and electrophysiologic measures have been reported in the peer-reviewed literature (Albers et al., 1988). The publication reports that F-wave latency measures were obtained for the tibial and ulnar

nerves. However, these results were not included in the University of Michigan Final Report.

1.6 Conclusions

Most epidemiologic studies of mercury-exposed workers have reported altered mood, impaired neurobehavioral function, tremor, peripheral neurotoxicity, and impaired renal function and other neurological abnormalities. Most of the studies have been descriptive in nature, have had generally small sample sizes, and involved currently exposed workers. Exposure (particularly chronic exposure) was poorly characterized, and referent groups were not appropriate or absent in many studies. Results are inconsistent among the studies, which are difficult to compare due to varying exposure levels and duration and the multitude of testing methods used.

The University of Michigan (1987) reported that a few of the most heavily exposed Oak Ridge workers had mild clinical conditions (polyneuropathy or tremor) possibly resulting from mercury exposure, and recommended follow-up surveillance of the cohort. This population was studied further because it was: (1) the largest cohort of mercury exposed workers studied to date, (2) a cohort with high exposures, (3) a cohort with the longest duration of exposure, and (4) a cohort with the longest latency since first exposure. Also, the University of Michigan study is the clearest example in the literature of subtle neurologic damage from exposure to an occupational neurotoxicant that persisted decades after exposure had ceased, and this finding needed to be confirmed. Another reason for further study of this population was the importance of determining if the effects observed in the University of Michigan study persisted at the level reported in this cohort or whether they worsened with age. To investigate additional cognitive effects of mercury exposure in this cohort , the current study

employed more recently developed methods and ones perhaps more sensitive to cognitive deficits than those previously used.

2. Methods

2.1 Subjects

2.1.1 Selection of Exposed and Comparison Subjects for Original Study

The cohort for the original study, completed in 1986, included 502 white males who had worked at least four months at the Y-12 facility between January 1, 1953, and December 31, 1966. This period encompassed the years during which elemental mercury was used in an industrial production process and the years during which cleanup operations for this process were performed. The cumulative average quarterly urine mercury measurements (in units of µgHg/L of urine) were calculated for all monitored Oak Ridge mercury workers, who were then ranked in descending order of exposure from 8,572 to 2 µgHg/L. To select study subjects for the mercury exposed group, individuals on this list were asked to participate beginning with the individual having the highest cumulative exposure and continuing downward on the list in order until approximately 250 individuals had agreed to be tested. This last individual's cumulative exposure was 2,144 µgHg/L quarter units of mercury. Unexposed control subjects were frequency matched to the exposed group by five-year birth intervals, active or retired job status, and six categories of job title groupings that corresponded to socioeconomic strata. Among the 502 cohort members were 247 exposed workers and 255 unexposed workers.

2.1.2 Composition of Current Study Cohort

All workers who were contacted to participate in the University of Michigan study (regardless of whether they participated) were also contacted to participate in the current study. Since many original study members declined to participate because of

advanced age, it was necessary to select some additional subjects for inclusion in the current study to ensure the number of participants was sufficient for meaningful analysis.

Computer listings with mercury workers ranked from highest to lowest cumulative exposure that had been used to select exposed subjects for the original study were used. To choose new exposed subjects for the present study, all individuals having cumulative exposures of at least 2,000 µgHg/L quarter units or known to have once excreted at least 600 µgHg/L were identified. Control subjects were selected for these 34 workers using the same criteria as the original study, and the new exposed and control subjects were invited to participate.

2.2 The Interview Questionnaire

All parts of the interview questionnaire were field-tested on a group of workers from the same facility similar in age, gender, and job title, but who were not in the study. Minor revisions were incorporated into the final questionnaire.

To the extent possible, the questionnaire was similarly structured to the one used by the University of Michigan (1987) including demographic and lifestyle questions, medical status, medications used, occupational history, and parts of the behavioral pretest. Since occupational histories were previously obtained, we attempted to update work histories from 1986 until each worker's retirement or termination from employment at the facility.

The questionnaire was mailed to all study participants before the day of their examination. Because of the advanced age of most of the study subjects, all parts of the questionnaire were reviewed by a trained interviewer on the day of their examination. The interviewer checked all parts of the questionnaire for completeness and clarity of responses before the study subject left the examination site.

The reproductive history was not collected because the University of Michigan (1987) study found no reproductive outcomes related to mercury exposure, and because of age, the cohort members were not likely to have reproduced since the last study.

2.3 Overview of Clinical Examinations

The examinations took place during seven sessions: November 11-12, 1994 (pilot), January 20-26, 1995, February 8-9, 1995, February 23-25, 1995, March 8-10, 1995, March 29-31, 1995, and April 26-28, 1995. The physicians and researchers from Emory traveled from Atlanta, Georgia, to Oak Ridge, Tennessee, for each of these periods. The required neurobehavioral and neurologic testing equipment was transported from Atlanta on each of these occasions. The examinations were performed in a suite of examination rooms at the ORAU Medical and Health Sciences facility in Oak Ridge.

The components of the current examination are listed in Table 2. To facilitate comparison of the elements of the present study (ORAU/Emory Exam) with those in the original (University of Michigan) examination, we have included a column in Table 2 that shows whether each test was a component of the original examination, and we

have listed some elements of the present examination that were not done in the University of Michigan exam. To the extent feasible, the tests selected to assess adverse health effects from mercury exposure were comparable to those methods employed by the University of Michigan (1987). The rationale for either adding or deleting a specific test is discussed in section 2.4.

Upon arrival at the examination site, each study participant was greeted and given an opportunity to ask any remaining questions he had concerning the study. After informed consent was obtained, blood was drawn and urine was collected. Each subject then circulated through seven "testing stations" with tests grouped to allow completion in 30 minutes or less at each station. In this way, up to seven subjects were tested in 4.0 hours. The tests performed at each of the testing stations (2 through 8) are listed in Table 3 and described in greater detail in the next section. Subjects moved from one testing station to the next in the order given in Table 3, but each participant began testing at a different station. Two testing sessions per day (morning and afternoon) were conducted on most testing days. All field personnel were blind to the exposure status of the subjects with exception of the research assistant reviewing the occupational portion of the questionnaire.

2.4 Description of the Components of the Examinations

Components of the neurologic and neurobehavioral examinations are described below. Instructional protocols for administering specific evaluations were adapted from those used in previous studies and are included as appendices.

2.4.1 Neurologic Physical Examination

Detailed neurologic physical examinations were performed on all study participants by a single board certified neurologist in a standard manner. The examination assessed cranial nerves, sensory function, motor strength and tone, deep tendon reflexes, coordination, tremor and gait. Unless otherwise specified, neurological tests were graded as normal, equivocal or abnormal. The data form employed is included as Appendix A.

Cranial nerves 2-12 were assessed in a standard manner according to the description of DeGowin (1987). The *sensory modalities* of pain (pinprick), vibration (128-Hz tuning fork), and light touch (soft brush) were tested in the upper and lower extremities bilaterally. Proprioception was tested in the lower extremities by grasping the sides of the great toe and passively moving it in flexion and extension until the subject showed the direction of motion.

Muscle strength of the hand intrinsics, wrist flexors and extensors, biceps, triceps, deltoids, hip flexors, knee flexors and extensors, and ankle flexors and extensors was manually tested. Strength was graded as normal, equivocal, or abnormal.

The *deep tendon reflexes* of the biceps, triceps and brachioradialis muscles were tested in the upper extremity. The patellar and Achilles deep tendon reflexes were tested in the lower extremity. If the reflex was not elicitable, reinforcing maneuvers were performed. Reflexes were recorded as absent, diminished, normal, and hyperactive.

Coordination was tested by having the subject perform the "heel-to-shin" and "finger-to-nose" maneuvers (DeGowin, 1987) and performing rapid alternating movements of the fingers. A standard Romberg test was performed with eyes open and closed. Gait was assessed by having the subject walk in his usual gait and walk heel-to-toe (tandem gait). Static and intention tremor of the upper extremity were assessed and graded as normal, equivocal, or abnormal.

The purpose of the physical examination was to: (1) provide incentive for participation in the hands-on examination by a neurologist, (2) identify other neurologic diseases or conditions that might result in exclusion of data from the data analysis of quantitative outcomes, (3) identify neurologic conditions that may require medical follow-up in the participants, and (4) contribute clinical information to the case definitions of peripheral neuropathy.

For data analysis, potentially abnormal findings were summed for each of the six broad physical examination categories. The number of equivocal or abnormal findings was summed for each of the four groups of findings: cranial nerve, motor strength, sensory, and coordination tests. For deep tendon reflexes the number of absent reflexes was summed for primitive reflexes. The number of equivocal or present findings was summed. Finally, these sums were combined to create a physical examination abnormality score.

2.4.2 Nerve Conduction Testing

Electrophysiologic studies of the ulnar motor and sensory nerve and the peroneal motor nerve were performed on all subjects enrolled in the study. The ulnar nerve was chosen for inclusion in the current study because significant and near-significant associations between the number of peak urine mercury samples >600 µgHg/L and ulnar nerve conduction parameters were observed in the University of Michigan (1987) study. The peroneal nerve was chosen because of the common pattern of impairment in toxic neuropathy in which the lower extremities are affected earliest in the progression of the disorder (Schaumburg, Berger & Thomas, 1992). The sural sensory nerve was not electrophysiologically evaluated in this population because of the high likelihood of absent evoked responses in this age group rendering difficult analysis and interpretation of the results. Besides evoked response amplitude, distal latency, and segmental conduction velocity, late response (F-wave) latency of the ulnar and peroneal nerves was obtained. The F-wave conduction measure is considered extremely sensitive for identification of diffuse toxic or metabolic impairment of peripheral nerves (Lachman et al., 1980; Kimura, 1989). All nerve conduction velocity measurements were made by a single board certified neurologist according to a standard protocol.

All measurements were made with a TECA Sapphire (TECA Corp., Pleasantville, NY) two channel electromyograph (EMG) using standard noninvasive techniques; sensory studies used antidromic stimulation. All electrophysiological measurements were performed on the nondominant limb. Limb temperature was maintained above 32°C with heat lamps and was continuously monitored with a digital thermometer fixed to the skin with surgical tape.

Ulnar motor nerve stimulation was made at the wrist and at the ulnar groove at the elbow. Compound motor action potentials were obtained with the active recording electrode placed over the abductor digiti quinti. Motor latencies were measured in milliseconds from stimulus to the onset of the negative takeoff of the compound motor action potential, and conduction velocity was calculated by the standard method. The recording electrodes were left in place for measurement of the ulnar nerve F-wave latency; the maximum and minimum of 10 F-wave latencies was recorded. For sensory studies, ring recording electrodes were placed on the fifth digit. Antidromic stimulation was made at the wrist. Motor and sensory stimulation were supramaximal, and when necessary, averaging was employed to assure adequate signal-to-noise ratios. Latencies and amplitudes were recorded, and a strip chart record of the potential was obtained. Conduction velocities were calculated in the standard manner after measurement of the distances from the stimulating electrode to the active recording electrode.

The deep peroneal nerve was stimulated distally at the ankle and proximally lateral to the fibular head. Compound motor action potentials were recorded with the active recording electrode placed over the extensor digitorum brevis muscle. Motor latencies were measured in milliseconds from stimulus to the onset of the negative takeoff of the compound motor action potential, and conduction velocity was calculated by the standard method. In addition, the maximum and minimum latency of 10 peroneal nerve F-waves was obtained following measurement of peroneal nerve conduction velocity.

Strip charts of all evoked responses were printed at the time of data collection and maintained with the subject's chart. Strip charts were reviewed at the end of each testing day and the nerve conduction parameters printed on each strip chart were

copied manually to the nerve conduction data form given in Appendix B for later data entry.

2.4.3 Quantitative Tremor Testing

Tremor was quantified using the Coordination Ability and Tremor System (CATSYS; Danish Product Development, Ltd., Snekkersten, Denmark). This system was produced by a collaborative research effort of occupational medicine specialists in Denmark (Gyntelberg et al., 1990). In this test the subject held a pencil-like stylus that contains a piezoelectric accelerometer sensitive to acceleration in two dimensions. Measurements were taken as specified by the instrument manufacturer: "with the elbow in 90° of flexion, the upper arm held loosely at side of body, the stylus grasped approximately 1 cm from the unattached end, and the stylus held approximately horizontal and parallel to the body." Two separate 10-second sampling intervals were recorded for each hand. Signals were amplified, conditioned and filtered by a microprocessor-based data recorder (CATSYS 5 Datalogger) and fed to a PC-based tremor analysis program. Data acquisition was monitored in real time on the PC monitor. Fourier analysis was performed on the recorded signal, and the calculated power spectrum in 0.1 Hz power bands from 0.9 to 15.0 Hz was displayed on the PC monitor. The root mean square (RMS) of accelerations calculated for the 0.9-15.0 Hz band was calculated for eight seconds of each trial. The primary summary measure used was the logarithm (base 10) of the median of the four trials. Additional information about the tremor measurement system is provided in the CATSYS Users' Manual, which is included as Appendix C.

2.4.4 Vibrotactile Threshold (VT) Testing

As an additional measure of peripheral sensory nerve function, cutaneous vibrotactile sensitivity testing was performed using a portable device called the Vibratron II (Physitemp, Inc., Clifton, NJ). Similar quantitative vibrotactile thresholds were measured in the University of Michigan (1987) study. Displacement (in microns) of the 1.6 cm diameter vibrating post is proportional to the square of the "vibration units" displayed digitally on the front of the Vibratron controller unit.

The protocol used proved to be more time-efficient and more reliable than the protocol recommended by the Vibratron II manufacturer (Gerr & Letz, 1988). During this procedure, the amplitude of the vibrating post is reduced until the participant can no longer feel it then vibration is gradually increased until it is felt by the participant. Variable delays before changing the stimulus intensity and variable rates of change of stimulus intensity are introduced to reduce the impact of temporal cues in determining a participant's responses. Three descending and two ascending runs were performed for each site tested. A trimmed mean (average of the two middle readings, excluding the first run) was calculated. The trimmed mean (in vibration units) was then converted to microns of displacement using parameters derived from a calibration procedure. The common logarithm of microns displacement was used as the summary measure for each site tested. Log transformation stabilizes the variance of these measures and linearizes their relationship with age (Gerr, Hershman, & Letz, 1990). Both index fingers and both great toes were tested for each participant.

A step-by-step presentation of the vibrotactile threshold testing protocol is provided in Appendix D.

2.4.5 Hand Strength Dynamometry

Bilateral hand strength dynamometry was performed on all study participants to assess neuromuscular function. This test was employed in the University of Michigan (1987) study. Grip strength and pinch strength were measured using an adjustable-handle Jamar dynamometer and B&L pinch gauge (Asimow Engineering Company, Santa Monica, CA). The method and instructions of Mathiowetz et al. (1984) were employed. A step-by-step presentation of the hand strength dynamometry testing protocol is provided in Appendix E.

2.4.6 Standing Steadiness Testing

Standing steadiness (sometimes called postural stability or postural sway) is an outcome that may be particularly sensitive to the effects of exposure to a variety of neurotoxicants. The task (standing upright and still) requires intact sensory (visual, vestibular, and proprioceptive) input, motor integrity, and complex neural integration. Although the University of Michigan (1987) did not use this type of measurement, quantitative measurement of postural stability is now feasible and can be reliably performed in field testing situations.

The instrument employed in this project was the NeuroTest SwayPlot Postural Sway Analyzer (NeuroTest, Inc.; Corona, CA). This device measures the position of the subject's head (in two dimensions) using a sound emitter attached to a lightweight

headset placed on the subject and two receivers on a tripod 10-15 cm from the source. Timing and data recording are accomplished by a dedicated IBM-PC-compatible laptop computer. Data are collected as a series of X-Y coordinates.

A step-by-step presentation of the postural sway testing protocol is provided in Appendix F. Standing in stocking feet, the subject was positioned 10-15 cm from the digitizer unit and asked to stand as still as possible with hands at his sides while either fixating visually on a 1-cm diameter circular mark on the wall one meter away or with eyelids closed. Foot and eyelid position were closely monitored by the investigator administering the test, who was ready to steady the subject in the unlikely event that he should begin to fall over with eyes closed. Eyes-opened and eyes-closed trials were alternated. The primary outcome variable analyzed was mean sway speed (equivalent to the total length of sway path). This protocol was determined to be optimal in our pilot testing with a force platform device and this head position monitor (Letz & Gerr; 1995).

2.4.7 Neurobehavioral Tests

A combination of computer-administered and traditional neuropsychological tests that have proven useful in previous studies of workers were used in the present study. Several computer-administered tests from the NES system (Baker, Letz, and Fidler, 1985) used by University of Michigan (1987) in the previous study were used in the present study. We used additional neurobehavioral tests that tap other important cognitive functions and have shown sensitivity to organic brain damage. The neurobehavioral tests included were intended to evaluate a wide range of CNS functions within a relatively brief testing session. The tests administered assessed cognition, memory, psychomotor skills, and mood.

The computer-administered tests selected from the Neurobehavioral Evaluation System (NES2) were Finger Tapping, Simple Reaction Time, Handeye Coordination, Symbol-Digit Substitution, Pattern Memory, Serial Digit Learning, Vocabulary, and Mood Scales. These tests assessed psychomotor speed, visual perceptual, visuomotor speed and coordination, memory, general intellectual, affective and attentional functions. Details of the NES tests administered and the test administration procedures can be found in Appendix G. All neurobehavioral tests were administered by one of the developers of the NES or a research assistant trained by the developer. Each participant was given a brief orientation to the computer-administration procedure and answered a brief computer-administered pretest questionnaire largely aimed at determining the participant's acute caffeine, nicotine, alcohol and drug condition at the time of testing. (Additional questions on chronic alcohol and recreational drug use were included in the health questionnaire administered by the interviewer.)

Three traditional, manually-administered neuropsychological tests, Grooved Pegboard, Trails A and B, and the California Verbal Learning Test, assessed additional motor and cognitive functions. Also, the Mattis Dementia Rating Scale was used to assess general intellectual function, including the presence of dementia.

It should be noted that direct comparison of the numerical results from the present study and from the University of Michigan (1987) study is not possible as minor improvements to many NES2 tests were implemented over the intervening years. From the NES2, only the Mood Scales were identical to those used in the University of Michigan (1987) study.

The ***Finger Tapping Test*** measured motor quickness and coordination. The participant pressed a button as many times as possible within ten second trials with preferred and nonpreferred hands and with preferred hand alternating between two buttons. Two trials of each trial type were administered and the number of button presses in each trial was recorded.

The ***Simple Reaction Time Test*** measured attention, concentration and visual processing. The subject reacted to a visual stimulus on the computer screen by pressing a button on the joystick box. The inter-stimulus interval was randomly varied, and the preferred hand was used. The 60 individual reaction times (in msec) were recorded by the computer and subsequently averaged (with some outlier detection). The University of Michigan (1987) used the NES version of this NES2 test in their study and observed a near-significant ($p=0.07$) difference between exposure groups. However, the University of Michigan group modified the version of this test by shortening the test and perhaps reducing its reliability.

The ***Hand-Eye Coordination Test*** evaluated manual dexterity and coordination. The participant used a joystick to trace a large sine wave pattern on the video display. Vertical deviation from the wave pattern was recorded (as root mean square error and mean absolute error). Five trials were given. The NES version of this NES2 test was the only neurobehavioral test used in the University of Michigan (1987) study that clearly showed relationships with mercury exposure indices. The current version was not identical to that used by the University of Michigan (1987) but was rather improved in the intervening years (i.e., a better joystick was employed, the task involved faster stimulus movement, and one additional testing trial was administered).

