Pergamon

Neurotoxicology and Teratology, Vol. 16, No. 1, pp. 113-122, 1994

0892-0362/94 $6.00 + .00

Covariates of Human Peripheral Nerve Function: III. Effects of Reported Drinking

FREDRIC GERR*†[1] AND RICHARD LETZ*‡

*Division of Environmental and Occupational Health, Emory University School of Public Health, †Department of Medicine, Emory University School of Medicine, ‡Department of Neurology, Emory University School of Medicine, Atlanta, GA 30329

Received 23 January 1993; Accepted 15 August 1993

GERR, F. AND R. LETZ. *Covariates of human peripheral nerve function: III. Effects of reported drinking.* NEUROTOXICOL TERATOL **16**(1) 113-122, 1994.—A cross-sectional epidemiologic study of the relationship between alcohol consumption and peripheral nerve function was performed using data from a cohort of 4462 male Vietnam-era Army veterans selected independently of either alcohol consumption history or clinical disorders associated with excessive alcohol use. Self-reported alcohol consumption, expressed as current drinking intensity (drinks per month), was the primary measure of alcohol use. The dependent variables were: (a) conduction velocity and amplitude of the median motor, median sensory, ulnar sensory, peroneal motor, and sural sensory nerves; (b) vibrotactile and thermal thresholds of the index finger and great toe. Drinkers who reported consuming <180 drinks per month had, in general, slightly faster mean nerve conduction velocities, slightly greater evoked response amplitudes, and slightly lower vibrotactile thresholds than did both never drinkers and drinkers reporting consuming more than 179 drinks per month. The heaviest drinking category (>179 drinks/month) had slightly slower mean conduction velocities and slightly smaller mean amplitudes than all other drinking categories. No consistent associations were observed between thermal thresholds and alcohol consumption. These results suggest that consuming up to 6 drinks per day alone does not cause slowed nerve conduction velocity, diminished amplitude of the evoked response, or elevated sensory thresholds in 35- to 45-year-old men.

Alcohol Nerve conduction Peripheral nerves Epidemiology Veterans

ALCOHOL consumption has long been associated with adverse effects on both central and peripheral elements of the nervous system. The peripheral neurologic consequences of alcoholism have been appreciated for over 100 years (38). The most commonly described pathologic consequences associated with alcoholic neuropathy are axonal degeneration of myelinated and unmyelinated fibers (3,39).

Because they are objective, physiologic, quantitative, and sensitive for detection of many conditions affecting the peripheral nerves, nerve conduction measures are considered the "gold-standard" for noninvasive clinical assessment of peripheral nerve function (19). Many studies have been published in which the effects of alcohol consumption on clinical electrophysiologic measures were estimated (2,4,6,11,17,20,24,25,26, 32,36,41). However, virtually all have been performed on subjects selected because of a diagnosis of alcoholism or following hospital admission for alcohol-related health problems. One study is available in which the drinking habits of patients with polyneuropathy were ascertained (18). Unfortunately, no comparison group was included to allow a true case-control analysis to be performed. We are aware of no cross-sectional nerve conduction studies of individuals selected independently of alcohol consumption history or clinical disorders associated with alcohol consumption. In particular, there seems to be no reports of the exposure-response relationship between alcohol consumption and objective measures of peripheral neurologic function.

Quantitative sensory testing has been employed by investigators needing rapid, quantitative, and nonaversive methods for assessing sensory function. Vibrotactile and thermal sensory threshold estimation are the most commonly performed quantitative sensory tests and have been used in a variety of studies of disease states, drugs, and intoxicants affecting peripheral nervous system function (5,14,22,34,37). Only one

[1] Requests for reprints should be addressed to Fredric Gerr, M.D., Division of Environmental and Occupational Health, Emory University School of Public Health, 1599 Clifton Road, Atlanta, GA 30329.

cross-sectional study has been published in which the effect of alcohol on vibrotactile thresholds was estimated (27).

The Vietnam Experience Study was a large cross-sectional epidemiologic study of a randomly selected group of veterans undertaken by the United States Centers for Disease Control (CDC) "to look for adverse health effects among men who had served in Vietnam" (ref. 7, p. 1). Two groups were defined in the study: (a) men who had served in Vietnam; (b) men who had served concurrently at duty stations other than Vietnam. An extensive telephone interview was conducted on more than 16,000 subjects, of whom over 4,000 participated in medical examinations. The medical examinations included measurement of multiple clinical outcomes, including nerve conduction velocity and amplitude as well as vibrotactile and thermal thresholds. The data from this study are available for public use.

In this article, we describe analyses of the relationship between measures of alcohol consumption and measures of (a) nerve conduction velocity and amplitude and (b) vibrotactile and thermal sensory thresholds observed among subjects who underwent medical examination as part of the Vietnam Experience Study. In addition, the relationship between reported alcohol consumption and serum gamma glutamyl transpeptidase (GGT), a sensitive biochemical indicator of alcohol consumption (1,28,40), is presented as a *positive control* to demonstrate validity of the self-reported measures of alcohol consumption.

METHOD

Subject eligibility criteria, subject selection and medical examination protocol used by the CDC are summarized in the initial companion paper in this series (21) and are presented in detail in CDC documentation (7). Only methods unique to this study are described below.

In brief, the cohort studied consisted of 4,462 male Vietnam-era veterans who underwent medical examinations at Lovelace Medical Center between June 3, 1985 and September 30, 1986. A large number of health outcome variables were obtained during the examinations, including a brief neurologic physical examination, peripheral nerve conduction measurements, and sensory threshold outcomes. Fasting blood samples were drawn on the morning of the second day. Breath alcohol levels were taken at the beginning of the second and third examination days.

Nerve Conduction Examination Procedures

Nerve conduction velocity (NCV) and amplitude for all nerves tested were measured using standard techniques (18) with a TECA TD10-MK2 electromyograph (TECA Corp., Pleasantville, NY) and surface electrodes. Specifically, median motor, median sensory, ulnar sensory, peroneal motor, and sural sensory NCVs and amplitudes were obtained from the dominant limb of each subject. All sensory conduction velocities were obtained using antidromic stimulation. Additional details of the electrophysiological testing protocol are provided the companion paper in this series (21) and in CDC documentation (8,10).

Skin temperature was recorded at the time of the electrophysiologic testing. Limbs with skin temperatures below 31°C were warmed with a water blanket. Forearm temperature was used as a covariate of median motor outcomes, palm temperature for median and ulnar sensory outcomes and mid-calf temperature for peroneal motor and sural sensory outcomes.

