Archives of Environmental Health: An International Journal

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/vzeh20

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Published online: 03 Aug 2010.

To cite this article: Fredric Gerr M.D., Dawn Hershman B.A & Richard Letz Ph.D. (1990) Vibrotactile Threshold Measurement for Detecting Neurotoxicity: Reliability and Determination of Age- and Height-Standardized Normative Values, Archives of Environmental Health: An International Journal, 45:3, 148-154, DOI: 10.1080/00039896.1990.9936708

To link to this article: http://dx.doi.org/10.1080/00039896.1990.9936708

Vibrotactile Threshold Measurement for Detecting Neurotoxicity: Reliability and Determination of Age- and Height-Standardized Normative Values

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ABSTRACT. Damage to the peripheral nervous system by neurotoxic agents can result in elevated sensory thresholds. In this study, the results of two studies in a program of validation of vibrotactile threshold test performance are presented. First, the test-retest reliability and time efficiency of two methods for generating vibrotactile thresholds were determined in a sample of subjects known to be at risk for peripheral neuropathy, 22 diabetics. Specifically, a forced-choice method was compared to a method-of-limits procedure. The method of limits was found to be as reliable as the forced-choice procedure and required less time to administer. The second study was undertaken to determine the magnitude of major effect modifiers on vibrotactile thresholds. Vibration thresholds were determined using a method-of-limits procedure in 131 blue-collar workers who were 29–76 y of age. Equations relating vibrotactile threshold estimated by the method-of-limits procedure to age and height are presented for the upper and lower extremities.

PERIPHERAL NEUROPATHY, either generalized or focal, is an adverse health outcome from exposure to various chemical substances or physical factors in the workplace.[1] It is unknown how many cases of occupational peripheral neuropathy occur in the United States each year. The pathology of most peripheral neuropathy of toxic etiology is reported to be large fiber axonopathy in which the most distal portions of the large myelinated axons are affected first.[2] Damage to these fibers affects perception of vibration, light touch, and position of the joints. The clinical correlate of this entity is the so-called stocking-glove neuropathy in which abnormal sensory function is initially detectable in the lower extremities and subsequently more proximally with disease progression. Physically induced neuropathy secondary to ergonomic factors usually involves focal nerve compression with localized sensory deficits.

Presently, three methods of assessing peripheral neurologic function have been used in epidemiologic studies of occupational neurotoxicity: (1) physical examination, (2) quantitative cutaneous sensory perception thresholds, and (3) electrophysiologic evaluation.[3] Physical assessment can be performed rapidly and with minimal equipment but is

nonquantitative, of unknown reliability, and requires a highly skilled examiner. Electrophysiologic methods are quantitative and reliable; however, they are uncomfortable, time-consuming, require sophisticated equipment, and must be administered by a skilled technician. Quantitative cutaneous sensory perception thresholds are nonaversive and can be administered rapidly with inexpensive equipment by a technician with minimal training. Several portable instruments designed to measure vibrotactile thresholds are available commercially, and a variety of psychophysical procedures have been recommended.

The use of quantitative cutaneous sensory perception thresholds has not been widespread, partly because of insufficient validation. Validation of quantitative cutaneous sensory perception thresholds should include the following investigations: (a) determination of reliability in both normal subjects and those at risk of neuropathy; (b) evaluation of effect modifiers such as age, height, and medical illness; (c) development of normative values while controlling for effect modification; (d) comparison with existing valid measures of peripheral nerve function, e.g., physical examination and nerve conduction velocity; (e) evaluation of the method's sensitivity and specificity for identification of clinical and subclinical neurotoxic disease by testing subjects with known exposure to neurotoxicants. These investigations should be performed with a standardized testing algorithm and a device capable of delivering well-defined vibratory stimuli.

