Reprinted from DIABETES CARE, VOL. 10, NO. 4, JULY–AUGUST 1987

Vibratory and Cooling Detection Thresholds Compared With Other Tests in Diagnosing and Staging Diabetic Neuropathy

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Increasingly more tests are being used to detect and characterize diabetic polyneuropathy, but their value in setting minimal criteria for the diagnosis of neuropathy and for staging severity remains inadequately studied. In 180 diabetics, we compared the percentage of patients with test abnormalities and associations among test results, evaluating neuropathic symptoms [neuropathy symptom score (NSS) and neuropathy scale of neuropathy symptom profile (NNSP)], deficits [neurologic disability score (NDS) and vibratory (VDT) and cooling (CDT) detection thresholds], or nerve dysfunction [nerve conduction (NC)]. The percentage of patients that were abnormal varied considerably depending on criteria for abnormality and the tests used. Abnormality (≥3 SD of 1 or more parameters) of NC of one or more of four nerves occurred in 80%, of two or more in 69%, of three or more in 46%, and of four in 21%. Similarly, for other tests, the rate of abnormality decreased with use of increasingly stringent criteria. Setting the criteria for abnormal NC at abnormality of two or more nerves, NSS at ≥1, NDS at >6, NNSP at ≥97.5th percentile, and at ≥95th percentile for the other tests, NC was abnormal in 69%, NSS in 54%, NDS in 48%, NNSP in 47%, VDT in 44%, and CDT in 35%. Abnormality of any two or more of the six tests evaluated occurred in 64% of patients. Of the 55 patients without abnormality of NC, NSS was abnormal in nine, NDS in five, NNSP in seven, VDT in six, and CDT in six patients. We estimated that at least 16% of patients without abnormal NC (<2 abnormal nerves) had other findings indicative of neuropathy. By regression analysis, results of one test were in almost all cases associated with those of another test, but the association was not close enough to be predictive. Therefore, although NC provides objective and repeatable results, symptoms and deficits must be measured independently. Assuming no differences between groups of patients, the standardized and validated test (NNSP, VDT, or CDT) should provide the same results at different medical centers. By contrast, the results of NSS or NDS tests, with less standardized approaches and based on the judgment of physicians, might not provide the same results at different medical centers. Tests such as the ones described here may be used to define minimal criteria for the diagnosis of polyneuropathy and for staging its severity. *Diabetes Care* 10:432–40, 1987

Sensitive and reliable evaluations are needed to detect and characterize the symptoms and deficits of diabetic polyneuropathy. Such evaluations are needed in prospective population-based epidemiological surveys, longitudinal assessments of risk factors, and conduct of trials of therapy.

Quantitative approaches to detect elevated thresholds of cutaneous sensation have been described (1–5). Steiness (6,7) found that vibratory perception threshold (VPT) was significantly higher and more variable in diabetics than in controls, was more abnormal in the toe than in the finger, and was associated with clinical sensory loss, areflexia, and duration of diabetes but not with neuropathologic symptoms or measures of glycemic control. He also observed that VPT was not always abnormal in diabetic neuropathy (7). Other authors have explored the use of VPT in diabetics (9–16).

A computer-assisted sensory examination (CASE) system was developed to meet the clinical need for a cost-effective,

flexible, sensitive, valid, and reliable approach to assessment of detection thresholds of vibratory, touch-pressure, and thermal sensations (17,18). Stimuli used were selected to be optimal for the modality tested, to have a constant waveform independent of magnitude, to be able to deliver a wide range of amplitudes, to be quantitative, and to deliver stimuli by instrument rather than by hand. To minimize response bias, a two-alternative forced-choice approach was incorporated. A computer was used to administer the test, find the threshold, compare it with that of controls, and print results.

It has been shown that in healthy individuals, thresholds vary with site, age, and sex (18). Percentiles specific for site, age, and sex were estimated for face, hand, and foot (18). The use of CASE in detecting neuropathy has been explored in various peripheral neuropathies (18) and in diabetic neuropathy (8).