The ***Symbol-Digit Substitution Test*** is a modification of the Digit-Symbol Substitution test from the Wechsler Adult Intelligence Scale. It measures coding skills, attention and concentration. Symbols are matched with the digits 1 through 9 in a "key" at the top of the screen and the participant must enter the digits associated with a row of the symbols in scrambled order below. The response latencies for completing five sets of nine pairs were recorded, and the summary measure used was the mean time per correct response. The NES version of this NES2 test was also used in the University of Michigan (1987) study.

The ***Pattern Memory Test*** evaluates visual memory. On each trial a single pattern consisting of a 10 by 10 character array is presented. Characters in the array are randomly selected blanks or filled squares. The stimulus is presented for four seconds, the screen is blanked for three seconds, and then the original stimulus and two altered variants of it are presented on the screen. The participant is asked to choose which pattern he saw before. The number of correctly matched items of the 25 trials and the response latencies for each answer are recorded. The preferred summary measure is the total number of correct trials. This test is a replacement in NES2 for the NES Visual Retention Test (which was used by University of Michigan 1987) for measuring visual memory.

The ***Serial Digit Learning Test*** (sometimes called Digit SupraSpan) measures learning, short-term memory and attention. It consists of presentation of the same long sequence of single digits on the computer screen and then having the participant press the numbered keys on the keyboard for as many digits as he can remember. The test continues until two correct, or a maximum of eight, trials are completed. We used this

digit memory test instead of the one used in the University of Michigan (1987) study because: (1) the first test was unique to the University of Michigan laboratory, (2) took a long time to administer, and (3) it was not related to mercury exposure in the original study.

The ***Vocabulary Test*** was originally developed from the Armed Forces Qualifying Test. It consists of 25 items and measures vocabulary ability. The score, the number of correct items, can be used as an index of native intellectual ability that is resistant to the effect of neurotoxicants, for "adjusting" the other neurobehavioral outcome variables in regression analyses (Baker et al., 1988). This NES version of this NES2 test was also used in the University of Michigan (1987) study.

The ***Mood Scales*** consist of 25 items similar to those in the Profile of Mood States (McNair, Lorr, & Dropleman, 1971). An average rating of five items (and standard deviation) is recorded for five mood dimensions: tension, depression, anger, fatigue and confusion. The NES version of this NES2 test was used in the University of Michigan (1987) study as well.

In the ***Grooved Pegboard Test*** the subject must place 25 notched pegs into a board with 25 matching holes. The time taken to insert all 25 pegs is recorded for dominant and nondominant hands. Since the One-hole test is no longer commercially available, we used the Grooved Pegboard test. This test is more widely used, and clinical norms are available.

The ***Trail-Making Test*** of visual conceptual and visuomotor tracking involves motor speed and attention functions. It is highly-sensitive to the effects of brain damage (Lezak, 1983). This test is given in two parts. In the first part many circles with digits inside are presented, and the subject must draw lines with a pencil from the circle with the digit "1" inside to each digit in sequence as fast as possible. The latency to complete the task and the number of errors are recorded. In the second part of the test, circles with both digits and letters are presented. The subject's task is to alternate between the two sequences, connecting the "1" to "A" to "2" to "B", and so forth, as quickly as possible. Although not used in the University of Michigan (1987) study, the Trail-making test is a sensitive one often used in neurotoxicologic and epidemiologic studies, and clinical norms are available.

The ***California Verbal Learning Test (CVLT)*** significantly extended the range of memory assessment from that employed in the University of Michigan (1987) study. It was thought that memory function was a necessary aspect of cognitive evaluation in these older subjects. The CVLT assesses most learning and memory parameters (acquisition, rate of learning, short-term retention, interference, cued-recall, delayed recall). The CVLT, which involves learning a 16-item shopping separately list presented has: (1) high face validity, (2) been widely used in clinical neuropsychology, and (3) clinical norms.

The ***Mattis Dementia Rating Scale (DRS)*** was employed to measure general level of cognitive functioning (Mattis, 1988). The DRS was originally designed to track cognitive decline in demented patients. Unlike many other brief screening instruments that do not screen specific cognitive functions, the DRS includes separate scales which

screen memory, attention, construction, behavioral initiation and perseveration, and conceptualization, which can provide a neuropsychological profile for each patient. The DRS is one of the most widely-used short mental status examinations with excellent test-retest reliability and content validity (Fillenbaum, et al. 1987). In the present study, the DRS was used to screen patients for the presence of dementia and to provide an estimate of general intellectual functioning. It was administered in a standardized format based on recent guidelines established by the National Institute on Aging.

The neurobehavioral tests were administered at three testing stations including one where the DRS was administered alone. The other two neurobehavioral testing stations included a mix of computerized and noncomputerized tests. The tester guided the subject through all the tests.

Except the Finger Tapping Test, which required rigorous attention to hand position, the tester moved away from the subject after the instructions and practice trials of each of the computerized tests. The tester was always nearby for questions from the participant and visual monitoring (from a short distance) of the subject's manner of responding. The computerized tests were programmed to check for proper responding during practice trials and, if the responding was grossly inappropriate, the tester was automatically called.

2.4.8 Peripheral Neuropathy Case Definition

A case definition of polyneuropathy based upon electrophysiological abnormality or a combination of neurological physical examination signs combined with electrophysiological abnormality was created. Specifically, a participant was classified as having peripheral neuropathy when three or more adjusted nerve conduction measures were greater than the 95th percentile. Also, peripheral neuropathy was defined if a participant had two nerve adjusted conduction measures greater than the 95th percentile with one of the below conditions:

- adjusted toe vibration threshold greater than the 95th percentile;
- adjusted finger vibration threshold greater than the 95th percentile;
- postural stability greater than the 95th percentile; or
- bilaterally absent ankle deep tendon reflexes.

When comparisons involving peripheral neuropathy case status in the current study were made to results obtained in the University of Michigan study, the classifications made by the University of Michigan investigators were used. The case definition they used was not, however, made explicit in their report or in the published results of the Albers et al. (1988) study, and, therefore, could not be applied to the data collected in the current study.

2.4.9 Biological Samples

Blood samples were drawn by trained phlebotomists using standard aseptic technique at the time of the individual examinations. Spot urine samples were also obtained.

Before venipuncture, the antecubital area was prepared with an alcohol swab. Via a single venipuncture using exchangeable vacutainer tubes, 30cc of blood was obtained. In a lavender top tube, 10 ml of blood was collected for a complete blood count (with platelet count) and 20 ml was collected in two red top tubes for multiple blood chemistry analysis (albumin, alkaline phosphatase, SGOT, SGPT, total bilirubin, BUN, calcium, chloride, cholesterol, creatinine, GGT, total globulin, glucose, iron, LDH, phosphorus, potassium, total protein, sodium, triglyceride, and uric acid), thyroid stimulating hormone, and rapid plasma reagin (RPR). All tubes were sent to a commercial clinical laboratory immediately after collection at the beginning of each half-day testing session. These tests allowed for identification of common conditions such as occult diabetes mellitus, renal failure, and hypothyroidism, which are known to cause both central and peripheral nervous system disease.

A single spot urine specimen was collected from all participants at the time of examination. An appropriate aliquot was decanted from the urine container and placed in plastic collection tubes. Routine urinalysis (opacity, color, appearance, specific gravity, pH, semiquantitative protein, semiquantitative glucose, occult blood, ketones, bilirubin, urobilinogen and microscopic examination of sediment) was performed by a commercial clinical laboratory.

No biological samples for mercury were obtained in the present study. In the University of Michigan study, urine mercury concentrations were near the detection limit for the method used and not significantly different between the exposure groups. Therefore, we concluded that such testing was not required in the present study.

2.5 Mercury Exposure

2.5.1 Exposure Data Source

In 1953 a urinalysis program was initiated at the Y-12 Plant in Oak Ridge, to monitor all workers likely to be exposed to mercury. Workers were monitored quarterly and any observation of a urine mercury concentration above the Plant Action Limit (PAL) of 300 µgHg/L of urine was reported to the individual's supervisor. Any observation of a urine mercury concentration above 600 µgHg/L resulted in the removal of the worker from exposure areas until the concentration fell to acceptable levels. Therefore, workers with high concentrations of mercury in their urine were found to have multiple tests in a quarter. Because of this practice, the average quarterly concentration was used in some of the calculations of cumulative excretion described below.

2.5.2 Definition of Exposure Variables

Candidate mercury exposure variables included those calculated in the University of Michigan study of this cohort, all based on Y-12 records of personal samples from the urine mercury monitoring program. The candidate mercury exposure variables were:

- HGU: A measure of cumulative exposure calculated by summing the average urinary concentration for every quarter when monitoring occurred. HGU is reported in units of µgHg/L of urine. This variable was used to rank potential study subjects for inclusion in the original study.
- HGDUR: Number of quarters mercury was detected through urinalysis.
- HGURATE: Average exposure intensity, calculated as the cumulative exposure (HGU) divided by number of quarters exposed (HGDUR).

- HGPAV: Number of quarters having urine mercury concentrations ≥ 300 µgHg/L, the plant action value (PAV).
- HGPAV2: Number of quarters having urine mercury concentrations ≥ 600 µgHg/L, twice the PAV.
- HGPEAK: Single highest urine mercury concentration.
- HGAVE: The average of all average quarterly values between January 1, 1955, and December 31, 1956, the period of highest exposure.

Many analyses in the original study were limited to HGU, HGPAV2, and HGPEAK.

2.5.3 Verification of Nonexposure Among Controls

For the University of Michigan study, 94 (36.9%) of the controls indicated on their study questionnaires that they had been "exposed" to mercury during employment at the Y-12 plant. As part of the current study industrial hygienists familiar with processes at the Y-12 plant were asked to investigate whether such exposures were a high enough level to affect categorization as an unexposed subject. To carry out this investigation, industrial hygienists familiar with the Y-12 departmental code file and the historical plant processes identified seven departments having probable high mercury exposure potential. All members of the original study cohort were checked for any periods of employment in at least one of these seven departments. The results of this inquiry (shown in Table 4) show only one instance of a control being employed in a high mercury exposure department, while 556 instances were noted of the designated exposed cohort members working in these same departments. This outcome provides

strong evidence that those workers chosen as controls were not likely to have received occupational mercury exposure.

2.6 Collecting and Securing the Data

When each participant arrived at the testing site, he was asked to sign a consent form that had been mailed to him for review before the examination date. Each participant was given a folder for storage of all study-related data forms. The folder had a page of labels with the participant's name and identification affixed to the front. At each examination station, one label was taken from the front of the folder and placed on the data collection form. All medical examination data forms were reviewed for completeness and clarity of responses before the study participants left the examination site. The questionnaires were locked in a secured area when not in use by study investigators or data entry personnel.

2.7 Data Management

Computer programs were developed and used to perform logic and consistency checks on all data. Discrepancies were reviewed and resolved by the principal investigators. All data from questionnaires and medical examination forms were entered by two independent data entry technicians in separate computer files. Using the SAS COMPARE (1990) procedure, the files were compared. Any discrepancies were reviewed by a third technician. If the review technician did not agree with the entry of the first or second data technician, data for that entry were reviewed with the principal investigators for final resolution.

Data from the NES tests were handled according to the procedures given in the *NES2 User's Manual* (Appendix G). NES2 test data and postural sway test data were automatically written to computer disks during data acquisition. Any exceptional circumstances during testing were noted in a log. At the end of each testing day all data files were saved on two additional diskettes and stored separately.

After creating backup copies of the raw data files, the raw data were reduced to summary measures using software provided by the instrument developers. The resulting summary data files were transferred to a mainframe computer for merging with other sources of data and for data analysis. Blood analysis data were provided on magnetic media by the contract laboratory.

Exclusion of data from data analysis occurred at three levels. First, detection and handling of individual outlier data points in tests having multiple trials was accomplished in the data summary programs mentioned above. Second, summary measures for a particular neurobehavioral test were voided because of notes of unusual circumstances in the testing logs.

Finally, data were excluded from analysis for the following reasons (for the types of testing noted): acutely intoxicated with alcohol or drugs (all outcomes), anti-convulsant or major psychiatric medication (neurobehavioral -- NB), admission of regular illicit drug use (NB), prior diagnosis of alcoholism (NB, NCV, VT), history of sustained loss of consciousness due to a blow to the head (NB), history of a stroke (NB), history of psychosis (NB), mental retardation (NB), diabetes (NCV, VT), prior cancer

chemotherapy (NCV, VT), history of renal failure (NCV, VT), serious trauma to the limb tested (NCV, VT, Grip), and history of vestibular disease (Sway). In addition, all data were voided for any subject who had grossly incomplete data. All these data rejection criteria were applied without reference to exposure status.

2.8 Data Analysis

Demographic data were initially summarized and described separately for exposed and unexposed study participants using standard descriptive statistics for demographic variables, mercury exposure data, and occupational history data. Comparisons were made between values for current study participants and nonparticipants (i.e., those who participated in the University of Michigan study, but not in the current study). A set of outcome variables calculated from the neurologic and neurobehavioral data collected are listed in Table 5. To the extent feasible, one variable was selected for each test.

A subset of the numerous outcome variables was designated as the primary outcome variables. These variables were hypothesized to differ between exposure groups from the results of the University of Michigan study (see Table 1). These primary outcome variables were ulnar motor nerve conduction velocity, peroneal nerve F-wave latency, number of physical examination abnormalities, peripheral neuropathy case definition status, RMS tremor amplitude, Handeye Coordination Test log RMS error (CNS), and Simple Reaction Time mean latency (CNS). The one-hole test performed by the University of Michigan was not included in the current study because test administration equipment is not commercially available and testing procedures are not standardized. Furthermore, the functional domains tested by the one-hole test, fine

motor skills and motor control were assessed by other tests in the current study (i.e., handeye coordination and tremor tests). In addition, given the advanced age of the cohort and concerns about potential cognitive effects of mercury exposure, dementia case definition status was included as a primary outcome variable.

The primary hypothesis to be tested was whether exposure to mercury was associated with scores on neurologic and neurobehavioral tests. Because many effects observed in the University of Michigan study appeared attributable to results obtained among the most heavily exposed subjects, crude analyses in the current study were performed using three exposure groups: unexposed, less-exposed and more-exposed. Multivariable analyses employing the various *exposure* variables used in the University of Michigan study were then performed. A limited set of variables appropriate for each outcome was considered as potential *covariates* (age, sex, race, level of education, and height). In addition, the interactions between age and the measures of exposure were examined to see if the effect of mercury exposure differed as a function of age. It was assumed that the errors about the regression line were independent, and that they were normally distributed with a mean of zero and a common variance (Wetherill, 1986). In this application, most dependent variables were continuous and the regressor variables were either continuous or categorical. In cases where the dependent variable was dichotomous (i.e., polyneuropathy present/absent and dementia present/absent, logistic modeling of prevalence odds of abnormal outcome was performed).

All analyses were performed using SAS software (1990). Separate multivariable models were fitted for each outcome, and models were fitted for each exposure variable

separately. We did not adjust the significance levels for these multiple comparisons. Rather, we considered the pattern of results achieving a $p<0.05$ level in the context of biological plausibility and consistency for interpreting the results of the data analyses.

3. Results

3.1 Participation

When inviting individuals to participate in the current study, there were 97 known to be deceased from the 502 persons tested originally. Of the remaining 405 persons, 46 (11%; 42 untraceable plus four more deaths) could not be contacted, and 172 (42%) agreed to participate in the study. Among the 68 newly-selected persons for the study, 33 (48%) agreed to participate. Approximately 75% of those who were contacted and did not participate cited advancing age and having been tested once before as reasons for not participating. The other 25% cited their personal health or the poor health of their spouse as the reason for not participating.

3.2 Exclusions

A total of 104 exposed and 101 unexposed subjects were examined. Twenty-five (24.0%) of the exposed subjects and 17 (16.8%) of the unexposed subjects met at least one criterion for exclusion from analyses of peripheral nervous system function. Similarly, 23 (22.1%) of the exposed subjects and 18 (17.8%) of the unexposed subjects met at least one criterion for exclusion from analyses of central nervous system function. The numbers of subjects in the exposed and unexposed groups meeting each of the exclusion criteria are given in Table 6.

3.3 Characteristics of Cohort Members

Descriptive statistics for demographic variables are presented by exposure group (unexposed, cumulative mercury exposure of 2,000-3,499 μgHg/L-quarters, cumulative mercury exposure >3,500 μgHg/L-quarters) in Table 7. Few differences were observed between the exposed and unexposed subjects on the demographic variables.

Cumulative alcohol consumption (reported in drinks/day - years) was slightly greater among the unexposed than either of the two exposed groups. Body mass index was slightly greater for the highest exposed group than for the lower exposed group and the unexposed group.

Descriptive statistics for mercury exposure variables are presented for the exposed subjects only in Table 8. The mean exposure duration (among the exposed subjects only) was 19.3 quarters (4.8 years) and ranged from less than a year to almost 13 years. The mean cumulative exposure (HGU) value was 3,362 µgHg/L-quarters. The average urine mercury concentration for the entire duration of exposure (HGURATE) for each worker was calculated by dividing the urinary lifetime equivalent measure by the total number of quarters of exposure. The mean HGURATE over all exposed subjects was 201 µgHg/L. The mean number of quarters during which the urine mercury concentration exceeded 300 µgHg/L (HGPAV; the "plant action value") was 3.6 and ranged from 0 to 11. The mean number of quarters during which the urine mercury concentration exceeded 600 µgHg/L (HGPAV2; twice the "plant action value") was 0.7 and ranged from 0 to 4. The mean peak urine mercury value (HGPEAK) was 635 µgHg/L and ranged from 187 µgHg/L to 1900 µgHg/L.

3.4 Correlation Among Exposure Variables

Correlations between mercury exposure variables, calculated for the 104 exposed subjects examined, are presented in Table 9. Cumulative mercury exposure (HGU) was only weakly correlated with average urine mercury (HGURATE; r=0.09) and weakly to modestly correlated with the peak urine mercury (HGPEAK; r=0.27) and number of occasions that urine mercury exceeded 600 µgHg/L (HGPAV2; r=0.26). The greatest correlation was observed between the peak mercury value and the number of quarters

during which the urine mercury concentration exceeded 600 µgHg/L (r=0.77). Interestingly, duration of mercury exposure was highly negatively correlated with average mercury exposure (r=0.60) and modestly correlated with the number of quarters that the mercury concentration exceeded 600 µgHg/L (r=0.24)

3.5 Correlations Between Exposure Variables and Potential Covariates

Correlations between the primary mercury exposure variable (cumulative mercury exposure) and important covariates are provided for all nonexcluded exposed subjects in Table 10. Only the correlation between education and cumulative mercury exposure was statistically significant; however, it was still relatively weak in magnitude (r=-0.23).

3.6 Descriptive Statistics for Outcomes

Descriptive statistics for physical examination outcomes are presented for the three cumulative mercury exposure groups in Table 11. Diminished motor strength was significantly associated with exposure group (p=0.01) and sensory abnormality and poor coordination were marginally significantly associated with exposure group (p=0.059 and p=0.055, respectively). The coordination summary variable included results obtained from examination of both postural and intention tremor. Interestingly, postural tremor was significantly associated with exposure (p=0.025), while intention tremor was not (data not shown). Finally, for the measure of overall physical examination abnormality, a value of 8 on this measure was selected arbitrarily to represent clinical neurologic abnormality. Using this criterion, this measure was significantly associated with the exposure group (p=0.013).