One widely used instrument for measuring vibrotactile thresholds is the Vibratron II, an electromechanical device designed to deliver vibratory stimuli. In our initial study of this device, the test-retest reliability and time efficiency of two testing protocols in a group of normal subjects were reported.[4]

In this paper the results of two additional studies of vibrotactile threshold test performance in our validation program are presented. In the first study, the test-retest reliability and time efficiency of two methods of threshold generation were determined in subjects with diabetes drawn from a hospital-based clinic. The two methods compared were a forced-choice procedure and a method-of-limits procedure. Forced-choice procedures require the subject to determine the presence of a discrete stimulus in either one of two (or more) intervals of time or at one of two (or more) spatial locations. A set of rules specify changes in stimulus intensity, typically based on the correctness of prior response(s). Alternatively, in a method-of-limits protocol, stimulus intensity is gradually increased and decreased. The subject is required to report the moments of stimulus recognition and extinction, respectively. Each stimulus presentation requiring a response from the subject is called a "trial." In comparison to the method of limits, forced-choice procedures are advantageous because they minimize the effect of a subject's "criterion shift," i.e., a change in the subject's criterion for reporting the presence or absence of a stimulus on different occasions.[5] Method-of-limits procedures are considered sensitive to this source of error. However, forced-choice procedures may produce unstable threshold estimates unless lengthy protocols involving many trials are administered.[6,7] Determination of both reliability and time efficiency is important to allow informed choices in situations with different time constraints and accuracy requirements. Finally, the optimal number of trials necessary for reliable determination of a threshold was investigated for the method of limits.

The second study was performed to determine major effect modifiers of vibrotactile thresholds measured with the method of limits (MOL) procedure and to provide provisional normative values. Vibration thresholds were determined in a group of 131 construction trades workers. Age has been shown by other investigators to have a significant effect on vibrotactile thresholds.[8–10] One goal of this study was to quantify this effect with the described MOL procedure and the Vibratron II device. An additional goal was to investigate the effect of height on vibrotactile thresholds. Equations relating vibrotactile threshold to age and height are presented to provide a provisional guide for those using the method described.

Study 1

Methods

Subjects. Twenty-two subjects with diabetes (11 male, 11 female) were tested on two separate occasions. There were 4 white, 8 black, and 10 Hispanic subjects. The average education was 12.4 y, with a range of 6–18 y. Twenty-one of the 22 subjects were insulin-dependent, and 1 was maintained euglycemic by diet alone. Average duration of disease was 14.5 y with a range of 1–40 y. Six of the subjects were diagnosed previously by their usual physicians as having diabetic neuropathy. All subjects provided informed consent in accordance with institutional guidelines.

Apparatus. The Vibratron II (Sensortek, Inc., Clifton, NJ), a vibrotactile threshold testing instrument, was used for all measurements. The instrument and associated testing protocols have been described previously.[4] In brief, the device consists of a controller unit and two identical electromechanical stimulus delivery units or transducers. A 1.4-cm-diameter plastic post protrudes from the transducer and delivers the stimulus. The stimulus frequency is fixed at 120 Hz. The amplitude is controlled by turning a knob on the controller unit and is displayed in "vibration units" ranging from 0–20.

To allow comparison of the thresholds generated in this study to those generated by other investigators, the measured thresholds were converted from "vibration units," a measure of vibration intensity idiosyncratic to the Vibratron II, to log microns of stimulator displacement. Vibration units are related to microns of peak-to-peak displacement by the for-

mula: microns = k^* (vib. unit)^2. The value of k was determined empirically for the equipment used in this study by measuring the peak-to-peak displacement of the stimulator post with a calibrated Kulite GY-125–20 accelerometer and relating the values to the vibration units displayed on the Vibratron.