Using CASE in diabetics with and without neuropathy, we found that thresholds correlated with clinical measures of polyneuropathy and neuropathologic abnormality of the sural nerve (1). Among 36 diabetics, two or more abnormal evaluations [of neuropathy symptom score (NSS), neurologic disability score (NDS), nerve conduction (NC), and vibratory (VDT) or cooling detection thresholds (CDT)] identified the same patients with (32 patients) and without (4 patients) neuropathy, as had the index of pathology (an index combining loss of fibers and abnormality of remaining fibers and normalizing results for age and sex) of the sural nerve.

This study extends our evaluation of VDT and CDT in the diagnosis of polyneuropathy to 180 diabetic patients. In addition to increasing the number of patients studied, we used a new algorithm combining into one percentile the percentiles for supersensitive and insensitive points and for threshold of sensitive points. Finally, we assess the agreement between these sensory detection thresholds and other measures of nerve function and of symptoms and deficits of neuropathy.

MATERIALS AND METHODS

Vibratory and cooling detection thresholds evaluated by CASE. The VDT and CDT of the dorsal surface of the great toe and foot, respectively, had been evaluated with CASE in >300 healthy subjects without disease known to predispose to neuropathy (17,18). Percentiles specific for site, age, and sex were estimated and entered into computer memory. The VDT results for a patient were expressed as number of points (of 9) that were sensitive, number of points that were supersensitive or insensitive, mean threshold (log of micrometers of displacement) of sensitive points, and estimated combined percentile considering site, age, and sex. The CDT results were expressed as sensitive, supersensitive, or insensitive, threshold (ln °C), and estimated percentile considering site, age, and sex. When not specified, abnormality is ≥95th percentile.

Combining supersensitive or insensitive points and threshold of sensitive points. The following algorithm was devised to combine percentiles based on number of insensitive points and threshold of sensitive points in the cohort of normal subjects.

1. Based on a priori considerations (e.g., puberty and height), we considered the age groupings 8–12, 13–19, 20–49, and ≥50 yr. Age groupings observed to be comparable with regard to the frequency of insensitive points, based on visual inspection of the data, were combined. Percentiles were obtained separately for the resulting groups.
2. Let n be the number of subjects in a given age group. Order the n subjects according to the number of insensitive points. Within each resulting subgroup, order inversely according to the number of supersensitive points. Within these subgroups, order the subjects according to their threshold percentiles (obtained from the sensitive points).
3. Assign a numerical rank to each subject according to overall position in the order resulting from step 2. For a given subject, the percentile will be the percentage of individuals having a lower rank.
4. To determine the percentile for a new subject or patient, determine the position in the ranking of normal subjects and then assign the percentile assigned to the normal group at or just above that position. If there are no normal subjects at or above the new person, assign a percentile value of $1 - (2n)^{-1}$.

Appendix 1 is an example in which we suppose that among 45 healthy subjects there were no supersensitive or insensitive points and with threshold values as indicated. If a new diabetic patient in this age group has one insensitive point and a threshold percentile of 0.99, his combined percentile will be 44/45. If a new person has two insensitive points and a threshold percentile ≥0.96 or has more than two insensitive points, his combined percentile will be $1 - (1/90)$.

Neuropathy scale of neuropathy symptom profile (NNSP). The neuropathy symptom profile (NSP) is a true or false questionnaire of symptoms encountered in neuropathy (18a). The questionnaire was evaluated with an optical reader, computer, and specially written computer program. Responses

APPENDIX 1

Subject	No. of insensitive points	Threshold of sensitive points (%)	Combined percentile
1	0	0.01	0/45
2	0	0.02	1/45
3	0	0.03	2/45
4	0	0.04	3/45
5	0	0.05	4/45
↓	↓	↓	↓
40	0	0.60	39/45
41	0	0.61	40/45
42	1	0.70	41/45
43	1	0.70	41/45
44	1	0.79	43/45
45	2	0.95	44/45

were grouped into scales of weakness, sensory symptoms, and autonomic symptoms and into a combined neuropathy scale. To estimate percentiles for these scales, the questionnaire was given to >300 healthy subjects without diseases known to predispose to neuropathy. Subjects with profiles suggestive of neuropathy were evaluated by neurologic history and examination, by evaluating VDT and CDT, and by performance of NC and needle electromyographic examinations. The profiles of the subjects who on further neurologic evaluation were found to have neuropathy were excluded. The percentiles for the different scales were entered into computer memory so that, in evaluating NSP in a given patient, percentiles for different scales were automatically printed and a profile plotted. Three levels of abnormality for NNSP were evaluated, ≥95th, ≥97.5th, and ≥99th percentiles. When not specified, abnormality was ≥97.5th percentile.