Results of nerve conduction outcome measures obtained in the current study and in the University of Michigan study are presented by exposure category in Table 12. The

prefix UM on some outcome variables designates data collected by the University of Michigan. In both studies, slightly poorer conduction velocities are generally observed across the exposure categories. In addition, longer peroneal F-wave latencies were observed across the exposure categories in the current study. F-wave results were not reported in the University of Michigan Final Report (1987).

Results of quantitative sensory and motor outcomes obtained in the current study and in the University of Michigan study are presented by exposure category in Table 13. No marked differences between exposure groups were observed in either study. Because of effects of exposure observed by the University of Michigan, tremor measures were of primary interest among these outcomes. In the current study, tremor acceleration values and the log transform of tremor acceleration values showed a small monotonic increase across the exposure categories. When limited to those subjects examined in the current study, the University of Michigan tremor results were also elevated in the highest exposure category; however, the low exposure group had lower tremor measures than the unexposed group. Finally, although not large in magnitude, greater vibrotactile thresholds of the great toe were observed among the highest exposure group when compared with the unexposed and the low exposed groups in the present study. No consistent effect of exposure was observed for vibration perception testing performed by the University of Michigan among those subjects examined in the current study.

Results of the neurobehavioral outcomes obtained in the current study and in the University of Michigan study are presented by exposure category in Table 14. Because statistically significant effects of exposure on neurobehavioral tests were observed by the University of Michigan for the Handeye Coordination test, results from that test are

of primary interest among these outcomes. In the current study, the RMS error scores were higher for exposed groups than for the unexposed group. The results for this test were similar for the University of Michigan subjects also examined in this study, although the summary measures from the two studies are not directly comparable. Only direct comparisons of mood scores can be made between the results of the current study and those obtained by the University of Michigan. The mood score results obtained in the current study were remarkably similar to those obtained in the University of Michigan study. Overall, only small differences in outcome were observed across the exposure groups.

3.7 Linear Models for Quantitative Outcomes

Exposure parameter estimates and their associated p-values are presented in Table 15 from the final linear regression and logistic regression models for each of four mercury exposure variables (mercury exposure status, cumulative mercury exposure, average mercury exposure, and peak mercury exposure) regressed upon a priori selected neurologic outcome variables. All covariates initially included in the model are listed in the column entitled "Covariates." Those covariates listed inside brackets were not significantly associated with the dependent variable and were therefore not included in the final model. Covariates outside brackets were significantly associated with the dependent variable and were retained in the final model. Because the unit of each parameter estimate is specific to both the units of the dependent variable and its exposure variable, comparisons of relative magnitude of effect cannot be made across the exposure variables or across the outcome variables. Since the sample sizes were very similar for all of the models presented in Table 15, the p-values can provide a relative index of the strength of association between the exposure and outcome variables. The overall pattern of probability (p-value) calculated for the associations

between the dependent variables and each of the four exposure variables was similar. For example, p-values for the associations between peroneal NCV and each of the five exposure variables were all of a relatively similar low magnitude, whereas p-values for the associations between simple reaction time and each of the exposure variables were all of a relatively similar high magnitude. Overall, the cumulative mercury exposure variable was more frequently associated, the more strongly associated, with the dependent variables than were the other three measures of exposure.

For efficiency, only results of linear models and logistic regression procedures in which associations were explored between the *cumulative mercury exposure* variable and the dependent variables will be provided in the text. Peroneal motor nerve F-wave was significantly associated with age, height, and cumulative mercury exposure. Ulnar motor nerve conduction velocity was significantly associated with age, height, and cumulative mercury exposure. Tremor was significantly associated with age but not with exposure. Handeye coordination test performance was associated with age, visual acuity, self-rated effort on the test, and cumulative mercury exposure. Simple reaction time was not significantly associated with any covariate or exposure variable. Physical examination score of greater than 8 and classification as having peripheral neuropathy were both significantly associated with age and cumulative mercury exposure. Dementia was significantly associated with age and education but not with mercury exposure.

3.8 Age-Exposure Interaction

An age-by-exposure interaction term was added to the "final" linear models described above, and the models were refitted. The age-by-exposure interaction was not statistically significant in the models for any of the outcome variables. In a few

instances, this interaction term approached statistical significance ($0.05 < p < 0.15$). In these cases the sign of the parameter estimate was in the opposite direction from that expected. That is, the estimated effect of exposure was less for the older subjects than for the younger subjects.

3.9 Comparing Characteristics of Current Study Participants to Nonparticipants

The original study included 502 subjects, 97 of whom were deceased before the current study began. Table 16 examines the differences between the current study population and those who were not examined (regardless of whether they were alive or deceased at the beginning of the current study) by exposure status. The participating exposed persons were younger, more educated, had a higher percentage of current drinkers in 1986 and were less frequently smokers than those who did not participate. The exposed participants were similar to the nonparticipants for all measures of mercury exposure. They had slightly less tremor than the exposed nonparticipants. Also, the exposed participants had a lower frequency of polyneuropathy diagnoses in 1986 than the nonparticipants.

The unexposed (control) group that was examined in the current study was more similar in age to the controls who did not participate than were the exposed participant and nonparticipants, although they were slightly younger. The participating controls were less likely to be drinkers in 1986 and slightly less likely to have been smokers than the nonparticipating controls. All outcome variables were similar between the two groups, with the exception of a higher percentage of the nonparticipating controls (21.5%) being diagnosed with polyneuropathy in 1986 than the participating controls (6.0%).

The 33 new study subjects are also described with respect to age in 1986. The unexposed group (n = 18) was about a year younger than the group that had been examined by the University of Michigan. The exposed group (n = 15) was similar in age to those who were reexamined from the Michigan group. Examination of the summary exposure variables for the 15 new mercury workers reveals that their duration of exposure and cumulative exposure were lower than those previously included, but their exposure rate and peak intensity measures were quite similar.

3.10 Comparison of Performance of Subjects Who Were in Both Studies

To compare exposure effects more directly between the current study and the University of Michigan study, results are reported in Table 17 of tests that are most comparable from each study for those subjects examined in both studies. In this restricted sample, associations were difficult to observe and effect sizes were small. For simplicity, the results of the dependent variables are provided only for the cumulative mercury exposure variable. Means and standard deviations of the dependent variables are presented by cumulative mercury exposure group. In addition, standardized regression coefficients for the continuous cumulative mercury exposure variable from backward-elimination stepwise regression models, similar to those models presented in Table 15, are also presented. These standardized regression coefficients allow for direct comparison of effect size across outcome variables. Little trend appeared for the tibial motor nerve conduction velocity (University of Michigan) or for the peroneal motor nerve conduction velocity (ORAU/Emory). A negative exposure-response relationship was observed in this restricted sample of subjects tested in both studies for ulnar motor NCV as measured in both studies. The estimated size of the effect was a decrease of 0.2 standard deviations in ulnar motor NCV per 1.0 standard deviation increase in cumulative mercury exposure.

For the Handeye Coordination test, in this restricted sample, the estimated effect sizes were also very similar across the two studies (i.e., the standardized regression coefficients were 0.15 vs. 0.14). The apparent trend of an exposure-response relationship for the Reaction Time test in the University of Michigan study was not observed in the results of the same test obtained in the ORAU/Emory study. Conversely, the apparent trend of an exposure-response relationship observed in the ORAU/Emory study for tremor RMS acceleration in this restricted sample was not apparent in the corresponding results obtained in the University of Michigan study.

4. Discussion

Several neurologic outcomes were statistically significantly associated with cumulative mercury exposure that had ended 30 years or more prior to neurologic testing. In this study population, cumulative mercury exposure was observed to have stronger associations with the health outcomes than did the other measures of mercury exposure including average urinary mercury exposure, peak mercury exposure, number of peaks greater than 600 µgHg/L and ever having a peak above 600 µgHg/L. When controlling for covariates, an index of physical examination abnormality (the physical examination score) and being classified as having peripheral neuropathy were both significantly associated with cumulative mercury exposure. Peroneal motor nerve conduction velocity, ulnar motor nerve conduction velocity, and peroneal motor nerve F-wave latency were also significantly associated with cumulative mercury exposure after controlling for covariates in this group. Results of the Handeye Coordination test were significantly associated with cumulative mercury exposure after controlling for covariates. No association was observed between cumulative mercury exposure and a quantitative measure of dementia, nor was quantitative assessment of tremor significantly associated with cumulative mercury exposure. No significant age-exposure interactions were observed for any of the outcomes for which a main effect of exposure was observed.

This study of formerly exposed Y-12 plant workers was performed as a follow-up to a study of these workers performed by the University of Michigan approximately ten years ago. The current study, because of its cross-sectional design, is one of surviving Y-12 workers. If workers who died or became disabled due to poor health between the previous study and the current study were more affected by exposure to

mercury than workers who were able to participate, then such susceptible workers would be under-represented in the current sample. Selective loss of this more susceptible subpopulation would produce a bias towards the null hypothesis.

While only 34% of the previous examined workers were examined in the present study, differences between participants and nonparticipants were minimal. As might be expected, the current study population was younger than the nonparticipants. With regard to exposure, the participants and nonparticipants were virtually identical for every exposure variable examined. There was a large differential of participation with regard to diagnosed polyneuropathy for both the exposed and the controls. Only 17.6% of exposed workers and 11.9% of the unexpected workers with diagnosed polyneuropathy participated in the current study. The Michigan study suggested that subclinical damage caused by mercury exposure was most apparent in oldest workers because of "unmasking effects due to the normal aging process." In spite of reduced participation in the current study, the relative similarity of the two groups with the exception of removal of a higher proportion of those who were older in 1986, offered an excellent opportunity to observe whether highly exposed younger workers showed the same neurologic abnormalities with the passing of time as the older cohort members did in 1986.

Differences in actual subjects enrolled in the studies, methods, and analyses made some comparisons between the results of the current study and results of the University of Michigan study difficult. However, some results can be compared. In both the current study and the University of Michigan study, assessment of tremor made during the neurologic physical examination was significantly associated with measures of exposure. However, quantitative measures of tremor were not

significantly associated with exposure in the current study whereas they were associated with exposure in the University of Michigan study. In the current study, a neurologic physical examination abnormality score greater than 8 was significantly associated with cumulative mercury exposure whereas in the University of Michigan study, a normal examination was associated (negatively) with ever having a peak urine mercury concentration greater than 600 µgHg/L. In the current study, meeting criteria for peripheral neuropathy was associated with cumulative mercury exposure whereas in the University of Michigan study an association between peripheral neuropathy and exposure was observed only in an ad-hoc analysis of subjects with peak exposure in excess of 850 µgHg/L in comparison to all other subjects. In the current study, peroneal motor nerve conduction velocity, ulnar motor nerve conduction velocity, and peroneal motor nerve F-wave latency were significantly associated with cumulative mercury exposure. In the University of Michigan study, significant associations were observed between the median motor nerve distal latency and median sensory nerve amplitude and at least one measure of exposure. No measure of conduction velocity was associated with any measure of exposure nor were associations observed between any measure of exposure and electrophysiologic test results of the lower extremity in the investigation performed by the University of Michigan.

Several factors may be responsible for differences between the results observed by the University of Michigan and the current study. First, many subjects examined in the University of Michigan study were not examined in the current study. Some were lost due to death while others elected not to participate. It appears that older subjects examined during the University of Michigan study were less likely to participate in the current study. To permit a more direct comparison of the results obtained by the

University of Michigan investigators with those obtained in the current study, the results of the University of Michigan study were stratified according to those who did and who did not participate in the current study. Only for RMS tremor acceleration and Handeye Coordination error were any appreciable differences observed between those examined and those not examined in either the exposed or unexposed categories. Specifically, for these two measures, the poorest average function was observed among those who were exposed, participated in the University of Michigan study and who did not participate in the current study. The results obtained by the University of Michigan of Handeye Coordination error in the restricted group consisting only of those who also participated in current study were slightly poorer among the exposed than the unexposed. Interestingly, the results obtained by the University of Michigan of RMS tremor acceleration in the restricted group consisting only of those who also participated in current study was virtually the same among the exposed and unexposed. These results suggest those subjects with greater RMS tremor when examined by the University of Michigan were unavailable to participate in the current study.

Another difference between results obtained by University of Michigan investigators and results obtained in the current study was the observation of age-exposure interactions for several health outcomes. No significant age-exposure interactions were observed in the current study. It is possible that the small number of older, heavily exposed subjects who made the major contribution to this effect were not available for participation in the current study. However, the observation of statistically significant associations with exposure among a group smaller than the sample studied nine years earlier, potentially biased toward healthier individuals, and without individuals having the highest exposure, is consistent with a hypothesis that older

individuals may exhibit greater effects of remote exposure than relatively younger ones.

The results of numerous statistical tests are reported. No formal correction for these multiple comparisons was made. We consider the coherence and consistency of the statistically significant results to be of most importance. To reduce the magnitude of a potential problem with multiple comparisons, we identified four outcome variables as "primary" a priori on the basis of results of the University of Michigan study. Of these four primary outcome variables, we observed statistically significant exposure effects on measures of nerve conduction and HandEye Coordination that were consistent with those observed in the University of Michigan study. Although we did not observe out a priori measure of tremor, which was from a test of resting tremor, to be associated with mercury exposure, we did observe a measure of postural tremor from the physical examination to be associated with mercury exposure. The tremor test results related to mercury exposure in the University of Michigan study were from a test of postural tremor. We did not observe a statistically significant exposure effect on the fourth primary outcome, Simple Reaction Time. In the University of Michigan study, the Simple Reaction Time outcome was associated with one exposure variable at eh p=0.07 level. The similarity of results across independent studies argues strongly against the observed statistically significant results being due to Type 1 error. In addition, although quite a number of p-values are presented in some tables, these p-values were used in a descriptive manner, as a rough index of the strength of association across exposure models, given that sample sizes were similar in models grouped together in those tables. The p-values presented in those tables were not presented to indicate formal statistical significance of each parameter estimate presented.

Several sources of bias may contribute to attenuation of observed effects in the current study. First, errors in estimation of exposure may have occurred. Exposure estimation was based on measurement of urine mercury concentration. These measures can be difficult to perform. No information is currently available about the quality control procedures used in the collection and measurement of these specimens. If error introduced by laboratory procedures was random, the effect on estimates of association would be toward the null hypothesis. If error was systematic, the effect could be either toward or away from the null hypothesis, depending upon the particular error. In addition, mercury levels collected periodically, (i.e., quarterly) represent an integrated average of exposure for that period and therefore underestimate large but short-term exposures. If such exposures were, in fact, causally related to the health outcomes studied, and were randomly distributed across all exposure categories, the resulting bias would be toward the null. If, however, such underestimation occurred preferentially among more heavily exposed individuals, then the resulting bias would lead to an underestimate of the exposure magnitude that produces chronic health effects.

The comparison group was chosen to be workers who never worked in the departments that processed mercury. The potential for other exposures still existed for this group of workers. The Y-12 Plant was a uranium processing plant and there was significant potential for workers to be exposed to the following materials during the course of their work at the facility: mercury, lead, beryllium, uranium, and thorium.

Of these, lead is the only substance known to have significant relationship with neurologic impairment. The UM study controlled for self reported lead exposure in their analyses. This control was not done in the present analyses because it was felt

that self-reported exposures to industrial materials was probably not reliable. Specific analyses of the likelihood of self-reported mercury exposure among the control population did not find these reports to be reliable.

It is also likely that there was some error in measurement of health effect. Given the use of standard procedures with which the investigators have considerable expertise, such error was not likely to be large. Also, it is not likely that such error was related to exposure, as the examiners were not aware of the exposure status of the participants. The effect of such error would be to alternate the observed association between exposure and outcome, if one exists.

5. Conclusions

1. Neurologic effects of relatively heavy exposure were still detectable more than 30 years after cessation of that exposure.

2. Effects were observed mainly for the peripheral nervous system, with physical examination and electrodiagnostic evaluation providing results with best associations with exposure.

3. Postural tremor, assessed by physical examination, was associated with past mercury exposure. Resting tremor, assessed by both physical examination and special instrumentation, was not observed to be associated with past mercury exposure.

4. No effects of past mercury exposure were observed on a quantitative measure of dementia nor for other measures of cognitive function.

5. No significant age-exposure interactions were observed. However, when compared to the results of the previous investigation, the results of the current study are consistent with a hypothesis that older individuals may exhibit greater effects of remote exposure than relatively younger ones.

6. Of all the exposure measures evaluated (exposed/unexposed, cumulative exposure, average exposure, number of exposure episodes > 600 µgHg/L) cumulative exposure was the summary exposure measure having the greatest number of associations or possible "strongest level of associations" with outcomes.

7. This cohort of workers should not be studied under a research protocol in the future. The advanced age of the group and the lack of medical interventions for any identified neurological conditions may also preclude medical surveillance.