Procedure. The Sensortek testing protocol (SFC) utilizes a two-alternative forced-choice procedure and requires both transducers. The protocol is detailed in the operating manual for the Vibratron II. In brief, the SFC requires that an initial amplitude be selected at a level readily detectable by the subject. On each trial the subject is asked to touch each post with the digit to be tested and then indicate which of the two is vibrating. With each correct determination of stimulus location, the amplitude is reduced by 10% and another trial is administered. A pseudorandom sequence is used to select the post on which the stimulus will be presented. When the subject is uncertain which post is vibrating, he or she is required to guess. After the first incorrect response, the procedure requires that two of three responses be correct before the stimulus intensity is lowered. Should two of three responses be incorrect, the intensity is increased by 10%. In addition, once the stimulus intensity descends to 0.7 vibration units, the two-out-of-three rule is employed, even if no errors have occurred. The procedure is terminated when a total of five errors have been made. The stimulus intensity on the five error trials and on the five lowest correct trials are pooled, and the highest and lowest values are discarded. The threshold for that test is defined as the average of the remaining eight values.

The MOL requires only one transducer. The subject is asked to rest a digit on the post. An easily detectable suprathreshold stimulus is presented and then reduced at a constant rate. The subject is asked to report verbally the earliest point at which he or she can no longer detect the stimulus. The value is recorded, and the subject is asked to lift the digit from the stimulator post. The amplitude is then reduced to a value well below that of the previous trial, and the subject is asked to place the digit back on the stimulator post. The stimulus intensity is gradually increased until the subject indicates that he or she can feel the vibration. The complete testing sequence consists of seven trials (four descending and three ascending). Threshold calculations are discussed below.

The dominant great toe of each subject was tested with the SFC protocol followed by the MOL protocol. In addition, the non-dominant great toe was also tested with the MOL. The subjects were tested a second time, the interval between tests ranging from 5 to 106 d (mean [$\bar{x}$] = 19.8; standard deviation [SD] = 20.5). The interval between test sessions was ≤ 28 d for 21 of the 22 subjects ($\bar{x}$ = 15.7, SD = 7.2). The time required to perform each protocol was measured with a digital stopwatch. The examiner did not have access during the second session to data collected during the first session.

An interviewer-administered questionnaire was completed after the second testing session. The questionnaire included demographic information, questions about the duration and treatment of diabetes, and whether the subject had a prior diagnosis of neuropathy.

Statistical analysis. Data were analyzed with the Statistical Analysis System (PC-SAS).[11] Test-retest correlation coefficients (Pearson) and paired t tests between sessions were calculated for both the SFC and MOL vibrotactile thresholds. For the MOL procedure, the initial descending trial was discarded, and vibrotactile thresholds were calculated by averaging various subsets of the remaining six trials. As in previous work, the correlations between test sessions was the basis for comparison among the alternative test summary measures.

Results

Vibration thresholds were calculated from various subsets of the six individual (three ascending and three descending) MOL trials. Thresholds with the highest reliability were obtained by averaging MOL runs two through seven (r = .81 or by dropping the highest and lowest values from runs two through five ("trimmed 2–5," r = .81). Consistent with previous work is the finding that all summary measures were, on average, lower for the second session when compared with the first. This difference suggests a systematic criterion shift between test sessions, perhaps related to learning about how to respond.

Results from the SFC and the trimmed 2–5 MOL procedure are presented in Table 1. Vibration thresholds determined with the SFC procedure were substantially lower than those determined with the MOL. The correlation between the two test sessions was slightly higher for the SFC than for the MOL procedure. As with the MOL, the SFC thresholds determined during the second test session were lower than those from the first. The SFC procedure took,

Table 1—Comparison of Method-of-Limits (MOL) and Sensortek Forced-Choice (SFC) Procedures for Estimating Vibration Thresholds for the Dominant Great Toe

	Trimmed 2–5 MOL		SFC	
	$\bar{X}$	SD	$\bar{X}$	SD
Threshold session 1 (log microns)	2.19	1.27	1.09	1.31
Threshold session 2 (log microns)	1.81	1.22	0.92	1.35
Difference between sessions (log microns)	0.38	0.76	0.17	0.70
Correlation between sessions	0.81		0.86	
Duration session 1 (s)	185.1	75.3	448.0	163.3
Duration session 2 (s)	151.8	48.1	403.7	105.0

on average, more than twice as long to perform than the MOL. The times presented for the MOL are for the collection of seven trials. However, only five trials are necessary to calculate a trimmed 2–5 MOL threshold, further reducing the administration time of the test.