Neuropathy symptom score. The NSS is the number of symptoms from a predetermined list of symptoms encountered in a patient with neuropathy. The NSS is abstracted from a neurologist's history that meet certain criteria (19). It is obtained for detecting neuropathic symptoms; inquiry is made about all symptoms listed in the NSS, and volunteered symptoms and sympathetic cross-examination regarding them are used to verify results. Whether a symptom is scored as 1 (present) or 0 (absent) is based on the judgment of the neurologist conducting the interview and his experience of what is normal, considering age and sex.

The neurologic history and the derived NSS were obtained from diabetics, with a few exceptions, by one of us (P.J.D.). Two levels of abnormality were evaluated (≥1 and ≥2). When not specified the level of abnormality was ≥1. Symptoms due to nondiabetic neural deficits, e.g., weakness due to polio, were scored as 0. Minor symptoms of light-headedness on arising in patients on antihypertensive drugs were scored as 0 for postural hypotension. Impotence was graded as 0 in men ≥70 yr old.

Neurologic disability score. The NDS is a summated score of graded assessment of the deficits of selected items from the neurologic examination (19). The examinations were performed to determine the NDS score, and all items of the NDS were made and evaluated, with the exception of a few cases, by one neurologist (P.J.D.). Muscle strength was scored as 0 for normal, 1 for 25% weakness, 2 for 50% weakness, 3 for 75% weakness, and 4 for 100% weakness. Fractional scores (to 1 decimal place) were permitted for scoring muscle strength. Tendon reflexes were scored as 0 for normal, 1 for decreased, and 2 for absent. Tactile, vibratory, joint-position, and pinprick sensations were scored 0–2, as for tendon reflexes. Fractional scores were not permitted for scoring the state of reflexes or sensation. The neurologist scored results by what he considered to be normal considering the area tested and the age and sex of the patient. The evaluation was performed after taking the neuropathic history but before VDT, CDT, and NC values were available. As for NSS, NDS is not a validated score but depends on the judgment of the neurologist. The levels of abnormality evaluated were >6 and ≥12; when not specified, abnormality was >6.

Nerve conduction. The amplitude, conduction velocity, and distal latency of motor fibers of the ulnar median (n = 117) or tibial (n = 63) nerves (elbow to wrist or knee to ankle, respectively) were obtained with surface stimulating and recording electrodes. Also obtained were the amplitude and latencies (or conduction velocities) of sensory fibers of the median and sural nerves. Abnormality of parameters of nerve conduction of individual nerves were values ≥3SD. The levels of abnormality evaluated were abnormality in one, two, three, or four (of 4) nerves. When not specified, abnormality was set at two or more nerves. Care was taken to use just supramaximal stimulation and avoid low limb temperature, faulty electrode placement, or misinterpretation of anomalous innervation.

Evaluation of diabetics. Results reported here are from an epidemiological study of diabetics in Rochester, Minnesota (Rochester Diabetic Neuropathy Study), a study of glycemic control and neuropathy (21), a study of the effect of an aldose reductase inhibitor (sorbinil) on neuropathy, and patients referred to us with problematic neuropathy. Only pretreatment evaluation results were employed. Are these patients typical of diabetics in a geographically defined region? By the criteria of the range in age (teens to the 70s), sex (both male and female), presence of neuropathy (with and without), and type of diabetes [insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) diabetes mellitus], the series is representative of population-based patients. However, we think that the series may have more IDDM than NIDDM patients compared with a population-based series of patients.

RESULTS

Combined percentiles of vibratory and cooling detection thresholds in healthy subjects. The distribution of combined percentiles of VDT for the foot is plotted against age in Fig. 1. The values from a standard Gaussian distribution corresponding to the percentiles on the vertical axis are also shown. A comparable distribution was found among healthy subjects for CDT.

Rate of abnormality among different evaluations. Of the 180 people evaluated, 89 had IDDM and 91 had NIDDM. The NSS, NDS, VDT, CDT, and NC were performed on all 180 diabetics; NNSP was performed on 147 and determination of index of pathology of the sural nerve on 42.