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Table 1. University of Michigan Findings for Each of Several Exposure Measures (P-values for Each Exposure Effect)

Outcome variable	Hg Status (Exp. vs. Unexp.)	Cumulative Hg	Peak Hg	# of Peaks >0.6	Peak Hg>0.6 (dichotomized)
Nerve Conduction:					
Median sensory DL	0.10	0.09	0.40	—	0.03
Median sensory amp.	0.05	0.12	0.24	—	0.31
Ulnar motor NCV	0.43	0.36	0.08	—	0.06
Quantitative Tremor:					
Acceleration RMS	*	*	<0.001	—	<0.002
Acceleration AAMP	*	*	<0.001	—	<0.002
Neurologic Examination:					
Normal examination	0.55	—	—	—	0.05
Polyneuropathy	0.48	—	—	—	0.38
Tremor	0.11	0.15	0.04	—	0.05
Neurobehavioral:					
Simple reaction time	0.08	>0.20	0.08	>0.20	—
Handeye coordination	0.001	0.03	0.003	0.10	—
One hole test	>0.20	>0.20	0.05	0.04	—

— Results not presented in Final Report (U of M, 1987)

* Results reported inconsistently in Final Report (U of M, 1987)

Table 4. Occurrences of Employment in Departments Having High Exposure Potential for Mercury		
Department Number	Among Exposed	Among Controls
2025	12	0
2026	45	0
2681	52	1
2682	92	0
2683	50	0
2685	198	0
2690	107	0
Total Occurrences	556	1

Table 5. Outcomes Variables for the Study

OUTCOME:	UNIT:
Peripheral neuropathy	present/absent
Nerve conduction tests:	
Peroneal motor NCV	m/s
Peroneal motor amplitude	μV
Peroneal motor F-wave latency	msec
Ulnar motor NCV	m/s
Ulnar motor amplitude	μV
Ulnar motor F-wave latency	msec
Ulnar sensory NCV	m/s
Ulnar sensory amplitude	μV
Sensory and other neurologic tests:	
Quantitative tremor (acceleration)	log10 mm/sec2
Non-dominant great toe vibrotactile threshold	log10 μ
Hand strength dynamometry	kg.
Postural sway speed with eyes closed	cm/sec
Neurobehavioral tests:	
Handeye Coordination	log RMS error
Simple Reaction Time mean latency	msec
CVLT acquisition	# correct (1-96)
Trails B time	sec
Grooved Pegboard dominant hand time	sec
Finger Tapping alternating	# of taps
Symbol-Digit Substitution	sec/correct digit
Pattern Memory	# correct (1-25)
Serial Digit Learning	log error
Vocabulary	# correct (0-25)
Mood scales:	
Tension, Depression, Anger, Fatigue, Confusion	avg. score (1-5)
Mattis Dementia Rating Scale	score (0-144)

Table 6. Exclusions by Exposure Status Group

	Unexposed		Exposed	
	Yes	No	Yes	No
Current medications:				
Hypoglycemic agents	4	97	8	96
Thyroid medications	5	96	3	101
Benzodiazepines	4	97	8	96
Antidepressants	2	99	6	98
Narcotic analgesics	1	100	0	104
Medical history of:				
Renal Failure	1	100	2	102
Head Injury	7	94	3	101
Brain Tumor	0	101	0	104
Stroke	5	96	7	97
Ear Surgery	3	98	7	97
Ear Infection (past year)	3	98	5	99
Blood glucose > 300 (non-fasting)	3	97	1	101
TSH > 8.0	3	97	3	99
Lifetime alcohol consumption (drinks/day years > 200)	1	100	2	102
Total # of PNS Exclusions	17 (16.8%)	84	25 (24.0%)	79
Total # of CNS Exclusions	18 (17.8%)	83	23 (22.1%)	81

Table 7. Descriptive Statistics for Demographic Variables by Exposure Group for all Nonexcluded Subjects

	Cumulative Mercury Exposure								
	0			2,000 - 3,499			≥3,500		
	N	MEAN	STD	N	MEAN	STD	N	MEAN	STD
Age at Last Exam (yrs)	84	71.19	6.56	47	69.43	5.53	32	71.50	6.20
Education (yrs)	84	12.08	2.57	47	12.79	2.43	32	11.75	2.09
Drinks/day-years	84	18.63	30.66	47	11.66	14.61	32	15.64	29.14
Height	84	68.11	2.30	47	68.94	2.82	32	68.75	2.11
Weight	84	186.14	29.40	47	192.21	32.52	32	195.53	45.36
Body Mass Index (kg/m2)	84	30.37	4.48	47	30.53	4.34	32	31.30	6.90
Arm Temperature (°C)	82	33.32	0.79	47	33.14	0.80	31	33.45	0.93
Leg Temperature (°C)	81	33.16	0.94	46	33.26	0.80	31	33.34	1.06
Visual Acuity (1-8)	83	4.88	1.48	47	5.32	1.45	32	5.09	1.09
Exp. VidGames/Comp. (1-3)	84	1.29	0.50	47	1.38	0.61	32	1.16	0.37
Effort on Comp. Tests (1-4)	84	3.39	0.86	47	3.43	0.77	32	3.56	0.80
# Quarters Exposed	84	0.00	0.00	47	16.91	8.88	32	24.19	8.04
Total Exposure / # Quarters Exposed	84	0.00	0.00	47	188.78	101.75	32	215.59	97.41
Highest Urinary	84	0.00	0.00	47	577.91	277.81	32	753.72	348.25
# Quarters Above Pav 0.3 mg/L	84	0.00	0.00	47	2.74	1.78	32	5.13	2.37
# Quarters Above 0.6 mg/L	84	0.00	0.00	47	0.57	0.83	32	1.06	1.13

Table 8. Descriptive Statistics for Mercury Exposure Variables

Variable	N	Mean	Std Dev	Minimum	Maximum
HGDUR # QUARTERS EXPOSED	104	19.3	9.08	3	51
HGU CUMULATIVE EXPOSURE	104	3362.2	1177.38	1089	6588
HGURATE TOTAL EXPOSURE/# QUARTERS EXPOSED	104	200.6	98.01	64.00	695.67
HGPAV # QUARTERS ABOVE PAV, 0.3 mg/L	104	3.59	2.25	0	11
HGPAV2 # QUARTERS ABOVE 0.6 mg/L	104	0.69	0.93	0	4
HGPEAK HIGHEST VALUE	104	635.1	319.66	187	1900

Table 9. Correlations Among Potential Mercury Exposure Variables for All Exposed Subjects Tested

Pearson Coorelation Coefficients / Prob > |R| under Ho: Rho = 0 / N = 104

	HGDUR	HGU	HGURATE	HGPAV	HGPAV2	HGPEAK
HGDUR # Quarters Exposed	1.00000 0.0	0.55687 0.0001	-0.60361 0.0001	-0.05941 0.5491	-0.22609 0.0210	-0.24236 0.0132
HGU Cumulative Exposure	0.55687 0.0001	1.00000 0.0	0.09057 0.3605	0.59338 0.0001	0.25609 0.0087	0.26708 0.0061
HGURATE Total Exposure/# Quarters Exposed	-0.60361 0.0001	0.09057 0.3605	1.00000 0.0	0.44631 0.0001	0.53104 0.0001	0.55856 0.0001
HGPAV # Quarters Above PAV, 0.3 mg/L	-0.05941 0.5491	0.59338 0.0001	0.44631 0.0001	1.00000 0.0	0.35814 0.0002	0.48182 0.0001
HGPAV2 # Quarters Above 0.6 mg/L	-0.22609 0.0210	0.25609 0.0087	0.53104 0.0001	0.35814 0.0002	1.00000 0.0	0.77445 0.0001
HGPEAK Highest Value	-0.24236 0.0132	0.26708 0.0061	0.55856 0.0001	0.48182 0.0001	0.77445 0.0001	1.00000 0.0

Table 10. Correlations between primary mercury exposure variable and covariates for all non-excluded exposed subjects

Pearson Correlation Coefficients / Prob > |R| under Ho: Rho = 0 /N = 75 to 79

	HGU	AGE	EDUC	INCOMCAT	DPD_YRS	PX_HT	BMI	ARMTEMP	LEGTEMP
HGU Cumulative Exposure	1.000 0.0 79								
Age Age at Last Exam (yrs)	0.090 0.43 79	1.000 0.0 79							
EDUC Education (yrs)	-0.233 0.04 79	-0.175 0.12 79	1.000 0.0 79						
INCOMCAT Income Category (1-5)	-0.209 0.07 75	-0.335 0.003 75	0.327 0.004 75	1.000 0.0 75					
DPD_YRS Drinks/day-years	0.083 0.47 79	-0.052 0.65 79	0.082 0.47 79	-0.090 0.44 75	1.000 0.0 79				
PX_HT Height	0.011 0.92 79	-0.260 0.02 79	0.147 0.20 79	0.171 0.14 75	0.088 0.44 79	1.000 0.0 79			
BMI Body Mass Index (kg/m2)	-0.021 0.86 79	-0.170 0.14 79	-0.060 0.60 79	0.101 0.39 75	0.035 0.76 79	0.075 0.51 79	1.000 0.0 79		
ARMTEMP Arm Temperature (°C)	0.081 0.48 78	0.022 0.85 78	-0.089 0.44 78	0.029 0.80 74	-0.119 0.30 78	-0.010 0.93 78	0.200 0.08 78	1.000 0.0 78	
LEGTEMP Leg Temperature (°C)	0.052 0.66 77	-0.016 0.89 77	0.131 0.26 77	-0.033 0.78 73	-0.197 0.09 77	0.182 0.11 77	0.123 0.29 77	0.335 0.003 77	1.000 0.0 77

Table 11. Descriptive Statistics for Physical Examination Outcomes by Exposure Group

			2,000 - 3,499		≥3,500		
	Unexposed (n = 84)		Lo (n = 47)		High (n = 32)		
	#	%	#	%	#	%	p-value*
Cranial nerve (>2 abn/equiv.)	13	15.5	5	10.6	3	9.4	0.370
Motor strength (>0 abn/equiv.)	2	2.4	0	0.0	4	12.5	0.012
Sensory (>2 abn/equiv.)	9	10.7	10	21.3	8	25.0	0.059
Deep tendon reflexes (>1 abn/equiv.)	16	19.1	8	17.0	7	21.9	0.743
Primitive reflexes (>1 abn/equiv.)	26	31.0	19	40.4	11	34.4	0.698
Coordination (>1 abn/equiv.)	15	17.9	8	17.0	11	34.4	0.055
Categories combined (>8 abn/equiv.)	12	14.3	5	10.6	11	34.4	0.013
Postural tremor (abn/equiv.)	15	17.9	10	21.3	12	37.5	0.025

*p-value associated with Mantel-Haenszel chi-square

Table 12. Descriptive Statistics for Nerve Conduction Outcomes by Exposure Group

	Urinary Lifetime Equivalent								
	0			2,000 - 3,499			> = 3,500		
	N	Mean	Std	N	Mean	Std	N	Mean	Std
Peroneal Motor NCV (m/s)	78	43.10	4.06	42	42.49	4.11	30	41.21	3.38
Peroneal Motor Amp. (muV)	80	3.72	2.27	43	4.14	2.13	30	3.33	1.94
Peroneal F-Wave Min (msec)	67	53.79	4.54	36	54.67	5.65	23	56.20	5.50
Ulnar Motor NCV (m/s)	82	57.67	3.39	46	56.47	4.26	31	55.99	4.21
Ulnar Motor Amp. (MuV)	82	9.51	1.74	47	9.95	1.62	31	9.99	2.99
Ulnar Sensory NCV (m/s)	75	50.96	3.78	41	51.28	5.04	29	50.15	5.73
Ulnar Sensory Amp. (muV)	75	13.68	6.09	41	14.76	7.35	29	14.96	4.30
Ulnar F-Wave Min (msec)	80	30.45	2.03	46	30.98	2.27	30	30.97	1.76
UM* Tibial Motor NCV (m/s)	52	45.00	3.75	26	45.12	4.67	32	43.94	5.80
UM Sural Distal Latency (msec)	49	3.62	0.38	26	3.65	0.33	32	3.73	0.34
UM Ulnar Motor NCV (m/s)	52	58.63	4.16	26	58.77	5.41	32	55.97	4.65
UM Ulnar Sensory NCV (m/s)	52	58.42	5.62	26	58.85	5.24	29	57.31	6.20
UM Median Sensory NCV (m/s)	52	56.75	3.85	26	56.19	4.29	31	55.65	5.43

*UM = University of Michigan

Table 13. Descriptive Statistics for Sensory-motor Outcomes by Exposure Group

	Cumulative Mercury Exposure Group								
	0			2,000 - 3,499			> = 3,500		
	N	Mean	Std	N	Mean	Std	N	Mean	Std
Contrast Sensitivity E	84	3.50	1.84	47	3.87	2.03	32	3.72	1.49
Vib. Threshold Digit 2 (log mu)	81	0.51	0.32	39	0.43	0.33	29	0.52	0.35
Vib. Threshold Digit 5 (log mu)	81	0.50	0.38	39	0.47	0.38	29	0.50	0.30
Vib. Threshold Gr. Toe (log mu)	81	1.87	0.33	39	1.81	0.47	28	2.02	0.22
Grip Avg (kg)	84	40.35	8.05	47	41.07	10.39	32	40.61	8.74
Lateral Pinch (kg)	84	9.46	1.97	47	9.73	1.79	32	9.74	1.77
Palmar Pinch (kg)	84	8.98	1.99	47	9.24	1.97	32	9.24	1.74
Sway Speed Eyes Open (cm/sec)	78	1.01	0.50	47	1.05	0.35	31	0.97	0.33
Sway Speed Eyes Closed (cm/sec)	78	1.61	0.86	46	1.63	0.57	31	1.61	0.74
Tremor Accel. (m/sec^2)	84	0.16	0.09	47	0.18	0.16	32	0.19	0.10
(log m/sec^2)	84	2.15	0.19	47	2.16	0.24	32	2.22	0.20
UM* Vibration Finger	70	7.68	3.07	38	8.13	2.16	32	7.75	2.37
UM Vibration Toe	70	14.09	4.58	38	15.82	4.91	31	13.81	5.06
UM Grip (kg)	69	45.23	7.39	38	43.61	9.53	32	46.91	6.57
UM Tremor RMS Acceleration	69	0.79	0.33	38	0.75	0.34	32	0.81	0.29
UM Tremor RMS Displacement	69	0.84	0.23	38	0.84	0.27	32	0.79	0.25

*UM = University of Michigan

Table 14. Descriptive Statistics for Neurobehavior Outcomes by Exposure Group

	Cumulative Mercury Exposure Group								
	0			2,000 - 3,499			> = 3,500		
	N	Mean	Std	N	Mean	Std	N	Mean	Std
Handeye Avg Log RMSE	82	2.33	0.33	53	2.40	0.41	28	2.41	0.29
Reaction Time Avg Lat (msec)	83	263.89	67.32	53	270.44	62.58	28	254.67	45.66
Finger Tapping # Pref. Hand	82	129.52	37.49	53	129.09	35.53	28	127.21	40.05
Grooved Pegboard (sec)	82	93.49	25.19	52	91.87	16.07	28	96.57	25.19
Trails A Lat. (sec)	83	41.83	16.26	53	40.60	11.90	28	38.54	13.33
Trails B Lat. (sec)	83	90.54	32.02	53	92.25	34.02	28	94.57	37.30
Symbol-Digit Avg Lat	81	4.02	1.54	53	3.78	0.94	28	3.88	1.13
Pattern Memory # Correct	82	6.66	1.81	52	6.51	1.88	28	6.29	1.51
Ser. Dig. Lrn. Log Error Score	82	2.68	1.47	53	2.96	1.33	28	2.47	1.76
CVLT Acq. Total # Correct	83	33.23	9.12	53	34.34	9.94	28	34.57	8.63
DRS Total Score (1-145)	83	133.95	7.73	53	135.38	6.59	28	132.39	6.53
Vocabulary # Correct	83	15.45	5.86	53	16.98	5.50	28	16.96	5.32
Mood Scales:									
Tension	80	2.22	0.71	53	2.33	0.64	26	2.35	0.77
Depression	80	1.84	0.67	53	1.88	0.65	26	1.78	0.49
Anger	80	1.67	0.59	53	1.69	0.71	26	1.52	0.56
Fatigue	80	2.72	0.74	53	2.86	0.70	26	2.86	0.63
Confusion	80	2.26	0.64	53	2.16	0.54	26	2.18	0.55
Mood Avg. Score*	80	2.14	0.52	53	2.19	0.52	26	2.14	0.40

*Higher score indicates poorer performance

Table 15. Summary of Linear Model Results for Selected Outcomes

		Parameter estimates (& p-values) for Exposure Variable				
Dependent Variable	Covariates**	HG Status	Cumul. HGU (mgHg/l)	Peak HGU (mgHg/l)	# Peaks >0.6	1 Peak >0.6
Peroneal NCV (m/s)	Age, height, dpd_yrs, [BMI, leg temperature]	-1.115 (0.073)	-0.307 (0.053)	-1.296 (0.098)	-0.715 (0.065)	-0.993 (0.174)
Peroneal F-Wave (msec)	Age, height, [BMI,leg temperature, dpd_yrs]	1.240 (0.112)	0.393 (0.049)	1.932 (0.057)	0.977 (0.058)	0.790 (0.392)
Ulnar NCV	Age, [height, BMI, arm temperature, dpd_yrs]	-1.578 (0.006)	-0.461 (0.002)	-1.666 (0.024)	-0.405 (0.273)	-0.766 (0.272)
Tremor acceleration RMS (log_{10} mm/sec^2)	Age, [height, BMI, dpd_yrs]	0.014 (0.070)	0.011 (0.166)	0.015 (0.671)	0.000 (0.979)	0.010 (0.767)
Handeye Coordination log RMS error	Age, visual acuity, tryhard, [education, dpd_yrs]	0.096 (0.044)	0.026 (0.036)	0.081 (0.166)	0.023 (0.456)	0.050 (0.392)
Simple Reaction Time (msec)	- [age, visual acuity, tryhard, education, dpd_yrs]	-1.099 (0.911)	-0.767 (0.796)	2.260 (0.851)	3.621 (0.568)	9.673 (0.413)
LOGISTIC REGRESSION:						
Px Exam: total # of abnormalities >8	Age, [height, BMI, dpd_yrs]	0.591 (0.181)	0.22 (0.042)	1.03 (0.045)	0.620 (0.010)	1.048 (0.029)
Dx Peripheral Neuropathy	Age, [height, BMI, dpd_yrs]	0.621 (0.099)	0.208 (0.026)	0.698 (0.122)	0.313 (0.152)	0.606 (0.150)
Dementia (DRS<128)	Age, education, [dpd_yrs]	0.239 (0.647)	0.114 (0.391)	0.149 (0.822)	-0.137 (0.739)	-0.014 (0.983)

**All covariates in the original model are listed. Those in brackets were not retained in the final models.

Table 16. **Comparison of Selected Demographic, Exposure, and Outcome Variables (Measured in 1986) for Those Examined and Not Examined in the Current Study by Exposure Status**

	Exposed						Unexposed					
	New (n = 15)		Examined (n = 89)		Not Examined (n = 158)		New (n=18)		Examined (n = 83)		Not Examined (n = 172)	
Variable	mean	std	mean	std	mean	std	mean	std	mean	std	mean	std
Demographic												
Age in 1986	61.17	6.90	61.56	5.54	65.65	7.60	61.94	6.30	63.30	6.62	64.79	7.69
Education			12.45	1.96	11.30	2.58			11.98	2.45	11.60	2.72
Vocabulary			17.78	4.11	15.45	4.73			16.95	4.68	16.42	4.72
Current drinker			34.8%	n = 31	20.9%	n = 33			28.9%	n = 24	34.9%	n = 60
Drink intensity*			5.45	3.96	5.88	5.00			6.75	5.33	6.87	5.14
Current smoker			20.2%	n = 18	27.2%	n = 43			19.3%	n = 16	22.1%	n = 38
Smoke intensity**			2.17	0.77	2.27	0.97			2.25	1.00	2.50	1.06
Exposure:												
HGDUR	9.20	4.75	21.03	8.51	21.08	9.10						
HGU	1946.00	401.47	3600	1094	3592	1245						
HGURATE	257.29	145.07	193.27	84.42	203.81	112.02						
HGPAV	3.0	2.07	3.68	2.27	3.47	2.61						
HGPAV2	0.67	0.81	0.70	0.95	0.78	1.07						
HGPEAK	738.40	483.13	617.6	283.6	664.8	410.0						
Outcome:												
Tibial Motor NCV			44.38	4.96	43.54	4.19			44.66	3.97	43.89	4.48
Ulnar Motor NCV			57.44	4.92	57.17	4.48			58.27	4.39	57.40	4.88
Tremor Acceleration RMS			0.78	0.30	0.95	0.57			0.80	0.33	0.82	0.31
Handeye Coord. Error			1.89	0.36	2.05	0.44			1.80	0.38	1.93	0.40
Simple React. Time			379.62	60.26	379.5	57.18			363.94	43.44	374.64	60.06
Polyneuropathy			6.7%	n = 6	17.7%	n = 28			6.0%	n = 5	21.5%	n = 37

*drinks per week; **packs per day

Table 17. Comparison of Exposure Effects for Selected Outcomes from the Michigan Study for and the Present Study for Subjects Who Participated in Both Studies