Sensory Threshold Procedures

Vibrotactile threshold examination procedure. The vibrotactile threshold examination procedure is described in detail the companion paper in this series (13) and in CDC documentation (10). A brief description follows. An electromechanical vibrometer (Vibratron, Chemo Tech, Inc., New Rochelle, NY) consisting of a controller unit and two identical transducers was used to measure vibrotactile thresholds. Attached to each transducer were hardened rubber posts which protruded through a Plexiglas plate so they could be contacted by either the toe or finger. The device produced vibration at 120 Hz. Voltage applied to the transducer units was read from an analog meter on the face of the controller unit. The voltage applied to the transducers was regulated by turning a knob on the controller unit. A two-alternative forced choice testing procedure was used to measure vibrotactile thresholds. The amplitude of the vibration (in microns) was proportional to the square of voltage applied. Because logarithmic transformation linearized the relationship between age and vibrotactile threshold and stabilized the variance, the common logarithm of the square of the voltage applied was used as the dependent variable in the statistical analyses. Higher thresholds indicate poorer sensory acuity.

Thermal threshold examination procedure. The thermal threshold examination procedure is also described in a companion paper (13) and CDC documentation (10). A brief description follows. A thermal testing device (Pfizer Thermal Tester, Sensortek, Clifton, NJ; now marketed as the NTE2 Thermal Tester, Physitemp, Clifton, NJ) consisting of two identical "thermal plates" or "stages" and a controller unit was used to measure thermal thresholds. The thermal plates were 4.6 × 4.6 cm and were temperature controllable to 0.1°C by manipulating the controller unit. Temperature control of the stages was achieved using a Peltier device and water perfusion. The temperature of each stage and the temperature difference between the stages are displayed digitally on the device. A two-alternative forced choice testing procedure requiring the subject to identify which of the two stages was cooler was used to determine thermal thresholds. During each trial one stage was always set at 25°C. The threshold was expressed in degrees centigrade. Because distributions for these thresholds displayed heteroskedasticity, the common logarithm of the calculated threshold was used in the statistical analyses. Higher thresholds indicate poorer sensory acuity.

Index finger and great toe skin temperatures were recorded with a digital thermometer at the time of sensory testing.

Measurement of Serum Liver Enzymes

As one of many blood tests, serum GGT concentrations were measured. GGT analyses were performed with a Kodak Ektachem 700 autoanalyzer. Concentrations of this liver enzyme are reported in IU/L. An elaborate quality control scheme was used to assure accurate and precise results (9). Briefly, "bench" and "blind" controls were used to monitor the precision of measurement over time as well as to monitor the repeatability of the measurement within the same analytical run. In addition, a statistical quality control program was used to monitor the quality of laboratory data obtained over the study period. Two full-time quality control supervisors and a board-certified clinical pathologist reviewed the quality control data daily.

Estimation of Alcohol Consumption

Standard questionnaires were administered to all subjects during the telephone interviews as well as during the medical

examinations to obtain information about a wide variety of health-related issues, including current and past alcohol consumption. During the telephone interview several questions about alcohol consumption were asked, including the dates and ages for beginning and ending of alcohol consumption, the average number of drinking days per month, and the average number of drinks consumed per drinking day. In addition, subjects were asked if there was a period of time of greater than 6 months duration during which they drank substantially heavier than at other times. Similar duration, frequency, and intensity information was obtained for this period of time as well. From this information an estimate of each subject's lifetime dose of alcohol was calculated. Two other alcohol consumption summary measures were derived from questions about current drinking practices asked during the medical examinations: average drinking intensity, expressed as the current average number of drinks per month and calculated from the average number of drinking days per month times the average number of drinks per drinking day, and recent heavy drinking, expressed as the number of occasions of drinking 5 or more drinks in 1 day during the past month. Because the distributions of these three alcohol summary variables (lifetime dose, current average drinking intensity, and recent heavy drinking) were highly skewed to the right and the shape of the dose response curves were not known, all three drinking variables were stratified into 5–7 easily interpretable ranges that left no fewer than 150 subjects in any group. Those subjects who reported during the telephone interview that they had never drunk as much a one alcoholic drink per month for a year and who also reported consuming no drinks per month at the time of the medical examination were considered "Never" drinkers.

Data Analysis

Exclusions. Of the 4,462 potential subjects, 328 (7.4%) were excluded from the present analyses. (Slightly fewer subjects were excluded in this paper than in the companion papers (13,21) because we did not want to exclude subjects who might have alcohol-related neurological impairment.) Only subjects with relatively rare conditions that might affect the nerve conduction and quantitative sensory outcomes or alcohol exposure measures were excluded in the present analyses. Other conditions potentially affecting the outcome measures that were more frequent were included as covariates in the statistical analyses. The numbers of subjects meeting each of the exclusion criteria are listed in Table 1. The exclusion criteria met most frequently were missing alcohol consumption or income information, history of diabetes mellitus, fasting blood glucose level greater than 140 mg/dL, elevated thyroid stimulating hormone level, unsatisfactory responses during the interview, or use of medications identified by the CDC as known to be associated with peripheral neuropathy (8). These medications were chloramphenicol, cisplatin, clioquinol, dapsone, diphenylhydantoin, disulfiram, ethionamide, glutethimide, gold, hydralazine, isoniazid, metronidazole, nitrofurantoin, perhexiline maleate, pyridoxine, sodium cyanate, thalidomide, and vincristine. Subjects were not excluded if they reported a history of cirrhosis, other alcoholic liver problems, or peripheral neuropathy, as it was thought that excluding such subjects might bias the analyses relating alcohol consumption to nerve conduction outcomes.

Data voiding. Inspection of initial descriptive statistics revealed several impossible values for some parameters. Therefore, a set of quality assurance void criteria were implemented. An individual nerve conduction data point was voided if it exceeded any of the following void criteria: (a) median motor amplitude < 400 mV; (b) median sensory amplitude < 0.5 mV; (c) ulnar sensory amplitude < 0.5 mV; (d) peroneal motor amplitude < 400 mV; (e) sural sensory amplitude < 0.5 mV; (f) median motor proximal latency < distal latency; (g) median sensory proximal latency < distal latency; (h) median sensory proximal distance < distal distance; (i) peroneal motor proximal latency < distal latency; (j) median motor NCV > 85 m/s; (k) median sensory NCV > 75 m/s; (l) ulnar sensory NCV > 75 m/s; (m) peroneal motor NCV > 85 m/s; (n) sural sensory NCV > 75 m/s; (o) finger or toe vibrotactile threshold > 50 volts; (p) finger or toe thermal threshold > 20°C. These void criteria were drawn in part from those used by CDC in their analyses of these data to determine the effects of the Vietnam experience (8). If a latency or distance was voided, the corresponding NCV was also voided. In addition, on occasion one or two wild outlier data points identified by visual inspection of plots were voided (e.g., two BMIs > 60.0).