The percentage of diabetics with abnormal test results is shown in Table 1. The rate varied considerably depending on which criterion for abnormality for a test was used. To illustrate this variability, consider NC. Abnormality of one or more nerves occurred in 80%, two or more nerves in 69%, three or more nerves in 46%, and four nerves in 21%. A similar decrease in percentage occurred when more stringent criteria were used for the other tests (Table 1).

The percentage of patients identified as abnormal varied considerably among tests. The order from the highest to the lowest rate was: NC (69%), NSS (54%), NDS (48%), NNSP (47%), VDT (44%), and CDT (35%). When VDT or CDT were considered separately and in combination, the percentage of patients having abnormality was (in decreasing

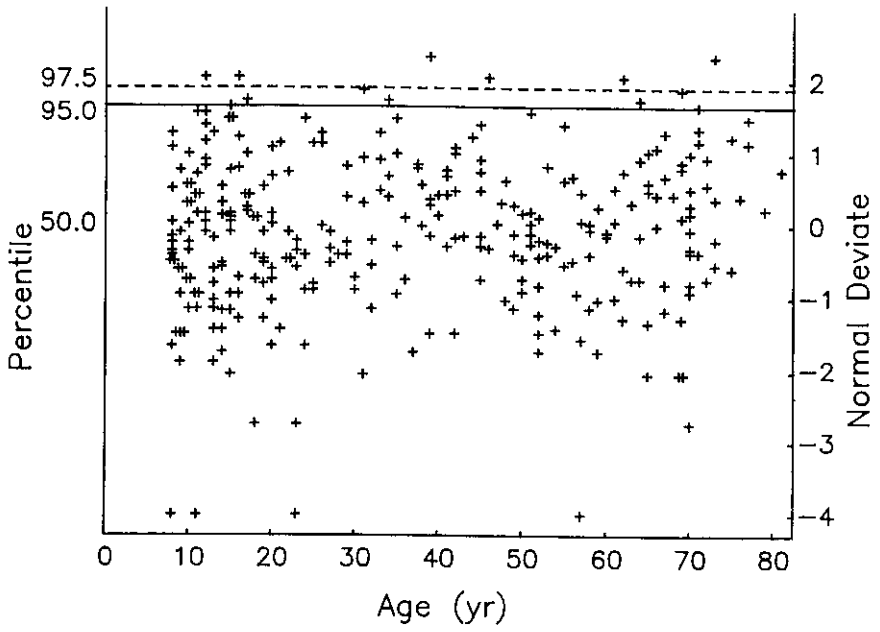

FIG. 1. Distribution of combined percentile values of vibratory detection threshold of toe in >300 healthy subjects.

order): VDT or CDT (54%), VDT (44%), CDT (35%), and VDT and CDT (26%). Rates of abnormality for various combinations of test abnormality are also shown (Table 2). Two or more abnormalities among NC, NSS, NDS, VDT, and CDT resulted in the highest percentage (65%) (Table 2). This criterion had been found to separate the same diabetics into those with (n = 32) and without (n = 4) neuropathy as had index of pathology of sural nerve (1).

Table 3 shows the percentage of diabetics with abnormality of conduction velocity and amplitudes of median motor, peroneal motor, median sensory, and sural sensory nerves. Median sensory amplitude was abnormal most often (49%), followed by sural sensory amplitude (47%), peroneal motor conduction velocity (44%), peroneal motor amplitude (37%), and other attributes.

Associations among results of different evaluations. To assess associations among results of different tests, three approaches were used. In the first, we regressed findings of a test on that of another test for each of the diabetic patients. The distribution of the values was visually inspected for nonnormality and nonlinearity, and lines were fitted by the method of least squares. Such regression lines were drawn for each of the test combinations. Table 4 shows the correlation coefficients for these associations. With only a few exceptions, the result of one test was associated with that of another and often to highly significant degrees. However, in no case was the association sufficiently close that one could predict the result of an evaluation from the result of another test. Index of pathology was significantly associated with VDT (r = −.625), NNSP (r = −.696), sural sensory amplitude (r = .672), and median sensory amplitude (r = .668). Different attributes of nerve conduction were often closely associated (Table 4).