	Urinary Lifetime Equivalent									
	0			2,000 - 3,499			> = 3,500			Standardized Regression Coefficient
	N	Mean	Std	N	Mean	Std	N	Mean	Std	
UM* Tibial Motor NCV (m/s)	45	44.80	3.86	25	45.08	4.55	26	44.42	6.16	0.001
Peroneal Motor NCV (m/s)	45	42.86	3.79	25	43.00	4.37	26	41.35	3.43	-0.037
UM* Ulnar Motor NCV (m/s)	48	58.58	4.43	29	58.17	5.96	27	56.19	4.57	-0.221
Ulnar Motor NCV (m/s)	48	56.58	4.41	29	55.76	4.49	27	56.23	4.25	-0.199
UM* Handeye Coord. Log Avg Error	66	1.75	0.34	42	1.89	0.38	28	1.91	0.41	0.150
Handeye Coord. Trimmed Mean Log RMSE	66	2.35	0.34	42	2.43	0.40	28	2.41	0.29	0.144
UM* React Time avg Lat/msec	62	258.24	39.37	42	283.92	52.55	28	286.55	76.89	0.213
Reaction Time Avg Lat (msec)	66	258.63	55.84	42	278.28	67.77	28	254.67	45.66	0.002
UM* One-Hole (# Pins)	64	30.50	5.99	40	29.66	6.57	28	29.02	5.21	-0.094
Grooved Pegboard (sec)	64	94.14	24.89	40	92.10	16.96	28	96.57	25.19	-0.012
UM* Tremor RMS Acceleration	69	0.79	0.33	38	0.75	0.34	32	0.81	0.29	-0.014
Tremor RMS Acceleration	69	0.16	0.10	38	0.18	0.18	32	0.19	0.10	
Tremor $\log_{10}$ RMS*1000	69	2.15	0.19	38	2.17	0.24	32	2.22	0.20	0.111

*UM = University of Michigan

APPENDIX A

Neurologic Physical Examination Data Sheet

Oak Ridge Study Neurologic Physical Examination Data Sheet

Date: ___/___/___ Participant ID: _____

Time: ___:___ Examiner: _____

Height: ____ in. Weight: _____ lbs. BP: _____/_____ mmHg Pulse: ____ bpm

A. Cranial nerves:		Normal	Equiv.	Abnormal
Olfactory	Left	O	O	O
	Right	O	O	O
Visual fields		O	O	O
Extraocular movement	Left	O	O	O
	Right	O	O	O
Trigeminal	Left	O	O	O
	Right	O	O	O
Facial	Left	O	O	O
	Right	O	O	O
Hearing	Left	O	O	O
	Right	O	O	O
Glossophar. (uvula)		O	O	O
Vagus (gag)		O	O	O
Accessory (shrug)	Left	O	O	O
	Right	O	O	O
Hypoglossal (tongue)		O	O	O

B. Motor:			Normal	Equiv.	Abnormal
Wrist	Flexion:	Left	O	O	O
		Right	O	O	O
	Extension:	Left	O	O	O
		Right	O	O	O
Elbow	Flexion:	Left	O	O	O
		Right	O	O	O
	Extension:	Left	O	O	O
		Right	O	O	O
Shoulder	Abduction:	Left	O	O	O
		Right	O	O	O
	Adduction:	Left	O	O	O
		Right	O	O	O
Ankle	Dorsiflexion:	Left	O	O	O
		Right	O	O	O
	Plantarflexion:	Left	O	O	O
		Right	O	O	O
Knee	Flexion:	Left	O	O	O
		Right	O	O	O
	Extension:	Left	O	O	O
		Right	O	O	O
Hip	Flexion:	Left	O	O	O
		Right	O	O	O

(OVER)

C. Sensation:			Normal	Equiv.	Abnormal
Vibration:	Finger	Left	O	O	O
		Right	O	O	O
	Toe	Left	O	O	O
		Right	O	O	O
Proprioception:	Finger	Left	O	O	O
		Right	O	O	O
	Toe	Left	O	O	O
		Right	O	O	O
Pinprick:	Finger	Left	O	O	O
		Right	O	O	O
	Toe	Left	O	O	O
		Right	O	O	O
Light Touch:	Finger	Left	O	O	O
		Right	O	O	O
	Toe	Left	O	O	O
		Right	O	O	O

D. Deep Tendon Reflexes		Normal	Dimin.	Absent	Brisk
Biceps	Left	O	O	O	O
	Right	O	O	O	O
Ankle	Left	O	O	O	O
	Right	O	O	O	O
Knee	Left	O	O	O	O
	Right	O	O	O	O

E. Release Signs		Absent	Equiv.	Present
Babinski sign	Left	O	O	O
	Right	O	O	O
Glabellar tap		O	O	O
Snout		O	O	O
Root		O	O	O
Palmomental	Left	O	O	O
	Right	O	O	O

F. Movement and Coordination		Normal	Equiv.	Abnormal
Romberg		O	O	O
Tandem gait		O	O	O
Resting tremor		O	O	O
Postural tremor		O	O	O
Finger-to-nose	Left	O	O	O
	Right	O	O	O
Rapid alt. movements	Left	O	O	O
	Right	O	O	O

NOTES:

APPENDIX B

Nerve Conduction Form

Oak Ridge Study Nerve Conduction Testing Data Sheet

Date: ___/___/___ Participant ID: _____

Time: ____:____ Examiner: _____

Start temperature: Leg: _____°C Arm: _____°C

	Peroneal Motor	Peroneal F-Wave	Ulnar Motor	Ulnar F-Wave	Ulnar Sensory
Distal:					
Distance	_____ cm	_____ ms	_____ cm	_____ ms	_____ cm
Velocity		_____ ms		_____ ms	_____ m/s
Latency	_____ ms		_____ ms		_____ ms
Amplitude	_____ mV		_____ mV		_____ μV
Proximal:					
Distance	_____ cm		_____ cm		
Velocity	_____ m/s		_____ m/s		
Latency	_____ ms		_____ ms		
Amplitude	_____ mV		_____ mV		

End Temperature: Leg: _____°C Arm: _____°C

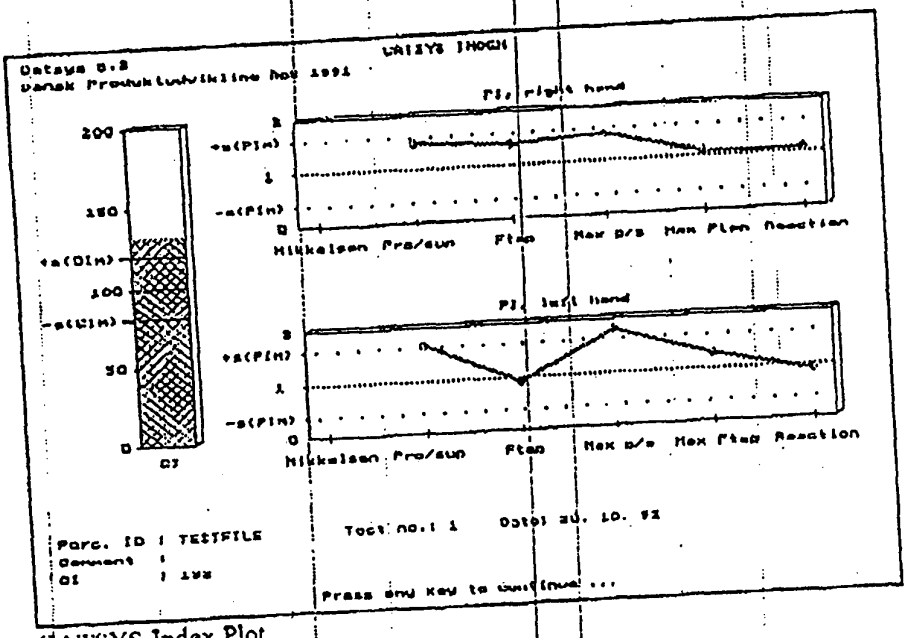
End time: ____:____

REMARKS:

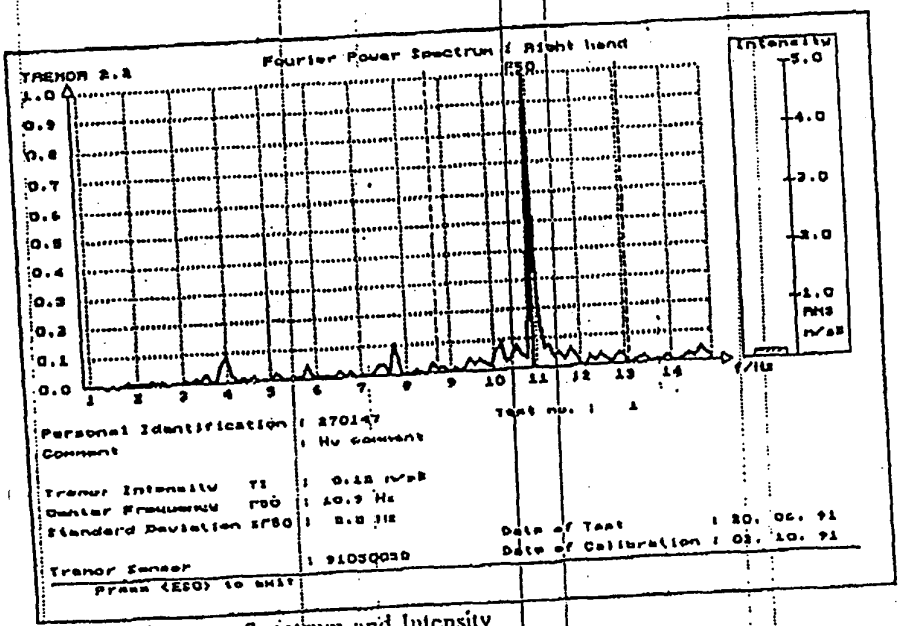
APPENDIX C

CATSYS User's Manual

QUANTITATIVE COORDINATION ABILITY
and
TREMOR ANALYSIS



CATSYS Index Plot



TREMOR Power Spectrum and Intensity

A SHORT PRESENTATION OF THE CATSYS COORDINATION - and TREMOR TEST SYSTEM

CATSYS means Coordination Ability and Tremor Test System. It is designed for quantifying coordination performance and tremor patterns.

The CATSYS test system consists of a few sensors, a microprocessor-based data recorder and a comprehensive state-of-the-art menu driven program system including a number of graphic data presentation and statistic facilities.

When should you think about quantifying coordination and tremor ?

- If you examine and treat patients with neurological diseases
- If you study neurotoxic effects from occupational exposure to hazardous chemicals
- If your scientific projects include examination of coordination performance or tremor patterns
- If you need to follow the development of symptoms with time
- If you need to establish the effect of drugs, used in the treatment of diseases with dyscoordination or increased tremor as symptoms
- If you need to know whether your patient's coordination or tremor is improving or getting worse
- If you need to know whether your patient's coordination ability or tremor is normal or abnormal.

The advantages of the CATSYS test system

- The system allows quick and efficient screening of subjects. This will save time and simplify case recording. On the same time CATSYS is powerfull in supervision of individual patients
- Clinic tests are standardized which means that results are no longer depending on qualitative estimates
- Tests can be carried out by all personnel categories after a minimum of training
- The system generates data, accessible from PC-based statistic program-

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systems and database-systems, which combined with fast individual tests makes the CATSYS test system very suitable for scientific projects involving screening of large populations

- A comprehensive reference material is available and integrated into the systems software, which automatically compares your patients performance to normal performance and calculate an index

The system is based on a number of well established clinic coordination tests, used for examining patients who suffer from cerebral dysfunction, brain damage, neurologic diseases, etc., where dyscoordination or tremor is an important symptom.

The CATSYS program allows the operator to carry out tests, to analyze test-results of individual tests, to store data, to review large amounts of data and to develop new user-specified coordination tests.

Who are Danish Product Development Ltd

DPD is a spin-off company from the Technical University of Denmark, which has developed a PC-Computer based instrument for quantifying coordination ability and tremor. Development took place in close cooperation with The Occupational Health Clinic, The National Research Hospital, Copenhagen.

What do we sell

We hope in the near future to be able to offer you an efficiant tool for screening and for supervision within the field of neurologic diseases and drug development. In a collaborative effort together with a number of medical research groups, we are working to pave the way for this commercialisation. We still need a little more clinic experience before we are ready to release our test systems, but quite a number of projects are under way.

How to keep informed

Sign up on our mailing list in order to receive a newsletter, that will give you a review of findings, new projects, articles, application notes etc.

Best regards

John Heebøll
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QUANTIFIED COORDINATION ABILITY and TREMOR

Projects in progress or sceduled, June 1993

1. Index Analysis: CATSYS Index sensitivity to anesthetics and alcohol.
   Clinic of Occupational Health
   National Research Hospital, Copenhagen

2. Degradation of coordination ability with age.
   Clinical Physiological Dept.
   Frederiksberg Hospital, Copenhagen

3. Tremor and drugs for the Treatment of Glaucom
   Clinic of Eye Diseases
   Hvidovre Hospital, Copenhagen

4. Coordination Ability and Tremor versus Isolation
   European Space Agency
   Astronaute Centre, Köln

5. Sclerosis and Tremor
   Hvidovre Hospital, Copenhagen

6. Sclerosis and Tremor
   Neuromedical Dept. N
   National Research Hospital, Copenhagen

7. Coordination Ability and Tremor versus Focal Lesions, Parkinson's Disease and Multiple Sclerosis
   Boston University
   School of Medicine
   Department of Neurology

8. Coordination Ability of Children
   Occupational Health Clinic
   National Research Hospital, Copenhagen

9. Tremor Reference Data
   Occupational Health Clinic
   County Hospital of Copenhagen
   Glostrup

10. Mangane and Coordination Ability
    Occupational Health Clinic
    National Research Hospital, Copenhagen

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Reference list, scientific personel.

1. Dr.med. Finn Gyntelberg +45 35 45 73 83
Occupational Health Clinic
National Research Hospital
Rigshospitalet
Tagensvej
2200 København N

Several projects within occupational health, involving coordination ability examinations.

2. Dr.med. Peter Arlien Søborg +45 36 32 36 32
Dept. of Neuromedicine
Hvidovre Hospital
DK 2650 Hvidovre

Examination of lithographers' coordination ability and tremor

3. Dr.med. Flemming Bonde-Petersen +49 220 36 001 23
European Space Agency
Astronaut Center
Lindehöhe
D 5000 Köln

Examination of astronaut candidates' coordination ability and tremor during an isolation experiment.

4. Dr. Simon von Sprechelsen +45 36 32 36 32
Clinic of Eye Diseases
Hvidovre Hospital
2650 Hvidovre

Examination of tremor on subjects taking different types of drugs for the treatment of glaucom.

5. Dr.med. Sigurd Mikkelsen +45 42 96 43 33
Occupational Health Clinic
County Hospital of Copenhagen
DK 2600 Glostrup

Several research projects including coordination ability. Establishment of reference data, coordination ability and tremor.

6. Dr.med. Jesper Mehlsen +45 38 34 77 11
Clinical Physiological Department
Frederiksberg Hospital
Nordre Fasanvej 57
DK 2000 Frederiksberg

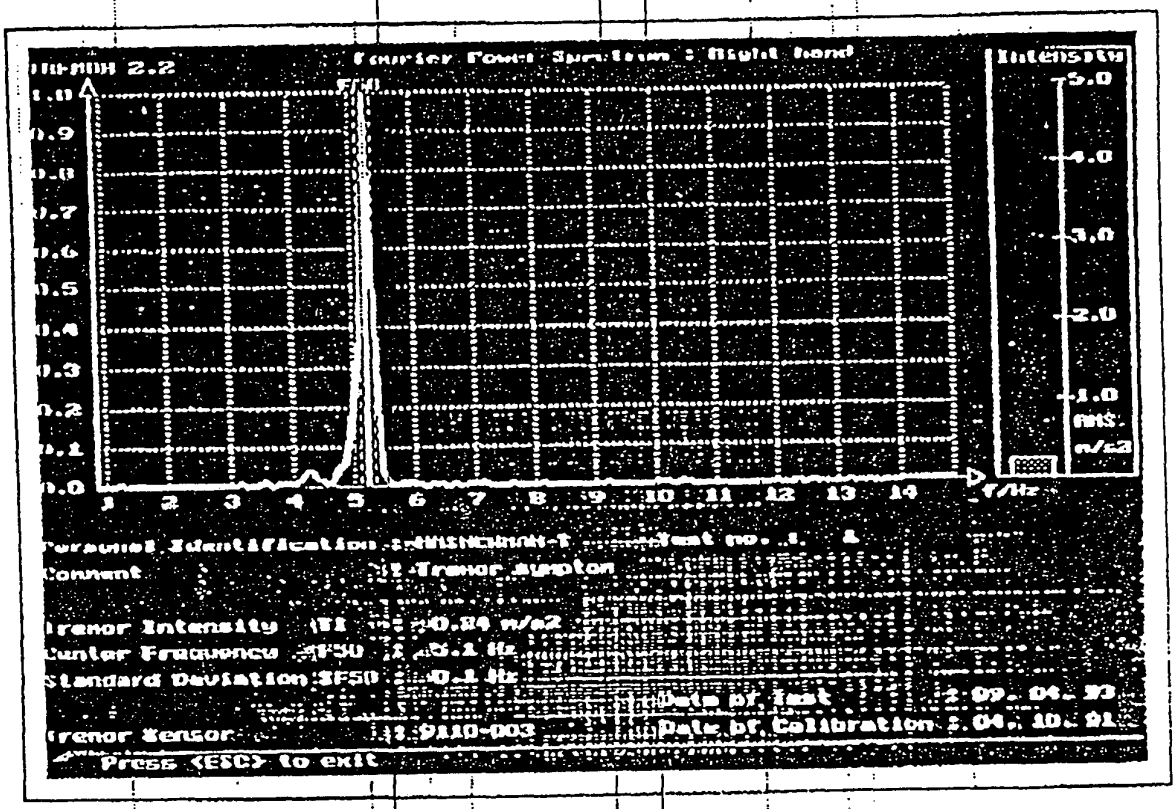
Investigation of coordiation ability degradation owing to senile decay.

7. M.Sc. John Heebøll +45 45 93 03 53
Danish Product development Ltd Fax +45 42 88 51 82
Stolbjergvej 19
DK 3070 Snekkersten

Development of CATSYS hard- and software. Definition and examination of CATSYS Index.

Danish Product Development

TREMOR SAMPLES



Recorded and analyzed with CATSYS 5 Datalogger and TREMOR 2 Program System

April 1993

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TREMOR SAMPLES 23. April 1993

The annexed screen-prints represent a collection of abnormal human tremors as recorded by CATSYS tremor equipment.

1. Normal tremor: notice the dyscoordinated Fourier spectrum, indicating a complex tremor without dominating harmonic contents. The centre frequency is in the middle of the spectrum: 6.8 Hz. The dispersion of the frequency contents is a typical 3.9 Hz. The tremor intensity is normal: 9 cm/sec².

2. Parkinson tremor recorded during an occupational health survey Copenhagen 1991: notice the dominating harmonic oscillation around 5.9 Hz and the high tremor intensity: 59 cm/sec².

3. Parkinson tremor of an elderly woman, right hand, recorded in Boston, 9. April 1993. Notice the dominating harmonic oscillation just below 5 Hz and a somewhat smaller just above 5 Hz.

4. Parkinson tremor, same subject, left hand. Notice again the twin peaks just below 5 Hz. More interesting however is the low tremor intensity, 11 cm/sec². This tremor is barely discernable: the intensity is normal, but the dominating harmonic contents around 5 Hz disclose an abnormal tremor. A test, unfortunately not recorded, produced same Fourier Spectrum at an intensity = 7 cm/sec², which is definitely outside the reach of qualitative observations.

5. Parkinson tremor of an elderly woman: Centre frequency 5.1 Hz is a very dominating harmonic oscillation. The intensity, 24 cm/sec² is visible allthough not very strong.