Exploratory analyses were performed to determine the effect of intertest interval on measured reliability. Correlations between the intertest interval and the difference in test score between sessions one and two were determined for both the MOL and the SFC. No significant associations were found. The analysis was repeated after removal of one subject with an unusually long intertest interval (106 d). Again, no significant associations were found.

The mean vibrotactile threshold (in log microns) of the six subjects diagnosed by their usual physicians as having peripheral neuropathy was 2.53 (SD = 1.61); for those who did not have a diagnosis of peripheral neuropathy it was 2.07(SD = 1.15). Because the diagnoses of peripheral neuropathy were not standardized, and the number of subjects with the diagnosis was small, tests of significance were not performed.

Study 2

Methods

Subjects. Subjects were drawn from a population of asbestos-exposed workers examined at The Mount Sinai Medical Center as a part of a large-scale screening for asbestos-related illness. A total of 131 male subjects who worked in construction (insulators, tapers, pipefitters) or building maintenance trades (custodians) were tested. There were 123 white and 8 black subjects who ranged in age from 29 to 76 y, with a mean of 52.5 y (SD = 12.1 y). Height ranged from 156 to 198 cm ($\bar{x}$ = 173 cm, SD = 7.4 cm). All provided informed consent in accordance with institutional guidelines.

Procedure. A questionnaire was administered in a private setting to each subject by a trained examiner. Demographic information, current and previous work, and a list of medications currently taken were obtained. Subjects were asked if they experienced numbness, tingling, weakness, or pain in any of the four extremities. Symptoms were recorded as "present" or "absent" for each extremity. Also included were questions to determine the presence or history of carpal tunnel syndrome; serious neck or back disorders, which were documented by CT scan or myelogram, or requiring surgery; trauma to the extremities resulting in nerve injury; alcoholism; diabetes; uremia; and other serious medical illness. Responses were coded as positive only if the subject had been informed of the problem by a physician. When a subject gave a positive answer, he was asked to provide additional information, which was recorded. Subjects were also asked whether they ever had extensive exposure to heavy metals, i.e., lead, arsenic, and mercury; solvents, i.e., n-hexane and methyl-n-butyl ketone; pesticides; or vibratory power tools. In addition, subjects were asked an open-ended question about "other hazardous exposures." When a subject gave a positive response to an exposure question he was asked to provide additional information and indicate whether he had any known health problems resulting from the exposure. Questionnaire results were not available to the technician obtaining the vibrotactile thresholds until after the measurements were made.

The Vibratron II (Sensortek, Inc., Clifton, NJ) vibrotactile threshold testing device was used for all measurements. The method of limits psychophysical procedure ("Trimmed 2–5," described in Study 1 above) was used to generate sensory thresholds. For the purpose of modeling the relationship of threshold to age and height, individuals who were unable to feel the stimulus at maximum amplitude were assigned a threshold value corresponding to the maximum deliverable stimulus.

All 131 subjects had vibrotactile thresholds determined bilaterally for the index fingertip and the pad of the great toe. In addition, the fifth fingertip was tested bilaterally in the final 44 subjects. The upper extremities were tested first, starting with the dominant hand. Upon completion of the upper extremities, the dominant great toe was tested, followed by the nondominant great toe. A total of 348 digits of the upper extremity and 261 digits of the lower extremity were tested. A few subjects had missing digits; this accounts for minor discrepancies in the numbers.