In the second approach, we calculated the rate of abnormality for each test by severity of abnormality as measured by another test (Table 5). Considering NC, one observes a

TABLE 1
Scores and percentages of 180 diabetics with test abnormalities by different criteria

Test	Scores					
NC	0 (20)	1 (11)	2 (24)	3 (24)	4 (21)	≥2 (69)
NSS	0 (46)	1 (16)	≥2 (38)			≥1 (54)
NDS	≤6 (52)	>6 to <12 (15)	>12 (33)			>6 (48)
NNSP	<95 (49)	≥95 to <97.5 (4)	≥97.5 to <99 (7)	≥99 (40)		≥97.5 (47)
VDT	<95 (56)	≥95 to <97.5 (14)	≥97.5 to <99 (4)	≥99 (26)		≥95 (44)
CDT	<95 (65)	≥95 to <97.5 (6)	≥97.5 to <99 (3)	≥99 (26)		≥95 (35)

Percentages of total given in parentheses. NC, nerve conduction; NSS, neuropathy symptom score; NDS, neurologic disability score; NNSP, neuropathy scale of neuropathy symptom score (evaluated in 147 patients); VDT, vibratory detection threshold; CDT, cooling detection threshold.

TABLE 2
Percentages of 180 diabetics with abnormality by different test abnormality combinations

Any 2 of NC, NSS, NDS, VDT, and CDT	NC plus NSS or NNSP	NC plus NSS or NNSP plus VDT, CDT, or NDS	NC plus NSS	NC plus VDT or CDT	NC plus NDS	NC plus NNSP	NC plus VDT	NC plus CDT
64	52	52	49	49	45	43	41	31

Tests as defined in Table 1 legend. Abnormality defined as NC, abnormality (≥3 SD of any attribute in nerve conduction) in 2 or more nerves; NSS, score ≥1; NDS, score >6; NNSP, ≥97.5th percentile; VDT and CDT, ≥95th percentile.

progressive decline in percentage of patients with abnormality for NSS, NDS, VDT, CDT, and NNSP with decreasing abnormality of NC from four to zero nerves. A similar trend (with exceptions) is also seen when patients are subdivided by severity of NSS, NDS, VDT, CDT, and NNSP.

From this second approach one can also recognize rates of abnormality among other tests, when no abnormality was found by the test being considered. To illustrate this approach, consider the 36 patients with no nerve abnormality in the NC test. Abnormality was found by NSS in 11%, NDS in 8%, VDT in 8%, CDT in 8%, and NNSP in 7%. Of the 55 diabetics with NC abnormalities in fewer than two nerves, 40% had one or more abnormalities of other evaluations. By contrast the 100 diabetics with normal VDT (threshold <95th percentile) had abnormalities of NC in 51%, NSS in 35%, NDS in 27%, CDT in 18%, and NNSP in 28%.

The third approach to assessing associations was to determine the percentage of patients showing abnormality among different tests by number of abnormal tests per patient (Table 6). There were 26 with 6 abnormal tests and 34 with no abnormal tests. The percentage of patients with abnormal tests fell progressively from 6 to 0 abnormal tests per patient for all tests except for NNSP, in which there was one exception. The ≥50% boundary is indicated by a broken line in Table 6.

Abnormality of nerve conduction as a minimal criterion. To determine whether abnormality of NC might serve as a sensitive and minimal criteria for the diagnosis of polyneuropathy, we reviewed in more detail the 21 (of 55) patients without abnormality of NC (<2 nerves abnormal) but with other test abnormalities. The other test abnormalities included three with abnormality of NSS only, one with abnormality of NDS only, two with abnormality of VDT only, three with abnormality of CDT only, five with abnormality of NSP only, and seven with various combined abnormalities. One of the three patients with the NSS abnormality only had neuropathic changes on needle electromyography of muscles, and another had persistent numbness of the toes described as "like novocaine." One patient with abnormality of VDT only also had an abnormality of nerve conduction of one nerve, needle electromyographic changes compatible with mild neuropathy, and an NDS value of 6 (just normal). Six patients with several test abnormalities had symptoms and findings of neuropathy. In one patient this was supported by needle electromyographic abnormality and in another by a low value of index of pathology (0.3; normal range 0.65–1.35). Therefore, of the 55 patients with normal NC velocity, unequivocal evidence of neuropathy was found in at least 9 patients (16% of patients with normal NC).