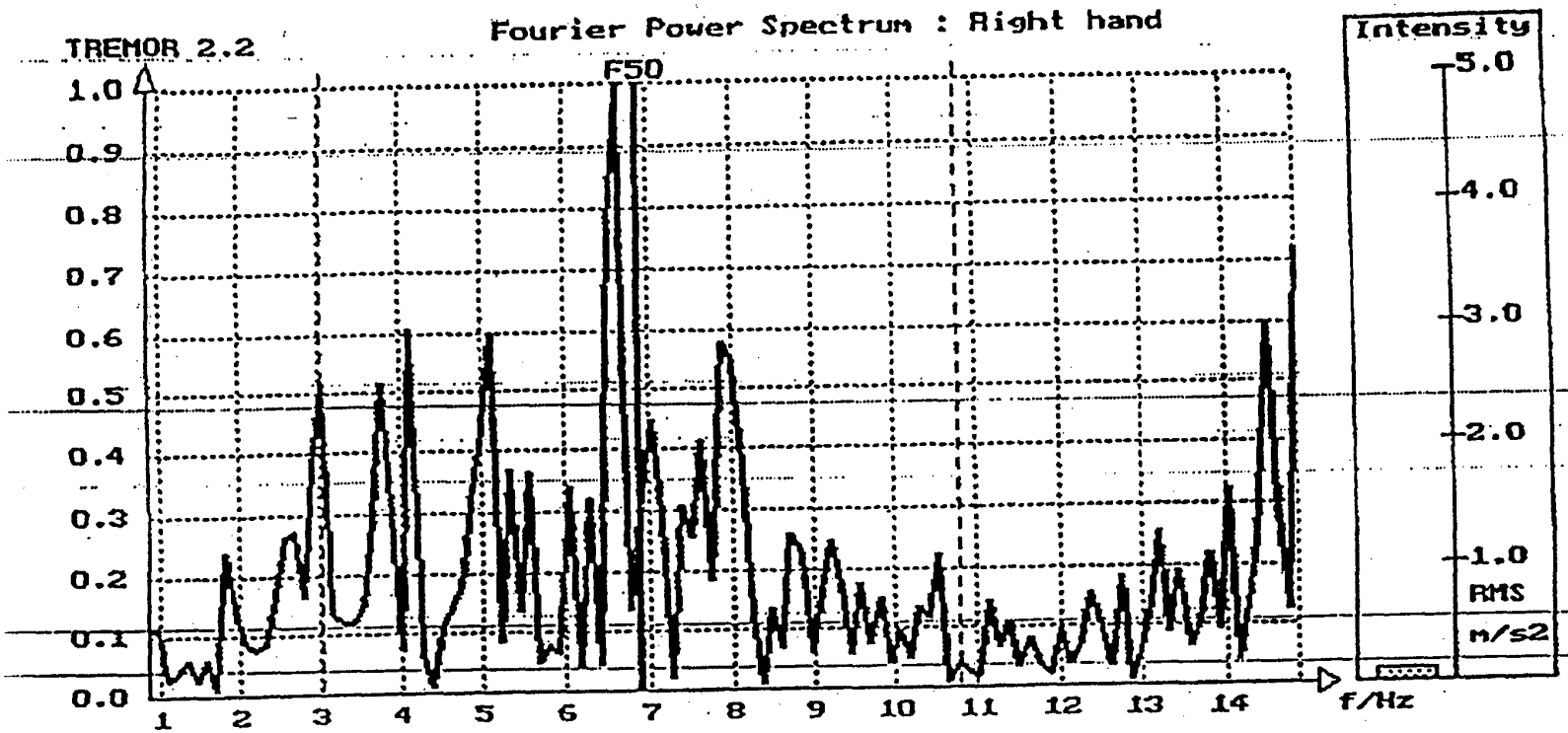
6. Parkinson tremor, same subject. Same dominating frequency. Intensity of the left hand tremor, 50 cm/sec² is twice as strong as the right hand intensity, which is in agreement with the qualitative estimate: this subject has a stronger left hand tremor compared to the right hand.

7. Ischias-tremor or inherited tremor? we don't know but we have not seen inherited tremors in the 11 Hz region before. Question from the lay observer: does ischias produce tremor?

8. Drug-induced tremor: a rather harmonic tremor with tremor intensity = 16 cm/sec², which is well above normal. This subject takes ventoline to dampen asthmatic symptoms.

9. Same subject, one week after taking medicine. Centre frequency and intensity are the same. However, the Fourier Spectrum has changed and reveals a tremor composed by many harmonic oscillations. In fact it looks as if the dyscoordinated normal pattern starts to develop. This spectrum inspired us to invent a dyscoordination index, quantifying the harmonic contents of the tremor.

Lyngby, 23. April 1993
John Heebøll



Personal Identification : 160642 0 Test no. : 1

Comment : No comment

Tremor Intensity TI : 0.09 m/s2

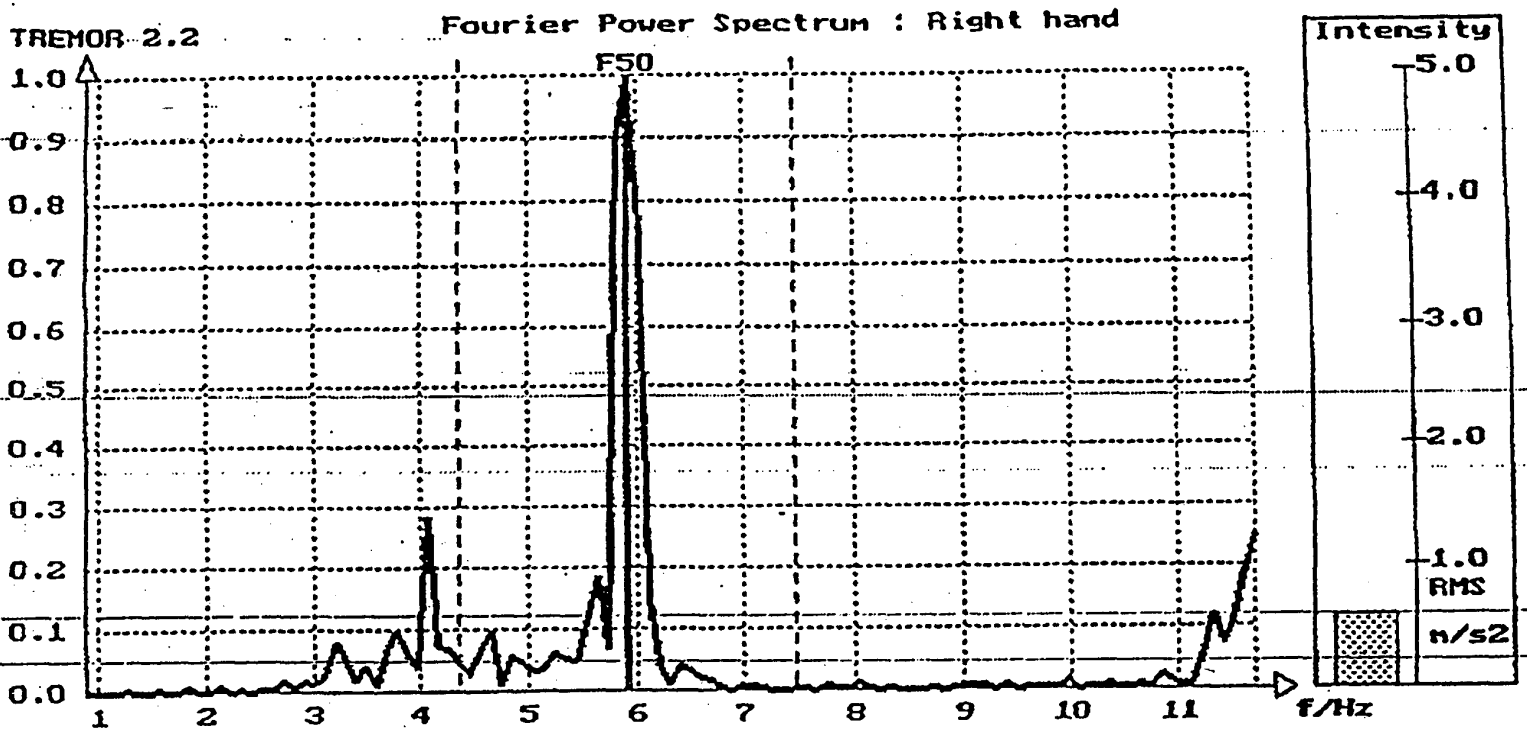
Center Frequency F50 : 6.8 Hz

Standard Deviation SF50 : 3.9 Hz

Date of Test : 17. 06. 91

Tremor Sensor : 9105005B Date of Calibration : 02. 10. 91

Press <ESC> to exit



Personal Identification : 190536 Test no. : 1

Comment : litografus

h parkinson obs

Trenor Intensity TI : 0.59 m/s2

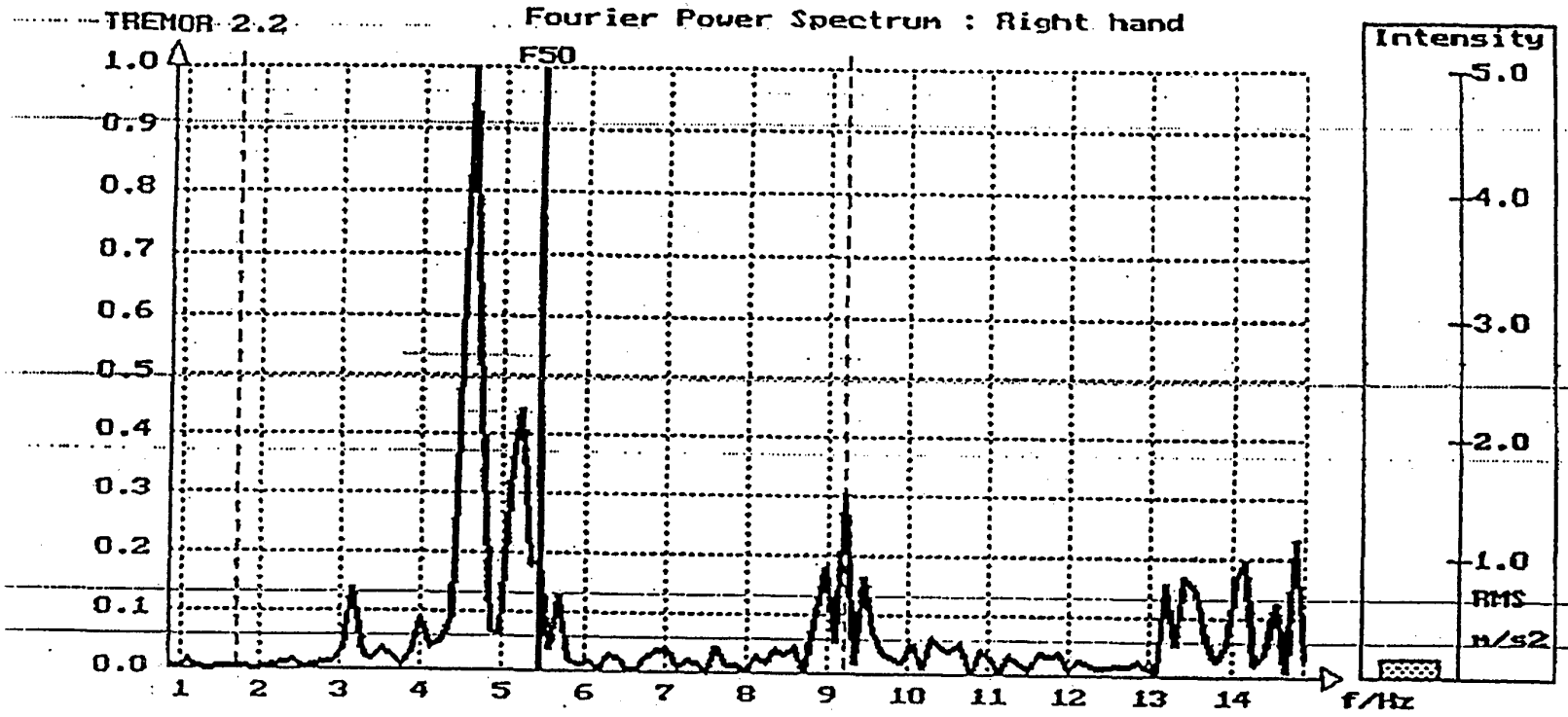
Center Frequency F50 : 5.9 Hz

Standard Deviation SF50 : 1.6 Hz

Date of Test : 07. 02. 91

Trenor Sensor : TR400PS Date of Calibration : 12. 05. 91

Press <ESC> to exit



Personal Identification : MRSLIVSTN-T Test no. : 1

Comment : Parkinson Tremor Test

Tremor Intensity TI : 0.15 m/s2

Center Frequency F50 : 5.4 Hz

Standard Deviation SF50 : 3.8 Hz

Date of Test : 09. 04. 93

Tremor Sensor : 9110-003 Date of Calibration : 04. 10. 91

Press <ESC> to exit

APPENDIX D

Vibrotactile Threshold Testing Protocol

INSTRUCTIONS FOR MEASURING VIBROTACTILE THRESHOLDS

BACKGROUND

The determination of vibrotactile threshold is a useful technique for identification of peripheral neuropathy. Vibratory stimuli are carried on large myelinated nerve fibers. These fibers are believed to be more sensitive to both diffuse and focal disruption than are fibers carrying other sensory information such as pain or temperature. As a result, abnormality of large fiber function may be the earliest sign of neurologic disease in an individual at risk. Many occupational and environmental hazards, including heavy metals, solvents, and organophosphate pesticides, can affect these fibers. Testing large fiber function may allow for early detection of neurotoxicity due to these and other agents.

The Vibratron II is a simple electromechanical vibrometer consisting of a controller unit and two identical transducer units that cause plastic posts protruding from their housings to vibrate. The intensity (amplitude) of the vibration is controlled by the OUTPUT knob on the face of the controller unit. The amplitude is provided in "Vibration Units" on a digital display on the face of the controller. The vibratron is a manually operated device and does not require computer interface for operation. It is relatively physically robust and readily portable. Set-up requires about 5 minutes. Each threshold requires about 2 minutes to obtain.

EQUIPMENT AND SUPPLIES

1. Vibratron II device:
   A. Controller unit
   B. Two identical transducer units
   C. Power cord
   D. Carrying case
2. Wood platform(s)
3. Multicolored foam pads
   A. Small (fits under transducer)
   B. Large (fits under wood platform)
4. Vibrotactile Threshold Data Recording Forms
5. Table and two chairs
6. Pad or sheet to insulate subject's feet during toe threshold measurements

TESTING CONDITIONS

Testing should be performed in a quiet, private setting with an electrical outlet for the Vibratron.

SET-UP

1. Plug the cords from the A and B transducers into the A and B connectors on the back of the controller unit.

2. Attach the power cord to the controller unit, plug it into an AC outlet, and place the POWER switch in the ON (up) position. The digital display should illuminate. Test the operation of the transducers by selecting the "20" (down) position on the RANGE switch and the "A" position (up) on the A-B transducer switch (the switch below the display closest to the OUTPUT knob). Turn the OUTPUT knob fully clockwise. Touch the post on the A transducer to determine whether it is vibrating. If post A is vibrating, select position "B" on the A-B transducer switch. Touch the post on the B transducer to determine whether it is vibrating. Select the "6.5" position on the RANGE switch and return the A-B transducer switch to the A position. (Note: The switch below the display furthest from the OUTPUT knob has no function.)

   If vibration is not present in either transducer, check all connections.

3. Determine the location for the transducer units. Testing of the upper-extremity requires that one be placed on a table. Testing of the lower extremity requires that one be placed on the floor. By convention, use transducer A for upper-extremity testing and transducer B for lower extremity-testing. Each transducer should be placed on one small multicolored foam pad.

   The wood platform is placed over the transducer so that the plastic post protrudes through the 7/8 inch hole. If the post does not extend above the surface by at least 1/16 of an inch, look to see if the wood platform is resting upon the power cord or other object. Depending upon the surface of the table or floor, it may be necessary to place a large foam pad under both the wood platform and transducer. This is necessary when using the device on a hard or uneven surface.

   When properly set-up, the transducer does not make any physical contact with the platform, thereby avoiding the possibility of transmitting vibration to the platform and, consequently, the subject.

TESTING PROCEDURE

1. Explain the procedure to the subject:

   > *"This is a test to see how well you can feel a slight vibration with your fingers [and toes]. The test is painless and risk-free. All you will be asked to do is tell me when you feel a slight vibration and when you don't."*

2. If testing of the great toe is to be performed, instruct the subject to remove his/her shoes and socks. A pad or sheet should be provided to the subject to prevent him/her from placing his/her bare feet on a cold floor.

3. Fill in the identifier information at the beginning of the data recording form, including the subject ID, date and time of the testing session.

4. Instruct the subject to place the finger (toe) to be tested on the transducer post and to rest his/her arm (foot) on the platform. Tell the subject:

> *"Just allow your finger (toe) to rest on the post. Do not press on the post, and do not lift your finger (toe). If you rest your palm (foot) flat on the platform, your finger (toe) will make good contact."*

The distal phalanx of the finger (toe) should completely cover the surface of the transducer post. The examiner assesses the contact pressure by grasping the finger (toe) and gently lifting it a couple of millimeters and releasing it. Finger (toe) contact is best maintained with only the elastic tension of the soft tissues of the finger. An alternate method of assessing contact pressure is to inspect the nailbed for blanching. The presence of blanching is an indicator of excessive pressure. Make sure that the post is not touching the wood platform.

5. Once correct contact pressure has been established, the examiner sets the vibration intensity at about 4.0 VU for the finger and about 7.0 VU for the toe. Ask the subject:

> *"Do you feel anything?"*

If the subject responds by saying "yes", ask:

> *"What do you feel?"*

If the subject responds by saying "vibration", "tingling", "buzzing" or other terms that indicate that (s)he feel the vibration, ask:

> *"Is the feeling of vibration clear to you?"*

If yes, proceed to #6 to administer the test.

If the subject responds by saying "no", increase the intensity by approximately 3 units, and ask again.

If the response is "yes", continue with #6 below. If the response is "no", increase the intensity by an additional 3 units, and ask again. If the response is "yes", continue with #6 below. If the response is "no", check to determine that the post is vibrating by touching it yourself. If the post is vibrating and the subject continues to respond negatively, turn the OUTPUT knob to the maximum intensity and ask the subject to respond again. If still unable to feel the vibration, mark >20 on the recording form and begin testing the next site. (Note: The maximum stimulus intensity available when the RANGE switch is in the 6.5 (up) position is about 7 VU. In order to increase the stimulus intensity past about 7 VU, you must move the RANGE switch to the "20" (down) position. If this is necessary, first turn the OUTPUT knob fully counter-clockwise, then change the RANGE. The lowest stimulation intensity on the 20 range is about 7 VU.)

6. Say to the subject:

> *"I will now decrease the vibration gradually until you can no longer feel it. When it is completely gone, you say 'gone'. Close your eyes and concentrate on your finger."*

Turn the OUTPUT knob gradually counter-clockwise until the subject says "gone". Turn the knob at the fastest rate that will still allow you to see each 0.1 VU change on the display when operated in the low (6.5) range, and each 0.2-0.4 VU change in the high (20) range. Record the value displayed on the digital readout as the first trial, and turn the OUTPUT knob so that the readout indicates a value at least 30% or 1.0 VU lower than the one recorded. Choose the value that lowers the threshold the most.