Statistical analysis was performed using the PC-SAS statistical package.[11]

Results

Because vibration amplitude is displayed on the Vibratron II in "vibration units," reporting of results in those units was considered. However, inspection of the distributions of thresholds expressed in vibration units and in microns revealed them to be skewed to the right. In addition, preliminary regression of these variables on age (the major effect modifier) revealed a violation of the assumption of homoscedasticity necessary for valid application of regression models. Logarithmic transformation of the threshold (in microns) both linearized the relationship with age and stabilized the variance (Fig. 1). Therefore, all regression analyses relating vibrotactile threshold to age were performed with vibrotactile threshold expressed in units of log micron peak-to-peak displacement of the stimulator surface.

Multiple linear regression analyses relating age and height to vibrotactile threshold were performed for each of the six sites tested. Inspection of the estimated parameters suggested that the effect of both age and height on vibrotactile threshold might be similar among the four fingers and also between the two toes. A model was fitted to test for homogeneity of the age and height parameters among the four fingers. A similar model was fitted separately for the

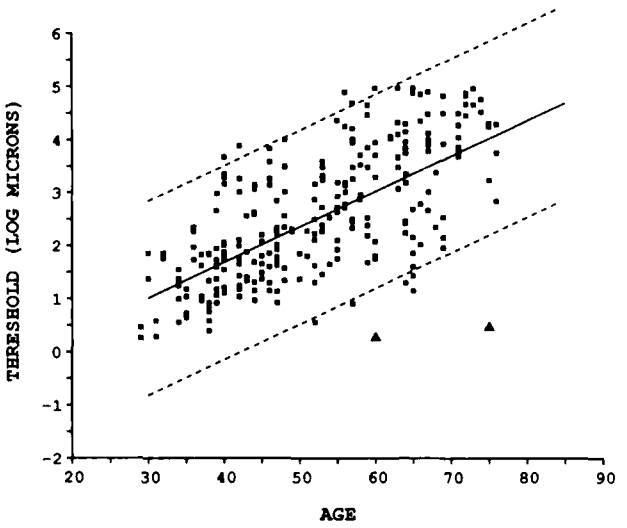

Fig. 1. Scatter diagram relating vibration threshold of both great toes to age. The regression line (*solid*) was calculated after deletion of influential values (identified with a *triangle*). The *broken lines* mark + or − 2* RMS error from the regression line. (See Table 2 for regression parameters).

toes. The upper–extremity age parameters were not significantly different from one another, nor were those estimated for height. The same results were found for the lower extremities. Another model was fitted with common age parameters, common height parameters, and separate intercepts for the four fingers. Similarly, a model was fitted with common age and height parameters and different intercepts for the two toes. When the intercepts were tested for homogeneity, no significant differences were found for either the upper or lower extremity. Because no significant differences in slopes or intercepts existed among the four fingers nor between dominant and nondominant toe, the final models had a common slope for age, a common slope for height, and a single intercept.

Once the model parameters were estimated, attempts were made to identify thresholds that were not representative of the underlying population, i.e., "outliers." For this purpose, outlier thresholds were defined as those for which the absolute value of the studentized residual statistic exceeded a value of 3.0. Such thresholds might markedly influence estimation of the model parameters and reduce the accuracy of the predicted age- and height-specific normative values. They would be expected to occur by chance less than .5% of the time in a normally distributed population. Four finger and 2 toe thresholds met this criterion. The toe thresholds are identified by a triangle in Figure 1. Three subjects accounted for all such thresholds. All thresholds for those subjects were deleted (10 finger values and 6 toe values), and the above described model–fitting procedure was repeated. The final regression parameters and associated model statistics estimated after deletion of the 3 subjects are presented in Table 2. Both age and height were significantly related to vibrotactile threshold. These effects were substantially larger in the lower extremies and also accounted for a much larger percentage of the total variance in vibrotactile threshold than in the upper extremities.