In some of the other 12 patients, the abnormal test result may be explained by another mechanism. In one, an abnormal VDT may have been due to an alleged but unproven hypoglycemic episode. High neuropathy scales of the NSP may have been due to overt depression (confirmed by psychologic tests) in two patients, by coexisting neurologic disease (chorea) in another patient, or by inadequate control values (for a 9-yr-old boy) in a fourth.

TABLE 3
Percentages of diabetics with abnormality in different nerves and different parameters of nerve conduction

	MMV	MMA	PMV	PMA	MSV	MSA	SSV	SSA
n	117*	117*	170†	180	159†	177	99†	180
Abnormal (%)	26	9	44 (47)‡	37	28 (31)‡	49	9 (16)‡	47

MMV, median motor velocity; MMA, median motor amplitude; PMV, peroneal motor conduction velocity; PMA, peroneal motor amplitude; MSV, median sensory velocity; MSA, median sensory amplitude; SSV, sural sensory velocity; SSA, sural sensory amplitude.

*Lower number reflects the fact that another nerve (tibial) was studied in 63 cases.

†Lower number reflects the fact that a response was not obtained in some nerves.

‡Value in parentheses reflects percentage when those without a response are included.

DISCUSSION

As for other diabetic complications, it is not a simple matter to detect polyneuropathy and grade its severity. Although the retina can readily be inspected, it has been necessary to develop systematic and validated approaches, with photographic records and standards, to grade the pathologic abnormalities with sensitivity and reliability (22,23). Assessment of the ability to concentrate urine, determination of plasma concentrations of creatinine and urea, various clearance tests, and other tests may be needed to recognize and characterize nephropathy.

TABLE 4
Correlation coefficients between results of various tests

	NSS	NDS	VDT	CDT	Max (VDT or CDT)	NNSP	IP	MMV	PMV	MMA	PMA	SSV	MSV	SSA	MSA
NSS															
NDS	.757														
VDT	.433	.537													
CDT	.390	.482	.470												
Max (VDT or CDT)	.442	.547	.854	.742											
NNSP	.486	.469	.313	.255	.306										
IP	−.458	−.521	−.625	−.505	−.674	−.696									
MMV	−.376	−.370	−.424	−.322	−.440	−.275	.369								
PMV	−.385	−.441	−.481	−.434	−.539	−.371	.470	.515							
MMA	−.469	−.376	−.365	−.314	−.371	−.348	.420	.211	.192						
PMA	−.462	−.559	−.461	−.431	−.485	−.356	.504	.362	.495	.435					
SSV	−.464	−.569	−.373	−.353	−.416	−.123*	.300*	.638	.666	.171*	.434				
MSV	−.434	−.526	−.412	−.425	−.474	−.360	.445	.712	.575	.278	.500	.540			
SSA	−.484	−.500	−.536	−.500	−.589	−.413	.672	.421	.509	.432	.591	.480	.534		
MSA	−.495	−.505	−.453	−.435	−.496	−.439	.668	.497	.498	.467	.541	.529	.688	.679	
NNA	.546	.577	.570	.490	.603	.443	−.591	−.604	−.664	−.456	−.628	−.650	−.738	−.685	−.768

Tests as defined in Table 1 legend. The NSS, NDS, VDT, and CDT were obtained in 180 diabetics; Max, VDT or CDT was used, whichever was greater; NNSP in 147 diabetics; and IP in 42 diabetics. IP, index of pathology of sural nerve, an index combining loss of fibers and abnormality of remaining fibers and normalized for age and sex; NNA, number of nerves abnormal (among 4 as described in text).
*$P > .05$; for all other values $P < .05$.

The detection and grading of diabetic neuropathy may be especially difficult because *1*) both hyperactivity (e.g., paresthesia and pain) and hypoactivity (deficits of function) must be assessed; *2*) involvement of several classes of motor, sensory, and autonomic fibers must be taken into account; *3*) different anatomic regions of the body may be affected; *4*) sensitivity and specificity of tests used for evaluation of neuropathic dysfunction need to be established; and *5*) tests may be complex, time-consuming, and sometimes uncomfortable.