7. Say to the subject:

> *"Do you feel anything now."*

I the subject says "no", continue:

> *"I will now increase the vibration gradually until you can feel it again. When you first feel the vibration, say 'now'. Tell me as soon as you feel it, but be certain that it is the vibration that you feel."*

If the subject says "yes", reduce the OUTPUT by the amount specified in #6 above, and return to #7. If the subject continues to respond by saying "yes" to the question "Do you feel anything now" after the OUTPUT has been reduced to zero, follow procedure #4 under PROBLEMS AND PITFALLS below.

Turn the OUTPUT knob gradually clockwise until the subject says "now". Record the value displayed on the digital readout as the second trial and turn the OUTPUT knob clockwise so that the readout indicates a value 30% or 1.0 VU (which ever is larger) greater than the one just recorded.

8. Repeat steps #6 and 7 above to obtain a total of three descending and two ascending values. The remaining trials do not require as much explanation. The remaining 3 trials can be initiated by saying:

> *"Tell me when the vibration goes away"*

and

> *"Tell me when the vibration comes back"*

Always turn the knob at the same rate, but delay for varying intervals in the range of 0.5 - 2.0 seconds after saying: "Tell me when..." before starting to turn the knob. This will minimize the effect of timing cues in eliciting the subject's responses.

9. Proceed to test the next site indicated in the research protocol by returning to step #4 above.

10. Record the Vibratron serial number (found on the nameplate on the top of the controller unit) and transducer designation (A or B) on the data form for each site tested.

11. Administer the questionnaire concerning demographics, medical conditions associated with peripheral neuropathy, symptoms, and potential exposures, if these questions are not asked in other parts of your study protocol.

PROBLEMS AND PITFALLS

1. Incorrect contact pressure. The examiner must be vigilant and inspect the contact between the subject's finger or toe and the vibrating post frequently.

2. Post in contact with platform. While inspecting for proper contact pressure, the examiner should also determine that the contact post is centered in the hole in the platform and is not making contact with the platform.

3. Subject does not feel the vibration. In this situation, determine that vibration is present. Do this by touching the post. If vibration is not present, check all connections. Also, check that the A-B transducer switch on the Vibratron controller is in the correct position. The switch on the right is a dummy switch. The switch on the left controls which of the two transducers is operating.

4. Subject continues to feel vibration after the OUTPUT is decreased to zero. In this situation, ask the subject if he/she still feels vibration. If yes, say:

   "I understand that you may have a sensation in your finger, but it is not the vibration from the test."

   At that point, turn the vibration up to a clearly perceptible level, and ask the subject if he/she feels anything. After the subject responds with an affirmative response, switch the vibratron off and ask if it went away. Switch the unit off and on several times and ask the subject to tell you when vibration is present and when it is not present. In this manner the subject will be better able to identify the stimulus. Attempt to test the subject in the usual manner. If the problem continues, document the problem on the data recording form, and move on to the next site to be tested.

5. Subject has a threshold near 7.0 units. In order to increase or decrease the stimulation intensity above or below 7 VU, it is necessary to move the range switch to the correct position. When performing an ascending trial, turn the OUTPUT knob fully counter-clockwise, then switch to the higher range. When performing a descending trial, switch to the lower range first, then turn the knob fully clockwise. With practice, the maneuver will be smooth, and the testing sequence will be minimally interrupted. Also, on some Vibratrons turning the knob clockwise from the full counter-clockwise position in the higher range causes an initial decrease in the VUs displayed before beginning to increase with more rotation. Do not be alarmed by this; just record the readings as they appear on the display.

THRESHOLD CALCULATION

In order to calculate a threshold, the first (descending) value is always discarded as are the highest and the lowest of the remaining four values. The threshold (in Vibration Units) for the site is the average of the remaining two values. The threshold can be

converted to more useful units (*e.g.*, microns) after each of the transducers is measured and calibration constants estimated.

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APPENDIX E

Grip Strength Dynamometry Testing Protocol

INSTRUCTIONS FOR GRIP STRENGTH TESTING

BACKGROUND

Measurement of grip and pinch strength provides useful information about the functional integrity of the voluntary motor system from motor cortex in the brain to the skeletal muscles in the periphery. Impulses for voluntary contraction of skeletal muscles are carried on large, myelinated nerve fibers with cell bodies located in the anterior horn of the spinal cord. In occupational and environmental health settings, the most common disorder affecting grip and pinch strength is sensory-motor axonopathy.

Grip strength is assessed with the Jamar dynamometer. It is a self-contained mechanical/hydraulic device that records on a dial the maximum force exerted by the subject's "power" or whole-hand grip. It is equipped with a "tell-tale" that retains the maximum excursion of the force indicator needle. It is used commonly by physical medicine and rehabilitation specialists for evaluation of patients with motor abnormalities.

Pinch strength is assessed with the B&L pinch strength gauge. It is a fully mechanical device that records on a dial the maximum force exerted by the subject with any of three types of pinch (tip, key and palmar). Like the Jamar dynamometer described above, it is also equipped with a "tell-tale" needle that retains the maximum excursion of the force indicator needle.

The devices are manually operated. Data are recorded either by writing the observed values on a data form or by direct entry into a personal computer. A full set of grip and pinch strength measurements requires approximately 4 minutes. The equipment requires no set-up. The devices are relatively robust, but may be damaged or loose calibration if dropped. They are easily transported.

EQUIPMENT & SUPPLIES

1. Jamar dynamometer
2. B&L pinch strength gauge
3. Grip and pinch strength data recording forms or IBM-PC-compatible computer with the data entry software installed
4. Table and 2 chairs (armless chair for subject)
5. Foam pad to cushion table top.

TESTING CONDITIONS

Testing should be performed in a quiet, private room.

SET-UP

1. Position the two chairs facing each other.

TESTING PROTOCOL

A. Grip strength measurement.

1. Make sure the Jamar dynamometer is set to the second smallest handle position.
2. Turn the chrome center knob fully counter-clockwise to set the red "tell-tale" needle to zero.
3. The subject should be seated during the entire testing sequence.

   Explain the procedure to the subject while (s)he sits in the chair.

   > *"We will be testing the strength of your hand grip and finger pinch."*

4. a. *Manual data recording*: Record all relevant information about the subject and testing session on the data sheet.

   b. *Computer-assisted data recording*: At the DOS "C:\>" prompt, type the command:

   ```
   GRIP
   ```

   and press <enter>. The computer should respond with a copyright message and then issue a prompt for a subject id. Follow the on-screen instructions. To abort the program at any time, type Ctrl-Break or Ctrl-C. If the computer asks "`Terminate batch job (Y/N)?`", answer "N".

5. Say to the subject as you demonstrate the proper arm position and grip:

   > *"I want you to hold the handle like this and squeeze as hard as you can. Let me show you."*

After demonstrating, say:

> *"We want everyone to do this in exactly the same way, so follow my instructions."*

6. Place the dynamometer strap around the wrist of the subject's dominant hand, and hand the device to the subject with the dial positioned upward.

   Instruct and manipulate the subject such that her/his:

   - arm is lightly touching her/his side her/his forearm is pointed forward, parallel to the floor (shoulder is adducted and neutrally rotated),
   - elbow is bent at 90° (90° elbow flexion),

- forearm is in neutral position, meaning that a pencil held in the subjects fist would be vertical in orientation (forearm is neither supinated nor pronated)

- wrist is straight so that 1) the dynamometer is held in-line with the forearm (negligible flexion or extension) and 2) no bending of the wrist towards the thumb or little finger occurs (negligible radial or ulnar deviation).

With the subject holding the dynamometer in her/his hand, say:

> *"When I tell you to begin, I want you to squeeze as hard as you can. Ready, begin NOW."*

As the subject begins to squeeze, say:

> *"Harder! ... Harder! ... Relax."*

The duration from "NOW" to "Relax" is approximately three seconds. With the subject holding the dynamometer loosely, read the position of the red indicator needle to the nearest kilogram (the ***outer*** number on the scale) and record the reading at the appropriate position on the recording form. Turn the center chrome knob counter-clockwise to reset the red indicator needle to zero.

7. Then say to the subject:

> *"We are going to repeat the test two more times. Ready, begin NOW."*

As the subject begins to squeeze, say:

> *"Harder! ... Harder! ... Relax."*

Record the second value and reset the dynamometer as described above.

8. Then say to the subject:

> *"One more time. Ready, begin NOW."*

As the subject begins to squeeze, say:

> *"Harder! ... Harder! ... Relax."*

Record the third value and reset the dynamometer as described above.

9. If testing of the non-dominant side is required, place the dynamometer strap around the non-dominant wrist and return to instruction #6.

10. Place the dynamomter back in its case.

B. Palmar (three-jaw) pinch strength measurement.

11. The seating position is unchanged.

Remove the pinch gauge from its case and set it to zero in the following manner: Grasp the pinch gauge from the sides, behind the dial. Turn the silver metal ring that surrounds the dial so that the black needle is aligned with the 0 (zero) mark. Then, turn the center knob counter-clockwise to set the red indicator needle to zero. Proceed with testing.

12. Say to the subject as you demonstrate the proper position:

    "I want you to place your thumb on one side and your first two fingers on the other side as I'm doing and pinch as hard as you can when I tell you to."

    Demonstrate the proper position.

13. Hold the pinch gauge with your non-dominant hand by its sides, behind the dial, in a vertical position. The gauge is always held in your non-dominant hand so that you can record the results with your dominant hand. Present it to the subject so the her/his arm is neither supinated nor pronated. Test the dominant side first. Do not let go of the gauge. The subject should place his/her fingers in the proper position. Verify the subject's proper pinch position by observation. Say:

    "When I tell you to begin, I want you to squeeze as hard as you can. Ready, begin NOW."

    As the subject begins to squeeze, say:

    "Harder! ... Harder! ... Relax."

14. Withdraw the gauge from the subject, read the position of the red indicator needle to the nearest kilogram (the ***inner*** number on the scale) and record the reading at the appropriate position on the recording form. Because the red needle is relatively wide, read the value indicated by the side closer to zero. Turn the center chrome knob counter-clockwise to reset the red indicator needle to zero.

15. Say to the subject:

    "We are going to repeat the test two more times."

16. Present the gauge to the subject in the manner described above. When you observe the proper position of the fingers, say:

    "Ready, begin NOW."

    As the subject begins to squeeze, say:

    "Harder! ... Harder! ... Relax."

    Record the second value and reset the pinch gauge as described above.

17. Then say to the subject:

    "One more time. Ready, begin NOW."

    As the subject begins to squeeze, say:

"Harder! ... Harder! ... Relax."

Record the third value and reset the pinch gauge as described above.

18. If testing of the non-dominant side is required, begin the same protocol at instruction #13.

C. Key (lateral) pinch strength measurement.

19. Say to the subject as you demonstrate the proper position:

"Now, I want you to place your thumb on top and your index finger below as I'm doing and pinch as hard as you can when I tell you to."

20. Hold the pinch gauge horizontally with your non-dominant hand by its sides, behind the dial, in a horizontal position. Present it to the subject so that his/her arm is neither supinated nor pronated. Do not let go of the gauge. The subject should place his/her fingers the in proper position. Verify the subject's proper pinch position by observation. Say:

"When I tell you to begin, I want you to squeeze as hard as you can. Ready, begin NOW."

As the subject begins to squeeze, say:

"Harder! ... Harder! ... Relax."

21. Withdraw the gauge from the subject, read the position of the red indicator needle to the nearest kilogram (the ***inner*** numbers on the scale) and record the reading at the appropriate position on the recording form.

22. Say to the subject:

"We are going to repeat the test two more times."

23. Present the gauge to the subject in the manner described above. When you observe the proper position of the fingers, say:

"Ready, begin NOW."

As the subject begins to squeeze, say:

"Harder! ... Harder! ... Relax."

Record the second value and reset the pinch gauge as described above.

24. Then say to the subject:

"One more time. Ready, begin NOW."

As the subject begins to squeeze, say:

"Harder! ... Harder! ... Relax."

Record the third value and reset the pinch gauge as described above.

25. If testing of the non-dominant side is required, begin the same protocol at instruction #20.

26. Place the pinch gauge back in its case.

DATA BACK-UP:

If you are using the computer-assisted data collection method, you should make two floppy diskette copies of the data on the hard disk at the end of each testing day. To do this, you will need two previously formatted diskettes. Place the first in the "A:" drive, and issue the command:

```
BACKGRIP
```

This should cause all the data files not previously copied to the diskette to be copied to it. The program will then ask you to replace the first backup diskette with the second. After you hit any key to go on, it will copy the files to the second diskette. Store the two diskettes in separate places until the next time for backup.

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APPENDIX F

Postural Sway Testing

INSTRUCTIONS FOR MEASURING POSTURAL STABILITY

by Fredric Gerr and Richard Letz

BACKGROUND

Measurement of postural stability allows for assessment of the integrated function of several components of the nervous system, including the vestibular apparatus, cerebellum, and proprioceptive system. Loss of functional integrity of any of these systems secondary to disease or toxic exposure may affect postural stability.

The NTI Postural Sway Analyzer assesses postural stability by determining the location of the subject's head in the X-Y plane, in real time, and storing the information. The device utilizes a sound source attached to a lightweight headset that is worn by the subject. A dedicated portable computer allows precise estimation of the distance of the sound source from a stationary receiver unit. The path of the sound source (and, therefore, the subject's head) is plotted on the computer video screen. The length and velocity of the sway path over a standard time period (*e.g.*, 60 seconds) is recorded. Other summary measures such as the average deviation in the lateral and anterior-posterior directions are calculated later. The subject performs the test several times with his/her eyes both open and closed.
The NTI Postural Sway Analyzer is relatively compact. All of its components are considered fragile and should be handled with care. Set-up requires approximately 15 minutes. A complete test session requires approximately 8 minutes.

EQUIPMENT & SUPPLIES

1. NTI Postural Sway Analyzer head position monitor device:
   - A. Tripod
   - B. Digitizer unit (rectangular beige metal box)
   - C. Sound emitter (1" plastic cylinder with a thin insulated cable and metal connector attached)
   - D. Adjustable plastic headset
   - E. Computer interface card (installed in an IBM-PC compatible computer)
   - F. Cable from digitizer unit (9-pin connector) to computer (37-pin connector)
   - G. Power cord for digitizer unit (24-volt DC transformer on one end and circular plug on the other)
2. IBM-PC-compatible computer with the SWAY software and NTI interface card installed, including power supply
3. Visual target (8.5x11-inch paper with a 1-inch circle in the center)
4. Roll of 3/4" masking tape
5. Table (for computer) and 2 chairs

6. Two floppy diskettes (previously formatted) for data backup

7. Testing logbook

TESTING CONDITIONS

Testing should be performed in a quiet, private room with an electrical outlet for the computer and sway device. The temperature should be maintained near 25°C to avoid having the subject feel cold with shoes off.

SET-UP

1. Open the tripod and extend the legs fully.

2. Place a 16-inch (40 cm) "+" made with masking tape on the floor where the subject is to stand. The center of the "+" should be six feet (2 m) from the wall that the subject will face and at least XX inches (YY cm) from the side wall to allow placing the tripod between the side wall and the "+". One arm of the cross should be perpendicular to (and the other parallel to) the wall that the subject will face.

3. Position the *center* of the tripod 16 inches (40 cm) to the side of the intersection of the masking tape "+" on the floor.

4. Adjust the tripod platform so that it is level with the floor, and attach the digitizer unit to the tripod platform.

5. Plug in the small DC power supply and attach it to the digitizer unit. DO NOT TURN THE DIGITIZER POWER SWITCH ON YET.

6. Plug the sound emitter into the digitizer unit, attach it to the plastic headset, and hang the headset on the digitizer unit.

7. Rotate the tripod platform so that its long axis of the digitizer is perpendicular to the wall that the subject will face.

8. Attach the paper target on the wall directly in front of the "+" on the floor, 68 inches (173 cm) above the floor.

9. Plug in the computer power supply, and attach its output to the left side of the computer.

10. Connect the cable from the digitizer unit to the 37-pin connector on the right side of the computer.

11. Open the computer top. CHECK TO SEE THAT THE POWER SWITCH ON THE DIGITIZER IS IN THE OFF POSITION. Then turn on the power switch to the computer (left rear).

12. Make sure that the computer is on and then turn the power switch on the back of the digitizer to ON.

TESTING PROTOCOL

1. Explain the procedure to the subject while (s)he sits in the chair.

> *"We will be testing to see how steady you can stand. Sometimes if the nerves in the inner ear or your muscles and joints are not functioning properly, there is loss of the ability to stand steady. All you will have to do is stand for four one-minute periods, two with your eyes open and two with your eyes closed. In order to do the test, you will need to take off your shoes, but you can keep your socks on."*

2. At the DOS "C:\>" prompt, type the command:

```
SWAY
```

and press <enter>. The computer should respond with the prompt "`Enter temperature in degrees C)`".

Enter the ambient temperature on the computer keyboard and press <enter>.

To the "`Save data on disk (y/n)?`" prompt, press "y" followed by <enter>.

To the "`Number of OPEN/CLOSED pairs per subject (1,2,3)?`" prompt, press "2" followed by <enter>.

To the "`Length of each test in SECONDS (15-60)?`" prompt, type "60" followed by <enter>.

The program will beep and say "`INSERT DATA DISK NOW!!!`" Do not be alarmed, just hit <enter>.

To the "`Enter PATH for DATA (A:\SWAY)`" prompt, type

```
C:\SWAY
```

followed by <enter>. ***Make sure that you use a backslash (\), not a forward slash (/).***

To the "`Choose 1 or 2`" prompt, type "`1`" for if the tripod is on the subject's right side or "`2`" if the tripod is on her/his left. After you hit <enter> a diagram will appear on the screen. If it is correct, press <enter>. If it is not, press CTRL-Break and start over.

Finally the software should identify itself with "`NTI Sway Test`" in the upper left of the computer screen. Check to see that the displayed date and time are correct. If they are not, press CTRL-Break, and issue the commands "DATE" and "TIME" at the DOS "C:\>" prompt.

To the "`Site:`" prompt, type _____ followed by <enter>.

To the "`Hardcopy output (y/n)?`" prompt, type "`n`" followed by <enter>.

3. To the "View/Quit/Subject ID:" prompt, type the subject ID (up to 8 characters) followed by <enter>. The program will not accept an ID that has already been used. If the ID you are attempting to use is correct, use a distinctive ID such as appending a "Z" to the correct id and make a note in your testing log for it to be corrected later.

   When the program prompts for the last name, enter the subject's initials. Just enter "1" followed by <enter> for the first name, age, and years of education. Then the program should clear the screen and say "Press ENTER to start test". Do NOT press enter yet.

4. Record relevant information about the subject and testing session in the testing log.

5. Say to the subject:

   "O.K., please stand here centered over the "X", facing the target on the wall. I need to place this headset on your head."

6. Place the headset on the subject's head, adjust the size of the headset with the knob on the back such that it sits snugly but comfortably on the subject's head, and check that the sound emitter is securely in its correct position.

   Then adjust the height of the digitizer on the tripod so that the microphones (1-cm diameter black rings on the face of the digitizer) are at the same level as the sound emitter.

7. Then say:

   "Please stand with your feet and ankles touching. Relax with your arms hanging loosely at your sides. Look straight ahead at the target on the wall. Each trial will go on for 60 seconds. Once the trial starts, don't move your head, don't talk, and try to stand as steady as you can. You will notice that you sway around a bit. That is perfectly natural. There will be a rapid clicking sound next to your left(right) ear. Just ignore it and try to stand as still as you can. Are you ready to begin?"