Subjects who reported neuropathic symptoms, neurotoxic exposures, and medical conditions known to predispose to peripheral nerve dysfunction were identified by questionnaire (Table 3). Numbness and tingling were the most prevalent symptoms in this group. Exposures that might cause injury to the peripheral nerves of the upper and lower extremities were reported by 45 and 32 subjects, respectively. No subject was aware of any health problems resulting from the exposures. Thirty subjects reported current or past medical conditions that might have current effects on peripheral nerve function.

For each digit tested, thresholds standardized for age and height were calculated. On a digit-specific basis the mean standardized threshold of those with each symptom was compared to the threshold of those without the symptom. The mean standardized thresholds were significantly higher in those subjects who reported numbness in either of the lower extremities than in those who did not (dominant toe: $t = -2.3$, $p = .02$; nondominant toe: $t = -2.8$, $p < .01$). In addition, significant elevations were found for those who reported weakness in the nondominant lower extremity ($t = -4.4$, $p < .001$). No significant differences were found when similar analyses were performed for subjects with and without both neurotoxic exposures and medical conditions known to predispose to neuropathy.

Discussion

The determination of vibrotactile threshold has been proposed as a useful method for screening working populations at risk for neurologic disease.[12] Screening instruments for occupational neuroepidemiology should be reliable, rapid, noninvasive, nonaversive, quantitative, and should produce a result of known correlation with disease in humans. The goal of these studies was to evaluate several performance characteristics of the Vibratron II and to develop superior testing protocols useful for worker screening and occupational neuroepidemiologic studies. Specifically, test-retest reliability, time efficiency, and the effect of age and height on vibrotactile threshold were determined. In addition, a simple interviewer-administered questionnaire was evaluated for its ability to identify subjects at risk of threshold elevation.

Table 2.—Regression Parameters Relating Vibration Threshold (In Log Microns) to Age and Height

	Intercept	Age	Height	RMS error	r^2
Finger	−3.808	0.0299	0.0167	0.695	0.20
Toe	−9.891	0.0758	0.0494	0.791	0.58

Table 3—Prevalence (%) of Neuropathic Symptoms, Prior Neurotoxic Exposures, and Medical Conditions Considered Predisposing to Peripheral Nerve Dysfunction

	Dominant Digit II (N = 127)	Nondom. Digit II (N = 127)	Dominant great toe (N = 128)	Nondom. great toe (N = 127)
Numbness	22.8	18.9	12.5*	14.2*
Tingling	16.5	14.2	10.2	12.6
Weakness	3.1	1.6	3.1	2.4*
Pain	11.8	7.1	8.6	6.3
Neurotoxic exposure	35.4	34.6	25.0	24.4
Predisposing medical conditions	21.2	18.9	19.5	18.9

*Statistically significant differences in mean age- and height-standardized thresholds found between subjects reporting these symptoms when compared to those who did not.

The test-retest reliability of both the MOL procedure and the SFC in the diabetic population was high and was comparable between the two procedures. The method of limits was, however, much more time efficient. Thresholds estimated with the SFC were lower than those estimated with the MOL, probably, in part, because forced-choice, step-down procedures produced estimates that are biased toward lower values.[6,7] In addition, thresholds estimated with the SFC do not have a well-defined psychophysical meaning.[4,10]

These results are consistent with our previous study on a normal population in which the MOL was found to be more reliable and substantially more time efficient than the SFC.[4] The current study addresses two limitations of the generalizability of the previous study. First, the current study was performed on a diabetic population—a group known to be at risk of symmetric distal peripheral neuropathy[13]; the previous work was performed on a group with no known predisposition to peripheral neuropathy. Second, the previous study group had an unusually high level of educational attainment; the current study population was more representative of a nonprofessional population. In summary, the rapidity of the MOL has not been dependent upon the health and educational status of the study subjects when the results of these two studies are compared, and the reliability of the MOL procedure remained high in the second, more heterogeneous, sample.