TABLE 1

EXCLUSION OF SUBJECTS FOR THE NERVE CONDUCTION ANALYSES

Exclusion Criterion	Number*
Age >46	1
Cancer (except skin)	29
Medications	36
Unsatisfactory interview	40
Alcohol or income information missing	114
Breath alcohol >0.1% BAC	1
Blood urea nitrogen >40 mg/dL	1
Thyroid stimulating hormone >8 mIU/L	47
Fasting blood glucose <40 mg/dL	1
History of diabetes mellitus	51
Fasting blood glucose >140 mg/dL	48
Total # of subjects undergoing examination	4462
Total # of subjects excluded	328* (7.4%)
Total # of subjects NOT excluded	4134 (92.6%)

*Some subjects met more than one exclusion criterion.

Statistical methods. Means and SDs were calculated for each exposure stratum of the three alcohol consumption variables (i.e., lifetime dose, current average drinking intensity, and recent heavy drinking), selected demographic characteristics, serum GGT, 10 nerve conduction outcomes, and 4 quantitative sensory outcomes. Boxplots of these data stratified by each of the alcohol exposure variables were inspected visually.

General linear models (31) were fitted separately for each of the 10 nerve conduction and 4 quantitative sensory outcomes including only one of the three exposure strata variables at a time. In the 42 analyses, the variables included as potential predictors in addition to an alcohol exposure stratum variable were age, height, BMI (weight in kg divided by height in m squared), skin temperature near the appropriate nerve segment, an indicator variable for race (nonblack/black), an indicator variable for place of service (non-Vietnam/Vietnam), a categorical variable for the eight examiners administering the nerve conduction tests, and an index for household income. Household income categories were: 1 = <$10,000; 2 = $10,000 to $19,999; 3 = $20,000 to $29,999; 4 = $30,000 to $39,999; 5 = > = $39,999.

A large number of parameters were estimated in these analyses and many of them could achieve conventional levels of statistical significance due to chance alone. In addition, considerable precision in the estimates due to the large sample size could lead to statistically significant parameters that have little biological significance. The pattern of results and consistency across outcomes was considered more important for interpreting findings than the probabilities associated with sampling variability. Therefore, for the descriptive statistics presented, no probabilities associated with rejecting a null hypothesis are provided. Indications of those parameter estimates from the multivariable analyses having associated probabilities less than conventional levels of statistical significance are included but only in the tabular presentation. In this context, no adjustment for multiple comparisons was attempted.

RESULTS

Description of Sample Demographics

To investigate the potential for confounding in the statistical analyses, the distributions of the other covariates as a function of drinking intensity group were examined. Descriptive statistics for several demographic and anthropometric variables are given in Table 2 for the drinking intensity groups. Age and height did not vary among the drinking intensity groups. Compared to the other drinking intensity groups, the highest two drinking intensity groups weighed slightly less, were slightly less educated, had slightly lower household income, were more likely to be black, and were slightly more likely to have served in Vietnam. Smoking status was clearly related to drinking intensity. These differences across drinking intensity groups suggested the need for multivariable analyses, but the magnitude of the associations with drinking intensity category indicated little need for concern about poor precision in parameter estimation in such analyses.

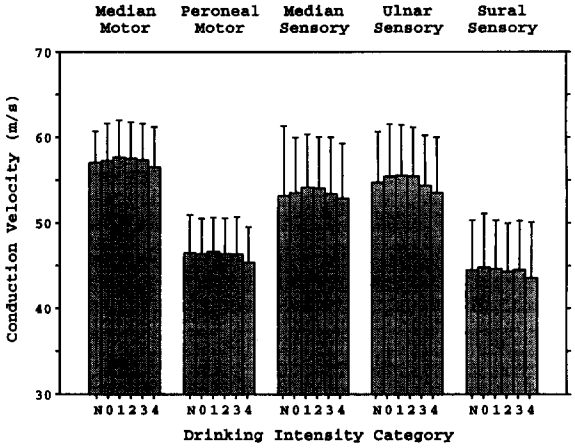

FIG. 1. Mean (+1 SD) nerve conduction velocity for each of the five nerves studied, stratified by drinking intensity category (N = Never-drinker, 0 = current nondrinker, 1 = 1–29 drinks/month, 2 = 30–89 drinks/month, 3 = 90–179 drinks per month, and 4 = >179 drinks/month).

The potential for bias in the statistical analysis due to missing data being differentially distributed across drinking intensity groups was also investigated. The number of subjects in whom evoked responses could not be obtained was negligible for all nerves except the sural. The proportion of subjects for whom sural nerve responses were not obtained is shown for each drinking intensity group in Table 2. Overall, sural nerve responses were not obtained in 3% of the subjects. The proportion of absent responses was similar for all the drinking intensity groups, except that the proportion for the 1–29 drinks per month group was slightly lower. Such small differ-

TABLE 2

DEMOGRAPHIC CHARACTERISTICS OF THE SAMPLE STRATIFIED BY DRINKING INTENSITY CATEGORY

		Drinking Category (Average Drinks/Month)						
		Never	0	1–29	30–89	90–179	>179	Overall
N		409	599	1553	1071	349	153	4134
Age (year)	(mean)	38.6	38.3	38.5	38.2	38.0	37.6	38.3
	(SD)	2.4	2.6	2.5	2.5	2.4	2.7	2.5
Height (cm)	(mean)	176.6	176.5	176.2	176.2	176.3	176.6	176.3
	(SD)	6.5	7.4	6.7	6.6	6.5	6.3	6.7
Weight (kg)	(mean)	85.0	84.9	83.7	83.1	82.0	81.4	83.6
	(SD)	15.1	17.0	15.5	14.4	14.4	14.6	15.3
BMI (kg/m^2)	(mean)	27.2	27.2	26.9	26.6	26.3	26.1	26.8
	(SD)	4.4	4.9	4.5	4.0	4.2	4.3	4.4
Race (% black)		11.7	9.0	9.4	12.6	14.3	20.9	11.3
Education (year)	(mean)	13.2	12.9	13.6	13.4	12.7	12.5	13.3
	(SD)	2.3	2.3	2.3	2.2	2.0	2.1	2.3
Income category	(mean)	4.2	4.0	4.6	4.5	4.1	3.7	4.4
	(SD)	1.4	1.4	1.5	1.5	1.5	1.7	1.5
Place of service (% Ever Vietnam)		55.5	57.1	53.1	54.7	59.9	64.0	55.3
Smoking status (% currently smoking)		24.2	43.7	39.0	51.5	66.5	69.3	44.9
Absent sural nerve evoked response (%)		4.5	3.4	2.3	3.7	3.9	4.5	3.0