   Make sure that the subject's feet are together, her/his hands are in the correct position, (s)he is looking at the target, and (s)he is relaxed. Wait until the subject says "Yes" or "Ready". Then say:

   "Here we go. Stand as still as you can until I tell you to stop. Eyes OPEN."

   Verify by observation that the eyes are open, and press the <enter> key on the computer to start the trial. The emitter should start clicking, and after 4 seconds the sway path will start to be plotted on the screen. Glance at the screen to see that it is plotting properly, but then WATCH THE SUBJECT, NOT THE SCREEN.

   Watch the subject carefully to see that there are no intentional movements, and be prepared to steady her/him if (s)he should begin to fall.

If the subject speaks, say promptly and firmly but without scolding "No talking, please." After the trial explain to the subject that talking increases the amount of sway.

8. When the trial ends, the computer will beep. Then say:

   "Good. Relax for a second."

9. There should be a prompt "O.K. (y/n) ?" at the bottom right of the screen. If there was any intentional movement, including speaking, during the trial, instruct the subject not to do that, answer "n" followed by <enter>, and run the trial over (begin at #7 above).

   If the trial went smoothly, answer "y" and <enter> or just <enter>, and say to the subject:

   "Now we are going to do exactly the same thing as before, but this time with your eyes closed. You may notice that you sway around a bit more than with your eyes open. That is perfectly natural. However, some people may loose their balance with their eyes closed. If you feel that you are going to fall, just open your eyes and steady yourself. Also, I will be right here watching you, and I will help to steady you, if necessary."

10. Continue with:

    "O.K., let's try it with your eyes closed. Please center your feet on the mark. Feet together. Hands at your sides. Look at the target. Now close your eyes. Relax. Stand as still as you can until I tell you to stop. Ready?"

    Make sure that the subject's feet are together, her/his hands are in the correct position, (s)he is facing at the target, and (s)he is relaxed. Wait until the subject says "Yes" or "Ready". Then say:

    "Here we go. Stand as still as you can until I tell you to stop. Eyes CLOSED."

    Verify by observation that the eyes are closed, and press the <enter> key on the computer to start the trial. Watch the subject carefully to see that there are no intentional movements, and be prepared to steady her/him if (s)he should begin to fall.

11. When the trial ends and the computer beeps, say:

    "Good. Open your eyes and relax for a second."

12. If there was any intentional movement, including speaking, during the trial, answer "n" to the "O.K. (y/n) ?" prompt, instruct the subject not to do that, and run the trial over (begin at #10 above).

    If the trial went smoothly, answer "y" and say to the subject:

"Now we are going to do exactly the same thing as before, just to make sure that we get your best effort."

13. Continue with:

"O.K., let's try it again with your eyes open. Please center your feet on the mark. Feet together. Hands at your sides. Look at the target. Eyes open. Relax. Stand as still as you can until I tell you to stop. Ready?"

Make sure that the subject's feet are together, her/his hands are in the correct position, (s)he is looking at the target, and (s)he is relaxed. Wait until the subject says "Yes" or "Ready". Then say:

"Here we go. Stand as still as you can until I tell you to stop. With your eyes OPEN."

Verify by observation that the eyes are open, and press the <enter> key on the computer to start the trial. Watch the subject carefully to see that there are no intentional movements, and be prepared to steady her/him if (s)he should begin to fall.

14. When the trial ends and the computer beeps, say:

"Good. Open your eyes and relax for a second."

15. If there was any intentional movement, including speaking, during the trial, answer "n" to the "O.K. (y/n)?" prompt, instruct the subject not to do that, and run the trial over (begin at #13 above).

If the trial went smoothly, answer "y" and say to the subject:

"Just one more time with with your eyes closed."

16. Continue with:

"Please center your feet on the mark. Feet together. Hands at your sides. Look at the target. Now close your eyes. Relax. Stand as still as you can until I tell you to stop. Ready?"

Make sure that the subject's feet are together, her/his hands are in the correct position, (s)he is facing at the target, and (s)he is relaxed. Wait until the subject says "Yes" or "Ready". Then say:

"Here we go. Stand as still as you can until I tell you to stop. With your eyes CLOSED."

Verify that the eyes are closed, and press the <enter> key on the computer to start the trial. Watch the subject carefully to see that there are no intentional movements, and be prepared to steady her/him if (s)he should begin to fall.

17. When the trial ends and the computer beeps, say:

"Good. Open your eyes."

18. If there was any intentional movement, including speaking, during the trial, answer "n" to the "O.K. (y/n)?" prompt, instruct the subject not to do that, and run the trial over (begin at #16 above).

    If the trial went smoothly, answer "y" and say to the subject:

    "That's all for this test. You can put your shoes back on now."

19. If the subject asks how (s)he did, just answer "Fine" without emphasis. Make your final notes to the testing log.

The program should now be presenting the prompt "View / Quit / Subject ID:". To begin another subject, go back to testing protocol instruction number 3. To quit the NTI data acquisition program, type "q" followed by <enter>. A DOS prompt should appear.

DATA BACK-UP:

You should make two floppy diskette copies of the data on the hard disk at the end of each testing day. To do this, you will need two previously formatted diskettes. Place the first in the "A:" drive, and issue the command:

```
BACKSWAY
```

This should cause all the data files not previously copied to the diskette to be copied to it. The program will then ask you to replace the first backup diskette with the second. After you hit any key to go on, it will copy the files to the second diskette. Store the two diskettes in separate places until the next time for backup.

REFERENCES

Postural Sway Analyzer User Manual. NeuroTest, Inc., Corona, CA, January, 1991.

APPENDIX G

Neurobehavorial Evaluation System (NES2) Test Procedures

NES2 TESTING INSTRUCTIONS

BACKGROUND

NES2 tests provide quantitative neurobehavioral outcomes as indices of nervous system functioning. NES2 is a flexible system consisting of more than 15 tests and questionnaires. The particular set of tests given in any testing situation depends upon the scientific questions being asked in the study, the nature of the exposures, the time available for testing, *etc.*

A complete description of the computer software, tests, and testing procedures is given in the *NES2 User's Manual.*

EQUIPMENT & SUPPLIES

1. IBM-PC-compatible computer with the NES2 software installed (See *NES2 User's Manual* for installation instructions)
2. Software Sentinel (5x3 cm white plastic case with a male DB-25 connector on one end and a female DB-25 connector on the other)
3. NES2 joystick
4. NES2 keyboard overlay
5. *NES2 Users Manual - Version 4.4*
6. Table and 2 chairs
7. Two floppy diskettes (previously formatted) for data backup
8. Testing logbook
9. Other: Grooved Pegboard

TESTING CONDITIONS

Testing should be performed in a quiet, private room with an electrical outlet for the computer. There should be adequate lighting, and the computer should be placed so that there is no glare on the video screen.

SET-UP

1. Attach the joystick connector to game controller adapter on the computer.
2. Place the male DB-25 connector of the Software Sentinel on the printer port ("LPT1:" or "PRN" or "Printer", a female DB-25 connector). The NES2 software will not run without this attached to the computer.
3. Place the keyboard overlay next to the keyboard.

4. Plug in and turn on the computer.

TESTING PROTOCOL

a. Ask the subject to take the seat next to the computer and seat yourself in front of the computer. At the DOS "C:\>" prompt on the computer, type the command:

NES2

and press <enter>. The computer should display a copyright message and take a few seconds to check the timing of the computer, that the joystick is plugged in, that at least 8000 bytes are free on the data disk, and other things.

b. Make an entry in the testing log of the date, time, subject ID, and a note that you began the subject on NES2. Then say to the subject:

"We are going to do several behavioral tests on this computer. However, you do not need to have had any experience with computers. First, I need to enter some identifier information."

c. Answer the NES2 MENU prompts for the interviewer ID (enter your initials), subject ID, and subject name (enter the subject's initials). (If prompts for the session number, just hit <enter> to accept session # 1. If prompted for "REGULAR SEQUENCE OF TASKS (+, -) ?", just hit "+".)

d. Ask the subject:

Are you right or left handed?"

If the subject claims to be ambidextrous, ask her/him which hand (s)he prefers to use for these tasks.

After a couple of seconds the instructions for the first test will appear on the screen.

The programs that administer the NES tests will be executed one after the other, and the data will be stored automatically at the end of each test.

e. REMEMBER:
(a) Always make a note in the LOG when you start a subject and when anything irregular happens.
(b) You can interrupt any of the programs at any time by pressing the **F1 and F8** keys simultaneously. (You may have to do this several times in succession.). Then answer the interrupt menu with your choice. Make a note of this in the LOG.
(c) When there is a "`Please call the interviewer`" message on the screen and program execution is suspended, press the "`F5`" key (no <enter> is required). A message of what has happened will appear on the screen. If the message indicates faulty performance, determine the subject's understanding of the task at hand, offer further instructions and press the "+" key to continue. If a program error has occurred, note the error number in the LOG and refer to Appendix 2. Make a note of your resolution of the problem in the LOG.

GROOVED PEGBOARD

a. Place the pegboard in front of the subject.

The prompt "`Please call the interviewer`" should be on the screen. Hit "`F5`" and the instructions for Grooved Pegboard will appear on the screen.

Read the instructions on the screen to the subject and press the "+" key to go on.

b. When you instruct the subject to begin, hit the "+" key to start the timer. The elapsed time should begin to appear on the screen. If the subject says (s)he was not ready, you can use the "-" key to zero the timer.

When the subject completes all the pegs, hit the "+" key to stop the timer. If you hit it too soon, you can just hit the "+" key again to restart it again where it was, and then stop it at the proper time.

Once the timer is stopped, you can record the latency and bring up the prompt for the number of dropped pegs by hitting the "-" key. (Hitting the "-" key while the timer is running causes it to reset, and hitting it while the timer is stopped causes it to save the latency and go on with the program.)

Type in the number followed by <enter>.

c. The screen for the non-preferred hand should appear. Instruct the subject to do the same thing, but this time to use her/his other hand. Tell the subject to begin, and press the "+" key to start the timer.

When the subject completes all the pegs, hit the "+" key to stop the timer. If you hit it too soon, you can just hit the "+" key again to restart it again where it was, and then stop it at the proper time.

Then hit the "-" key to record the timer's value and bring up the prompt for the number of dropped pegs. Type in the number followed by <enter>, and the program will end.

Remove the pegboard from in front of the subject and say "*Good*".

PREPARING FOR THE COMPUTERIZED TESTS

a. Carefully place the keyboard overlay over the computer keyboard. If it is not placed properly, it may press down continuously on one of the keys, causing the computer to make a high-pitched, rapid beeping sound. If this happens, remove the overlay immediately and carefully re-place it over the keyboard.

b. Place the joystick squarely in front of the screen between the subject and the computer. If the table or desk top is not deep enough, place the joystick next to the keyboard on the side of the subject's preferred hand, running the cable between the computer and keyboard if necessary.

c. Then exchange seats with the subject and say to the subject:

> *"All you will have to do is press these red and blue buttons or these gold keys as I tell you. We will go through each test together. Can you see the screen clearly?"*

If the subject requires reading glasses and does not have them with her/him, abort the test (see #4(b) above, and select option 9 (exit NES2 entirely) on the interrupt menu).

If the subject can see the screen clearly, say:

> *"We read the instructions to everyone, so that everyone gets exactly the same instructions. You can read along with me. I will help you get started with each test, and then move back out of the way while you finish the test. You will need to let me know when a test ends and the instructions for the next test appear on the screen."*

GENERAL CONSIDERATIONS FOR THE COMPUTERIZED TESTS

a. For each test read the instructions to the subject. If (s)he seems uncertain at that point it is usually appropriate to say:

> *"Go ahead and press the plus key. What you are expected to do will become clear as we go along."*

b. In general, it is appropriate to speak to the subject during the practice trial of an NES test (or during the first 6-8 trials of SRT or CPT), but once the "for the record" trials have begun, you should not speak to the subject or move within her/his field of vision.

c. If the subject speaks out loud, do not answer unless (s)he abandons the task and looks at you for an answer. Then, say, "*Please just concentrate and complete the task without talking.*" Make a note of this in the log.

FINGER TAPPING TEST

a. Read the first page of the Finger Tapping instructions on the screen. Emphasize the "AS MANY TIMES AS YOU CAN" part of the instructions.

b. Before pressing the "+" key, demonstrate how to press the key quickly.

c. Press the "+" key to get the instructions for the first preferred hand trial on the screen. Have the subject position her/his finger on the blue joystick button properly (*i.e.*, on the near end and lightly touching it). Read the instructions on the screen, again emphasizing the "AS MANY TIMES AS YOU CAN" part of the instructions.

c. Ask "*Ready?*", and when the subject says yes, say "*Go!*". During the first trial, which is an unannounced practice trial, you may speak to the subject saying "*Put as many little squares on the screen as you can!*" and "*Keep going as fast as you can until you hear a beep!*".

   Make sure that the subject maintains the correct finger and wrist positions during each of the trials, and correct her/him immediately if, *e.g.*, (s)he begins to lift her/his wrist off the joystick box.

d. After the practice trial, wait 10 seconds to bein the second trial with the preferred hand. Do not speak during the trials after the 1st.

e. After the second trial, continue immediately in the same manner with the non-preferred hand and the both-hands trials.

f. When the test ends, say "*Good*".

SIMPLE REACTION TIME TEST (SRT)

a. Read the first page of SRT instructions on the screen. Emphasize the "AS FAST AS YOU CAN" part of the instructions.

b. Demonstrate how to press the key quickly. Have the subject position her/his finger on the blue joystick button properly (*i.e.*, on the near end and lightly touching it).

c. Ask "*Ready?*", and when the subject is ready, press the "+" key to start the test. Make sure (s)he keeps her/his finger in contact with the button and does not hold it down too long. It is fine to speak to the subject during the first 10-20 seconds of the task, as the first 10 trials of data are not included in the SRT summary measures. Then move back out of the way and use the time to work on coding other data, *etc.* Remain quiet and move about as little as possible.

   Glance at the subject from time to time to assure that the correct finger position is maintained.

   If the subject asks how much longer the test will go on, say "*Just a little while longer. Please concentrate and respond as quickly as you can.*"

d. When the test ends, say "*Good*".

HANDEYE COORDINATION TEST

a. Read the Handeye instructions on the screen, and then demonstrate while saying:

> *"It's easier to explain by demonstrating than with words. You will be moving this stick up and down. See how it moves smoothly up and down, but it returns to the center when it is moved to the side."*

b. Press the "+" key to get the pattern on the screen and say:

> *"See how the moving the stick up and down moves the little square up and down. When you place the little square directly on the first point on the line it will move quickly to the right. You only control the up and down movement, so you keep the stick in the center groove, and just move it up and down. Move the square down to the first point to start the practice trial."*

c. When the square begins to move to the right, coach the subject by saying "*up ... up ... up, down ... down ... down*" during the practice trial.

If the subject does very poorly, the "`Please call the interviewer`" message will appear. Just press "`F5`" and coach the subject through the practice trial again.

If the subject fails the practice trial three times, tell the subject that you are running out of time, hit "`F1/F8`" simultaneously, and select option "`3`" (go on to the next test). Make a note of this in the log.

If the subject gets the idea, then the other trials will go quickly. Do not continue to coach the subject with "up ... up ... down ... down" after the practice trial.

d. When the last trial is complete, say "*Good*".

SYMBOL-DIGIT SUBSTITUTION TEST

a. Read the Symbol-Digit instructions on the screen, and then press the "+" key to get the practice trial on the screen. Demonstrate while saying:

> *"You look for this first symbol in the top row. See how it is matched with the number "2". You touch the "2" key, and "2" gets entered here. The little flashing line moves over to the next symbol and you look for it in the top row. What number is it matched with?*

b. When the subject answers "6", say:

> *"Good. Enter the 6 and fill out the rest of the row."*

c. When the subject finishes the row, read the second set of instructions, emphasizing "AS FAST AS YOU CAN".

Make sure that the subject is using just one finger, then move back out of the way after the first 2-3 responses.

Monitor the subject's responding. If (s)he uses more than one finger, say (quietly):

> *"Just use one finger."*

d. When the last trial is complete, say "*Good*".

PATTERN COMPARISON TEST

a. Read the Pattern Comparison instructions on the screen, and then say:

> *"Let's do a practice trial together."*

b. Press the "+" key to get the practice trial on the screen. Demonstrate while saying:

> *"Two of these patterns are exactly the same and one is slightly different. Which one is different from the other two?*

If the subject has difficulty, point to the differences on the screen with your finger.

c. When the subject answers, press the correct key (1, 2 or 3). Then, before pressing the "+" key, point out that (s)he can change an answer:

> *"If you hit a wrong key, you can just press the correct one. When you have pressed the correct number, you will need to press the "+" key to enter your answer and go on. Press it now."*

d. Read the additional instructions on the screen, emphasizing the "**AS FAST AS YOU CAN**".

Watch the subject during the first trial, then move back out of the way while (s)he finished the additional 24 items.

e. When the last trial is complete, say "*Good*".

SERIAL DIGIT LEARNING TEST

a. Read the Serial Digit Learning instructions on the screen. When the subject is ready, press the "+" key to start the first trial.

b. Read the "`There will be 4 digits`" message and the four digits out loud. When the answer screen comes up, say

"Now enter the four numbers."

c. Once the subject enters the digits, before (s)he can hit the "+" key, demonstrate that the "-" key can be used to erase an answer. Just do one digit, and the put the same digit back in the last position.

d. Then point out that (s)he will always have to put in the full number of digits and that (s)he must hit the "+" key to enter the answer and go on.

e. Move back from the subject.

Watch the subject closely. If (s)he just sits there after entering all of the numbers, wait about 5 seconds and then say quietly *"Hit the "+" key to go on".*

If the subject does not enter all the digits quickly, wait about 10 seconds and then say quietly *"If you don't remember them all just guess. They will appear on the screen again."*

f. The test will continue for eight trials or until the subject answers the 8-digit sequence correctly on two trials in a row.

g. When the test ends, say "*Good*".

VOCABULARY TEST

a. Read the Vocabulary instructions on the screen. When the subject is ready, press the "+" key to start the first trial.

b. When the subject completes 25 items or answers 4 of 5 in a row wrong, the test will end.

   If it is apparent that the subject cannot read, abort the test, *i.e.*, press "`F1/F8`" simultaneously, and select option "`3`" (go on to the next test). Make a note of this in the log.

c. When the test ends, say "*Good*".

MOOD SCALES

a. Read the Mood Scales instructions on the screen. When the subject is ready, press the "+" key to start the first trial.

b. After the subject completes the word, move back out of the way.

   If the subject asks for definitions of the words, indicate that you are not supposed to give any help on this test. If it is apparent that the subject cannot read, abort the test, *i.e.*, press "`F1/F8`" simultaneously, and select option "`3`" (go on to the next test). Make a note of this in the log.

c. The test will end when the subject completes the 25 items.

d. When it ends, say "*Good.*".

END OF COMPUTER-BASED TESTS:

Say "*Good, that completes these computer tests.*".

DATA BACK-UP:

You should make two floppy diskette copies of the data on the hard disk at the end of each testing day. To do this, you will need two previously formatted diskettes. Place the first in the "A:" drive, and issue the command:

```
BACKNES2
```

This should cause all the data files not previously copied to the diskette to be copied to it. The program will then ask you to replace the first backup diskette with the second. After you hit any key to go on, it will copy the files to the second diskette. Store the two diskettes in separate places until the next time for backup.

REFERENCES

NES2 User's Manual (Version 4.4). Neurobehavioral Systems, Inc., Winchester, MA, January, 1991.