The relationship between vibrotactile threshold determined with the Vibratron II using the MOL procedure and age and height in this predominantly construction-trades population was modeled. Age and height were significantly related to vibrotactile threshold measured in both the upper and lower extremities and accounted for a substantial portion of the total variability in vibrotactile thresholds. The percentages of variance accounted for by the multiple regression models in this population for both the upper and lower extremities are comparable or superior to those reported by others who investigated the relationship between vibrotactile threshold and age.[14–17]

Also consistent with the results of other investigators, more variability was explained in the regression models for the lower, in comparison to the upper, extremities. Although the reasons for this are unclear, differences in callus thickness and focal and/or repetitive trauma may add to the variability observed for the upper extremity.

The effect of height on vibrotactile threshold was statistically significant and of substantial magnitude, especially in the lower extremity. A consistently significant effect of height on vibrotactile threshold has been reported previously.[9] In addition, nerve conduction velocity in the lower extremity has been shown to be significantly related to the subjects' height.[18] The physiologic basis for these findings is not well understood. The current study appears to be the first that reports regression parameters that allow for standardization of vibrotactile threshold for both age and height.

The estimated slopes from the regression model relating vibrotactile threshold to age were not significantly different among the four fingers tested nor between the two great toes. This finding is consistent with the physiologic expectation that the four fingers should age at the same rate, as should the two toes. Of interest was the observation that thresholds of the fingers tested on the dominant hand were, on average, higher than those of the respective fingers of the nondominant hand, although the difference was not significant. This is consistent with the reports of Halonen[16] and Goff et al.[19] In the present study, the observed effect may have been due to ordering or learning, as dominant hand thresholds were always collected before those of the nondominant hand. Future studies in which the ordering of testing is randomized with respect to hand preference will clarify this issue.

The screening questionnaire administered in this study was not useful for identification of those at risk of elevated vibrotactile threshold because of underlying medical conditions. Specifically, those subjects identified by questionnaire as having a condition believed to predispose to sensory performance deficits did not have significantly elevated age- and height-standardized vibrotactile thresholds when compared with those without such conditions. This is consistent with the findings of Era et al.,[9] who failed to find an association between vibrotactile threshold and either major medical illness or drinking habits. Lipton et al.[20] did find an association between increased vibrotactile threshold and alcoholism, but not with medical illness or occupation. Similar analyses were performed for those subjects who reported prior exposure to neurotoxicants. Again, no significant differences were observed between those who reported exposures and those who did not. Mean age- and height-standardized thresholds were significantly higher among those who reported numbness in either lower extremity, as well as among those who reported weakness in the nondominant lower extremity.

In summary, the MOL is a reliable and time-efficent procedure. Age and height are significant effect modifiers and should be controlled for when vibrotactile thresholds are measured for either clinical or epidemiologic purposes. Other sources of variability must be identified. Specifically, the effects of calluses, local trauma, medical illness, substance use, and other demographic parameters should be evaluated systematically in large populations. Additional validation must include comparison of these measurements to conventional clinical tests, including physical examination and electroneurography. Finally, their utility as early markers of disease must be evaluated in prospective studies of populations at risk of disease while conventional methods are applied simultaneously.

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This study was supported by a National Institute of Environmental Health Science Center Grant (P30-ES00928) and a grant from the U.S. National Institute for Occupational Safety and Health (K01-OH00064).

The authors would like to thank Jane Metzger, R.N., Jean Nizalowski, M.S.W., and Donald Smith, M.D., of the Mount Sinai Hospital Diabetes Clinic for their enthusiastic support in the recruitment of diabetic subjects for Study 1.

The authors also wish to thank Drs. Irving J. Selikoff and Stephen Levin of the Division of Environmental and Occupational Medicine, Mount Sinai Medical Center, for their assistance with the recruitment of workers for Study 2; and Dr. James Godbold, also of the Division of Environmental and Occupational Medicine, for his advice on statistical analysis issues.

Submitted for publication July 21, 1989; revised; accepted for publication January 19, 1990.

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