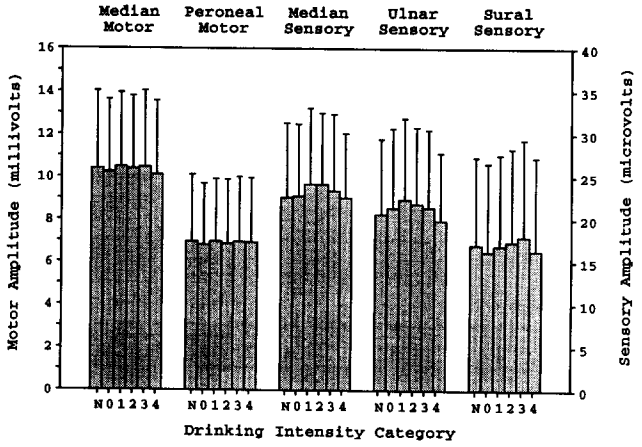

FIG. 2. Mean (+1 SD) nerve conduction amplitude for each of the five nerves studied, stratified by drinking intensity category (designated as in Fig. 1).

ences across drinking intensity groups were considered unlikely to result in substantially biased estimates in the multivariable analyses.

Description of Nerve Conduction and Threshold Outcomes

Bar charts of the mean conduction velocities for the five nerves studied stratified by drinking intensity group are presented in Fig. 1. As expected, motor and sensory conduction velocities were slower in the lower extremity than in the upper extremity. Similarly, bar charts for motor and sensory nerve conduction amplitudes (Fig. 2) reveal that the amplitudes were smaller in the lower extremity than in the upper extremity. Bar charts of the mean vibrotactile and thermal thresholds for the two sites tested stratified by drinking intensity are presented in Fig. 3. Vibrotactile thresholds were lower in the finger than in the toe. Thermal thresholds were similar between finger and toe.

The mean nerve conduction velocities of drinkers consuming 1-29, 30-89, and 90-179 drinks per month were, in general, slightly faster than those of either the Never-drinker group or the group drinking >179 drinks per month. For all nerves studied the slowest mean conduction velocities were observed in the heaviest drinking category. The difference in mean conduction velocity between the heaviest drinking category and all other categories was small, however. Specifically, the difference in mean nerve conduction velocity between the heaviest drinking category and any other category was about two meters per second or less for all nerves studied. The difference in mean conduction velocity between the heaviest drinking category and Never-drinkers was less than 1.3 meters per second for all nerves studied.

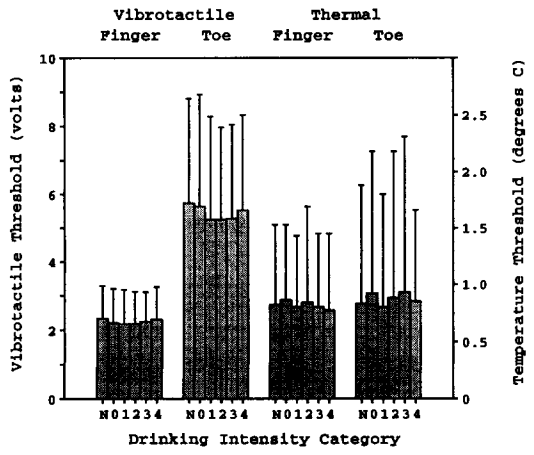

FIG. 3. Mean (+1 SD) vibrotactile and thermal thresholds for fingers and toes, stratified by drinking intensity category (designated as in Fig. 1).

For most measures of amplitude a similar pattern of slightly greater mean amplitude was observed for the categories of 1-29, 30-89, and 90-179 drinks per month when compared to either the Never-drinkers or to the heaviest drinking category. For all nerves studied except the peroneal motor nerve, the smallest amplitudes were observed in the heaviest drinking category. As was the case for nerve conduction velocities, the difference in mean amplitude between the heaviest drinking category and any other category was small. Specifically, the difference in mean sensory amplitude between the heaviest drinking category and any other category was about 2.5 mV or less for all three sensory nerves studied. The difference in mean sensory amplitude between the heaviest drinking category and Never-drinkers was 0.8 mV for all three sensory nerves studied. The difference in mean motor amplitude between the heaviest drinking category and any other category was 0.4 mV or less for the two motor nerves studied. The difference in mean motor amplitude between the heaviest drinking category and Never-drinkers was 0.3 mV or less for the two motor nerves studied.

The mean vibrotactile thresholds of virtually all drinking categories, including those currently consuming no alcohol, were slightly lower (i.e., better sensory function) than the Never-drinker category. For both finger and toe vibrotactile thresholds, the best sensory function was observed in the 1-29 and 30-89 drinks per month categories. No clear association was observed between alcohol consumption category and either finger or toe thermal thresholds.

To illustrate the relative magnitude of these effects better, boxplots are presented in Fig. 4 of the nerve conduction outcome showing the strongest relationship to alcohol consumption (i.e., ulnar sensory NCV). For comparison purposes, a corresponding set of boxplots of GGT data are also presented in Fig. 4. For comparison purposes, a dotted line is used to extend the median of the Never-drinkers distribution through the boxes for the other drinking exposure categories. The small magnitude of the differences in ulnar sensory NCV between drinking exposure intensity groups relative to the total variance in ulnar sensory NCVs is evident. On the other hand, a large, monotonic increase in GGT levels with increasing alcohol drinking intensity level can been seen in Fig. 4. The effect of alcohol consumption on GGT is seen for the group consuming 30-89 drinks per month and all higher consumption categories. The highest drinking intensity group had a mean GGT of more than three times that of the Never-drinker category.

Results of the General Linear Models

Because several variables that might affect the outcomes of interest were not equally distributed across the alcohol consumption categories, general linear models were fitted to assess the potential for confounding by them in these crude

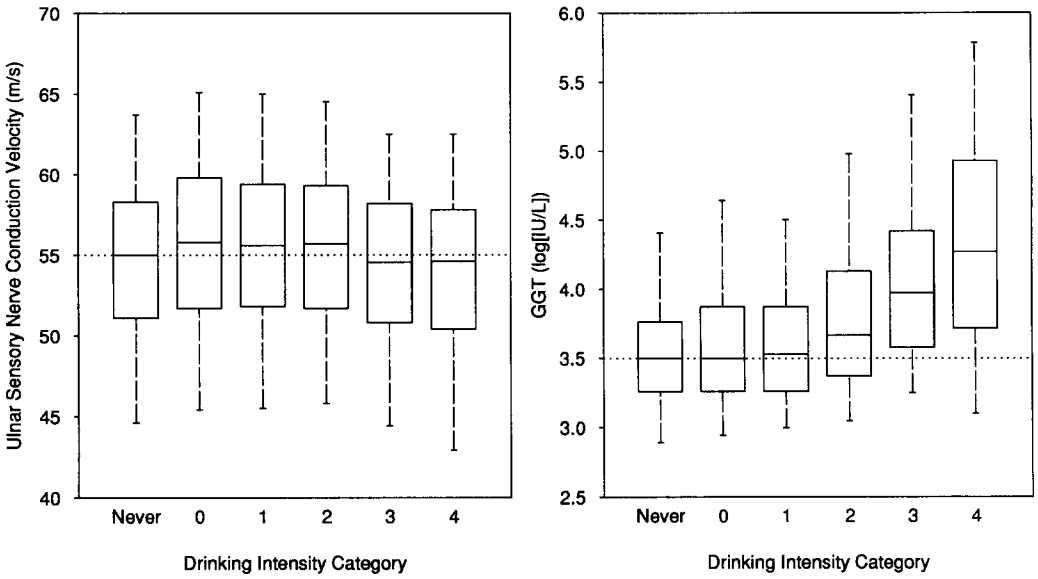

FIG. 4. Boxplots (5th, 25th, 50th, 75th, and 95th percentiles) of the distributions of ulnar nerve conduction velocity (A) and GGT (B) as a function of drinking intensity category (designated as in Fig. 1). The lower and upper sides of each box represent the 25th and 75th percentiles, respectively, of the distributions of these outcomes for the drinking intensity category, and the horizontal line inside each box represents the median. The line below each box extends to the 5th percentile and the line above the box extends to the 95th percentile.

analyses. Most nerve conduction outcomes differed significantly as a function of age, nerve conduction examiner, BMI, height, skin temperature, race, smoking status, and household income. Place of military service was not related to any of these nerve conduction outcomes. These relationships are explored in greater detail in a companion paper (21).

Vibrotactile thresholds differed significantly as a function of height, BMI, age, race, income, and examiner. Thermal thresholds differed significantly as a function of skin temperature, height, BMI, race, income, and examiner. These relationships are explored in greater detail in a companion paper (13).

To assess the magnitude of potential confounding by the covariates identified above, comparison was made between the differences observed in the neurologic outcomes between the Never-drinker group and all other alcohol consumption groups for both the crude and adjusted results. A summary of this comparison is shown in Table 3 for nerve conduction outcomes and in Table 4 for quantitative sensory outcomes. The "crude" results represent the difference between the raw means for each alcohol exposure group and the Never-drinker group, and the "adjusted" results represent the parameter estimates from the general linear models fitted to the raw data. Changes in the magnitude of the estimated effect of heavy alcohol consumption on nerve conduction outcomes were small and inconsistent after adjustment for potential confounders. In the general linear model analyses the only statistically significant differences between the Never-drinker group and the other drinking groups were better function on several outcomes among the 1–29 and 30–89 drinks per month groups and slower peroneal NCV in the >179 drinks per month group.

Changes in the magnitude of the estimated effect of heavy alcohol consumption on vibrotactile thresholds were also small after adjustment for potential confounders. In the general linear model analysis of finger vibrotactile threshold, significantly better thresholds were observed among the 0, 1–29, and 30–89 drinks per month categories when compared to the Never-drinker category. Differences between the heaviest drinking category and the Never-drinkers were not significant. In the general linear model analysis of toe vibrotactile threshold, significantly better thresholds were observed among the 1–29 and 30–89 drinks per month categories when compared to the Never-drinker category. Differences between the heaviest drinking category and the Never-drinkers were not significant.

After adjustment for potential confounders, significantly lower (better) finger thermal thresholds were observed in the >179 drinks per month group when compared to the Never-drinker group. No significant differences between the Never-drinker category and any other drinking category was observed for toe thermal threshold after adjustment for potential confounders. No systematic effect of alcohol consumption category on either finger or toe thermal threshold was observed.

Similar analyses were conducted using the other two alcohol consumption variables, lifetime alcohol dose, and recent heavy drinking. The results obtained in these analyses were essentially identical to those shown using drinking intensity to categorize alcohol consumption. Specifically, the magnitude and pattern of the effect of alcohol consumption on the 14 neurologic outcomes reported in this paper were essentially no different from those shown. For this reason, only results with drinking intensity are presented.

DISCUSSION

In this cross-sectional study of Vietnam-era veterans, only small effects of alcohol consumption were observed for measures of (a) nerve conduction velocity and amplitude and (b)

TABLE 3

EFFECT OF ALCOHOL ON NERVE CONDUCTION OUTCOMES—DIFFERENCES RELATIVE TO NEVER-DRINKERS

		Drinking Category (Drinks/Month)					Never-Drinker	
Outcome	Analysis	0	1–29	30–89	90–179	>179	Mean	(SD)
Median motor NCV (m/s)	Crude	0.21	0.69	0.55	0.36	−0.46	57.00	(3.66)
	Adjusted	0.20	0.58*	0.53*	0.47	−0.29		
Median sensory NCV (m/s)	Crude	0.45	1.04	0.96	0.25	−0.26	53.14	(6.15)
	Adjusted	0.41	0.90†	0.89†	0.37	−0.24		
Ulnar sensory NCV (m/s)	Crude	0.72	0.82	0.76	−0.37	−1.20	54.71	(5.90)
	Adjusted	0.65	0.72*	0.89†	0.05	−0.57		
Peroneal motor NCV (m/s)	Crude	−0.13	0.18	−0.07	−0.16	−1.15	46.47	(4.51)
	Adjusted	−0.07	0.14	−0.04	−0.01	−0.94†		
Sural sensory NCV (m/s)	Crude	0.34	0.22	−0.09	0.07	−0.89	44.41	(5.82)
	Adjusted	0.13	0.04	−0.17	−0.01	−1.08		
Median motor amp. (mV)	Crude	−0.17	0.08	0.03	0.07	−0.27	10.38	(3.63)
	Adjusted	−0.05	0.09	−0.02	0.14	−0.28		
Median sensory amp. (μV)	Crude	0.11	1.55	1.62	0.82	−0.07	22.57	(8.72)
	Adjusted	0.33	1.25*	1.31*	0.65	−0.11		
Ulnar sensory amp. (μV)	Crude	0.78	1.79	1.38	0.85	−0.80	20.56	(8.81)
	Adjusted	0.92	1.42*	1.19	0.77	−0.26		
Peroneal motor amp. (mV)	Crude	−0.120	−0.034	−0.027	−0.017	−0.023	6.91	(2.93)
	Adjusted	−0.036	0.042	−0.024	−0.071	−0.062		
Sural sensory amp. (μV)	Crude	−0.47	0.13	0.60	1.14	−0.51	16.70	(10.34)
	Adjusted	−0.56	−0.23	0.39	0.86	0.09		

*Designates $p < 0.05$ and †designates $p < 0.01$ that the parameter estimate is equal to 0.

vibrotactile and thermal thresholds. Very heavy drinking (i.e., greater than 179 drinks per month) was associated with slower conduction velocity and smaller amplitudes for virtually all nerves studied. A similar, though smaller, effect was also associated with never drinking; the best nerve conduction function was observed for groups of low to moderate consumers of alcohol. A similar pattern in which the best nerve function was observed among groups of low to moderate consumers of alcohol was found for vibrotactile thresholds. Essentially no consistent relationship between alcohol consumption group and thermal thresholds was observed.

Although many studies of alcoholics using nerve conduction measures to identify peripheral nervous system effects have been published, none have included subjects chosen independently of alcohol consumption or clinical disorders associated with alcohol consumption. Therefore, the results of this study are not directly comparable to others in the literature. Several studies using vibrotactile thresholds of such subjects have been published (12,27,35). After exclusion of subjects with a diagnosis of alcoholism or major health or social consequences of drinking (i.e., alcohol withdrawal seizures, morning shaking, conflicts with the law, or use of professional assistance for drinking problems) none of the investigators found significant associations between alcohol consumption and vibrotactile thresholds.

Never-drinker subjects were considered a better comparison group than subjects not drinking at the time of the study because of concern that some of the latter group may have

TABLE 4

EFFECT OF ALCOHOL ON QUANTITATIVE SENSORY THRESHOLDS OUTCOMES—DIFFERENCES RELATIVE TO NEVER-DRINKERS

		Drinking Category (Drinks/Month)					Never-Drinker	
Outcome	Analysis	0	1–29	30–89	90–179	>179	Mean	(SD)
Finger vibration [log (V^2)]	Crude	−0.051	−0.065	−0.061	−0.027	−0.011	0.665	(0.348)
	Adjusted	−0.054*	−0.053*	−0.053*	−0.024	−0.023		
Toe vibration [log (V^2)]	Crude	−0.030	−0.089	−0.078	−0.077	−0.025	1.402	(0.463)
	Adjusted	−0.021	−0.061†	−0.052*	−0.053	−0.021		
Finger temperature [log (°C)]	Crude	0.025	−0.006	0.004	−0.005	−0.031	−0.184	(0.294)
	Adjusted	0.009	−0.005	−0.003	−0.023	−0.060*		
Toe temperature [log (°C)]	Crude	0.041	−0.006	0.018	0.024	0.036	−0.242	(0.352)
	Adjusted	0.031	0.001	0.015	0.002	−0.006		

*Designates $p < 0.05$ and †designates $p < 0.01$ that the parameter estimate is equal to 0.

ɔ abstain due to a health condition and might there-
ɜ biased the comparisons. However, in general, nerve
of the current nondrinking group was similar to that
ɜver-drinker group.

ɔossible reason for the small magnitude of the effects
in these data is imprecision in the ascertainment of
ɔonsumption. The fact that all three summary mea-
alcohol consumption showed a strong dose-effect re-
th serum GGT consistent with that reported by other
tors (1,28,40) suggests that the ascertainment of alco-
ɹmption was valid in this population.

ɪer potential concern is that the data voiding criteria
/ have resulted in masking of the effect of alcohol on
ɔduction measures. Voiding was performed on a
ɔset of the data points to remove physiologically un-
impossible values. Despite rigorous quality control
ɨ, some recording and coding errors are inevitable in
ɔlogic studies of thousands of subjects. Void criteria
sen to maximize the removal of erroneous data while
ng removal of abnormal, but correct, values. To
ent, these choices are arbitrary. The number of data
ɔided was small, and the magnitude of any potential
he analyses resulting from voiding is likely to have
ɹll.

analyses employing drinking intensity as the measure
ɔl consumption were reported in this paper. This alco-
umption variable may not have been the one most
ɜlated to peripheral nerve function, however. It was
ɹs the primary measure of alcohol consumption be-
) evidence exists in the literature that alcohol-related
hy is at least partially reversible (15,16), and there-
ɜent drinking intensity seemed the most biologically
ate alcohol consumption measure to relate to current
al nerve function; (b) neither of the other two alcohol
ɔtion indices considered, lifetime alcohol consump-
recent heavy drinking, showed more of an effect on
ɔmes than did current drinking intensity.

xtremely unlikely that the small magnitude of alcohol
ɹ these analyses resulted from low statistical power
effects. Some error in the dependent variables was
ed by the use of multiple examiners and perhaps by
ɜtors as well. However, the sample size of this study is
one and two orders of magnitude larger than virtually
ɔus studies examining the same research issues. The
ɜy present did not obscure strong relationships be-
e nerve conduction outcomes and other expected pre-
ɹriables such as height and skin temperature.

ɜesults reported for the sural nerve may be slightly
ecause the analyses did not include data from those
with unobtainable evoked responses. Although ab-
l responses may indicate disease, they are also known
in a small proportion of healthy subjects (19). The
l bias in these analyses is likely to be small because (a)
all proportion of subjects for whom responses could
ɔtained was small and (b) the differences across drink-
ɡories in the proportion of subjects with absent re-
were small. In addition, this potential bias does not
results of the nerve conduction outcomes for the
ɹr nerves studied, as the number of subjects in whom
ɜesponses could not be obtained for those nerves was
e.

ɪs were made to determine whether differences be-
cohol consumption groups on other potentially con-
ɡ variables affected the observed results. Specifically,
ɜes were observed between alcohol consumption groups for race, BMI, place of military service, socioeconomic status, and education. Multivariable analyses were performed in which the effect of alcohol consumption group on nerve conduction and quantitative sensory outcomes was estimated while simultaneously controlling for the effect of these potential confounders. Differences between the crude and the adjusted estimates of the effects of alcohol were very small and inconsistent in their direction. It is unlikely that confounding was the cause of the weakness of the observed effects of alcohol on the outcomes of interest.

Nor is it likely that the weak effects observed in this population resulted from inadequate consumption of alcohol by the participants. This population included a large number of moderate and heavy drinkers. Specifically, 34% of this population met U.S. National Institute on Alcohol Abuse and Alcoholism criteria for "moderate" drinking, and 17% met its criteria for "heavy" drinking (42). These proportions are consistent with other reports of military veterans being heavier consumers of alcohol than nonveteran comparison subjects (29).

The lack of a larger effect of alcohol consumption on nerve conduction measures may be due to the selection criteria for study subjects. All subjects passed initial health screening examinations (most at age 18 years) to be inducted into military service. The more substantial effects of alcohol on nerve conduction presented in the existing literature were virtually all observed in chronic alcoholics or patient groups. This is the only large cross-sectional study of the effects of alcohol consumption on peripheral nerve function performed on subjects who were not chosen on the basis of either a diagnosis of alcoholism or the presence of a known alcohol-related health event. Care should be taken in attempting to extrapolate these results outside a group of initially healthy young males.

The results of this study suggest that other factors in addition to heavy alcohol consumption are necessary for the development of peripheral nerve dysfunction. Nutrition has been widely suggested as a cofactor in the development of alcohol-related neuropathy (33,38). No measure of nutritional status was available for use in these analyses; therefore, it was not possible to assess its impact on nerve function in this study. These results do suggest, however, that heavy alcohol consumption, per se, is not directly neurotoxic, as has been proposed by some investigators (3,26).

The finding of the best nerve function among light and moderate drinkers is consistent with studies of the effect of alcohol consumption on other health outcomes, such as better cardiovascular function (30) and fewer hospitalizations (23) in light and moderate drinkers than among nondrinkers. These results suggest that light and moderate alcohol consumption either results in improved function of several organ systems or is associated with other personal attributes (e.g., diet and lifestyle) that result in better function. Prospective studies of neurologic function are needed to clarify this issue.

In conclusion, there was no evidence of a negative effect on these neurologic outcomes of even moderately heavy drinking in these initially healthy, relatively young subjects. A small negative effect of very heavy drinking was observed. The remarkably modest effects observed were not likely the result of poor ascertainment of exposure or outcome, nor of confounding.

These results have important implications for both clinical practice and epidemiologic research. They suggest that in their late 30s and early 40s, male consumers of up to 6 drinks per day are not at increased risk of poor nerve conduction as measured by standard electrophysiologic methods nor of di-

minished vibrotactile or thermal sensory acuity. Furthermore, most drinkers of more than 6 drinks per day do not exhibit abnormally slowed peripheral nerve conduction velocity, reduced amplitude, or decreased sensory acuity. Therefore, other factors alone or in combination with alcohol consumption should be sought to explain reduced peripheral nerve function when observed electrophysiologically or clinically in heavy drinkers. In addition, these results suggest that failure to control for alcohol consumption in epidemiologic studies using nerve conduction or quantitative sensory threshold measures will not result in substantial confounding of the observed results. In fact, controlling for alcohol consumption in epidemiologic studies of potentially toxic agents with which ethanol may interact in an adverse way (e.g., solvents) may reduce the observed magnitude of an effect attributable to the neurotoxic agent.

Finally, these results should not be interpreted as suggesting that even moderate levels of alcohol consumption are without potential adverse health effects. The chronic effects of alcohol consumption on other organ systems as well as the social and behavioral consequences of acute alcohol intoxication are serious medical and public health hazards.

ACKNOWLEDGEMENTS

This work was supported in part by a cooperative agreement with the U.S. National Institute for Occupational Safety and Health (NIOSH) and the U.S. Agency for Toxic Substances and Disease Registry (U50/CCU403261) and in part by a grant from the NIOSH (K01 OH00098). Data tapes and extensive study documentation were provided by the National Center for Environmental Health and Injury Control, U.S. Centers for Disease Control. The authors thank Ms. Deborah Harris-Abbott for her assistance with data management and helpful suggestions for this manuscript.

REFERENCES

1. Bagrel, A.; d'Houtaud, A.; Gueguen, R.; Siest, G. Relations between reported alcohol consumption and certain biological variables in an "unselected" population. Clin. Chem. 25:1242–1246; 1979.
2. Ballantyne, J. P.; Hansen, S.; Weir, A. Whitehead, J. R. G.; Mullin, P. J. Quantitative electrophysiological study of alcoholic neuropathy. J. Neurol. Neurosurg. Psychiat. 43:427–432; 1980.
3. Behse, F.; Buchthal, F. Alcoholic neuropathy: Clinical, electrophysiological and biopsy findings. Ann. Neurol. 2:95–110; 1977.
4. Blackstock, E.; Rushworth, G.; Gath, D. Electrophysiological studies in alcoholism. J. Neurol. Neurosurg. Psychiat. 35:326–334; 1972.
5. Bove, F. J.; Letz, R.; Baker, E. L., Jr. Sensory thresholds among construction trade painters: a cross-sectional study using new methods for measuring temperature and vibration sensitivity. J. Occ. Med. 31:320–325; 1989.
6. Casey, E. B.; Le Quesne, P. M. Electrophysiological evidence for a distal lesion in alcoholic neuropathy. J. Neurol. Neurosurg. Psychiat. 35:624–630; 1972.
7. Centers for Disease Control, Health status of Vietnam veterans. Vol.I, Synopsis. Atlanta, GA: U.S. Department of Health and Human Services; 1989.
8. Centers for Disease Control, Health status of Vietnam veterans. Vol. III, Medical examinations. Atlanta, GA: U.S. Department of Health and Human Services; 1989.
9. Centers for Disease Control. Health status of Vietnam veterans. Supplement A, Laboratory methods and quality control. Atlanta, GA: U.S. Department of Health and Human Services; 1989.
10. Centers for Disease Control, Health status of Vietnam veterans. Supplement C, Medical and psychological procedure manuals and forms. Atlanta, GA: U.S. Department of Health and Human Services; 1989.
11. Claus, D.; Eggers, R.; Engelhardt, A.; Neundorfer, B.; Warecka, K. Ethanol and polyneuropathy. Acta Neurol. Scand. 72:312–316; 1985.
12. Era, P.; Jokela, J.; Suominen, H.; Heikkinen, E. Correlates of vibrotactile thresholds in men of different ages. Acta Neurol. Scand. 74:210–217; 1986.
13. Gerr, F.; Letz, R. Covariates of human peripheral nerve function: II. Vibrotactile and thermal thresholds. Neurotoxicol. Teratol. 16:000–000; 1994.
14. Halonen, P.; Halonen, J. P.; Lang, H. A.; Karskela, V. Vibratory perception thresholds in shipyard workers exposed to solvents. Acta Neurol. Scand. 73:561–565; 1986.
15. Hawley, R. J.; Kurtzke, J. F.; Armbrustmacher, V. W.; Saini, N.; Manz, H. The course of alcoholic-nutritional peripheral neuropathy. Acta Neurol. Scand. 66:582–589; 1982.
16. Hillbom, M.; Wennberg, A. Prognosis of alcoholic peripheral neuropathy. J. Neurol. Neurosurg. Psychiat. 47:699–703; 1984.
17. Jurko, M. F.; Currier, R. D.; Foshee, D. P. Peripheral nerve changes in chronic alcoholics: A study of conduction velocity in motor nerves. J. Nerv. Ment. Dis. 139:488–490; 1964.
18. Kempainen, R.; Juntunen, J.; Hillbom, M. Drinking habits and peripheral alcoholic neuropathy. Acta Neurol. Scand. 65:11–18; 1982.
19. Kimura, J. Electrodiagnosis in diseases of nerve and muscle: Principles and practice. Philadelphia: F.A. Davis; 1983.
20. Lefebvre D'Amour, M.; Shahani, B. T.; Young, R. R.; Bird, K. T. The importance of studying sural nerve conduction and late responses in the evaluation of alcoholic subjects. Neurology 29: 1600–1604; 1979.
21. Letz, R.; Gerr, F. Covariates of human peripheral nerve function: I. Nerve conduction velocity and amplitude. Neurotoxicol. Teratol. 16:000–000; 1993.
22. Lindblom, U.; Tegner, R. Thermal sensitivity in uremic neuropathy. Acta Neurol. Scand. 71:290–294; 1985.
23. Longnecker, M. P.; MacMahon, B. Associations between alcoholic beverage consumption and hospitalization, 1983 health interview survey. Am. J. Pubic Health 78:153–156; 1988.
24. Mawdsley, C.; Mayer, R. F. Nerve conduction in alcoholic polyneuropathy. Brain 88:335–356; 1965.
25. Mayer, R. Peripheral nerve conduction in alcoholics. Psychosom. Med. 28:475–483; 1966.
26. Melgaard, B.; Andersen, K.; Ahlgren, P.; Danielsen, U. T.; Sorensen, H. Peripheral neuropathy, cerebral atrophy, and intellectual impairment in chronic alcoholics. Acta Neurol. Scand. 70: 336–344; 1984.
27. Melgaard, B.; Saelan, H.; Hedegaard, L. Symptoms and signs of polyneuropathy and their relation to alcohol intake in a normal male population. Acta Neurol. Scand. 73:458–460; 1986.
28. Papoz, L.; Warnet, J. M.; Pequignot, G.; Eschwege, E.; Claude, J. R.; Schwartz, D. Alcohol consumption in a healthy population: Relationship to gamma glutamyl transferase activity and mean corpuscular volume. J.A.M.A. 245:1748–1751; 1981.
29. Richards, M. S.; Goldberg, J.; Rodin, M. B.; Anderson, R. J. Alcohol consumption and problem drinking in white male veterans and nonveterans. Am. J. Public Health 79:1011–1015; 1989.
30. Rimm, E. B.; Giovannucci, E. L.; Willett, W. C.; Colditz, G. A.; Ascherio, A.; Rosner, B. et al. Prospective study of alcohol consumption and risk of coronary disease in men. Lancet 338: 464–468; 1991.
31. SAS User's Guide: Statistics (Version 5). Cary, NC: SAS Institute; 1985.
32. Scholz, E.; Diener, H. C.; Dichgans, J.; Langohr, H. D.; Schied, W.; Schupmann, A. Incidence of peripheral neuropathy and cerebellar ataxia in chronic alcoholics. J. Neurol. 233:212–217; 1986.
33. Shields, R. W. Alcoholic polyneuropathy. Muscle & Nerve 8:183–187; 1985.
34. Sosenko, J. M.; Gadia, M. T.; Natori, N.; Ayyar, R.; Ramos, L. B.; Skyler, J. S. Neurofunctional testing for the detection of

diabetic peripheral neuropathy. Arch. Intern. Med. 147:1741–1744; 1987.
35. Sosenko, J. M.; Kato, M.; Soto, R.; Ayyar, D. R. Determinants of quantitative sensory testing in nonneuropathic individuals. Electromyogr. Clin. Neurophysiol. 29:459–463; 1989.
36. Tackmann, W.; Brennwald, J.; Nigst, H. Sensory electroneurographic parameters and clinical recovery of sensibility in sutured human nerves. J. Neurol. 229:195–206; 1983.
37. van der Hoop, R. G.; Vecht, C. J.; van der Burg, M. E.; Elderson, A.; Boogerd, W.; Heimans, J. J.; Vries, E. P.; van Houwelingen, J. C.; Jennekens, F. G.; Gispen, W. H.; et al. Prevention of cisplatin neurotoxicity with an ACTH(4–9) analogue in patients with ovarian cancer see comments. N. Engl. J. Med. 322: 89–94; 1990.
38. Victor, M.; Adams, R. D. On the etiology of the alcoholic neurologic diseases. Am. J. Clin. Nutr. 9:379–397; 1961.
39. Walsh, J. C.; McLeod, J. G. Alcoholic neuropathy: An electrophysiological and histological study. J. Neurol. Sci. 10:457–469; 1970.
40. Whitehead, T. P.; Clarke, C. A.; Whitefield, A. G. Biochemical and haematological markers of alcohol intake. Lancet 1:978–981; 1978.
41. Willer, J. C.; Dehen, H. Respective importance of different electrophysiological parameters in alcoholic neuropathy. J. Neurol. Sci. 33:387–396; 1977.
42. Williams, G. D.; Dufour, M.; Bertolucci, D. Drinking levels, knowledge, and associated characteristics, 1985 NHIS findings. Public Health Rep. 101:593–598; 1986.