This study, an assessment of symptoms (NSS and NNSP), deficits (NDS, VDT, and CDT), and nerve dysfunction (NC), provides information on the relative sensitivities of these tests. The NC, employing the criterion of abnormality in two or more (of 4) nerves, would appear to be most sensitive, followed by NSS, NDS, NNSP, VDT, and CDT. The sensitivity of NC and the other tests, however, depends on the criteria used. The percentage of diabetics with abnormality of NC declines progressively from 80 to 21% when the criterion changes from abnormality in one to four of four nerves. The use of the criterion of abnormality in two separate nerves appears to be a reasonable one for polyneuropathy, as this degree of abnormality is the first increment greater than can be accounted for by a mononeuropathy. Because abnormality of NC is sensitive and, by general agreement, objective and repeatable (assuming careful attention to technical details), might it serve as an only minimal criterion for diabetic neuropathy? Our study indicates that some (at least 16%) patients had neuropathic abnormalities not recognized by abnormality of NC. Generally, abnormality of conduction velocity and amplitudes was associated with abnormality of NSS and NNSP and with NDS, VDT, and CDT. The association was not close enough, however, that these can be predicted simply from knowing the severity of the NC abnormality. The number of nerves with abnormality of NC appeared to provide a somewhat better measure of overall clinical abnormality than severity of the NC velocity abnormality.

Because symptoms and deficits cannot be predicted from abnormality of nerve conduction, they must be evaluated independently. In this study a lower percentage of patients had symptoms and signs of neuropathy than had NC abnormalities. This result and the association of number of nerves with abnormal NC and NSS, NNSP, NDS, VDT, and CDT indicate that abnormality of NC (2 abnormal nerves) in general detects a lesser degree of neuropathy than these other measures.

Why evaluate NNSP, VDT, and CDT when NSS or NDS was found to be as, or more, sensitive? The VDT, CDT, and NNSP results are based on standardized tests for which levels of abnormality have been determined by evaluation of healthy subjects. By comparison, NSS and NDS are less standardized or validated and might show more variability among medical centers.

Measuring sensory detection thresholds accurately in controls and diabetics may be useful for determining whether sensation is normal in patients, following the course of the sensory abnormality, monitoring quality control of the clinical sensory examination, characterizing type of sensory loss, relating type of sensory abnormality to risk factors and phys-

TABLE 5
Rate of abnormality among different evaluations by categories of severity of one evaluation

Scores	n	Abnormal (%)					Normal NSS, NDS, VDT, CDT, and NNSP (%)	Abnormal NNSP		Normal NSS, NDS, VDT, CDT, and NNSP (%)
		NC	NSS	NDS	VDT	CDT		n	%	
Abnormal NC										
4	38		97	95	76	61	0	33	76	0
3	44		71	61	66	41	11	36	64	11
2	43		47	42	37	33	21	33	46	21
1	19		26	11	26	21	32	18	28	33
0	36		11	8	8	8	75	27	7	78
Abnormal NSS										
≥2	68	91		85	72	50	1	57	81	2
1	29	90		59	45	41	7	22	64	5
0	83	45		13	24	19	40	68	15	37
Abnormal NDS										
≥12	59	97	90		80	58	0	49	80	0
>6–<12	27	89	82		44	33	4	25	60	4
≤6	94	47	23		24	20	35	73	22	34
Abnormal VDT										
>99	47	96	77	75		62	0	40	68	0
≥95–<99	33	88	79	73		45	6	28	75	7
<95	100	51	35	27		18	33	79	28	33
Abnormal CDT										
≥99	46	94	83	72	80		2	38	79	3
≥95–<99	16	81	56	69	50		13	14	43	14
<95	118	59	42	36	31		29	95	37	27
Abnormal NNSP										
≥99	59	90	88	78	70		54			5
≥95–<99	16	81	88	81	63		25			6
<95	72	50	18	21	26		21			35

iologic and morphometric abnormalities, assessing various regimens in prevention or treatment of neuropathy, and comparing results among centers.

Evaluation of sensation, as performed by neurologists, is less than ideal for the purposes listed above because *1*) reproducible, quantitated, and graded stimuli are not administered; *2*) algorithms for testing and assessing threshold are not defined or are not reproducible; and *3*) normative results have not been determined and might vary depending on the examiner's experience. The CASE systems that have been developed appear to be suitable for the purposes listed above (17). It should now be possible to fabricate systems having the general design features of CASE at a reasonable price. In our judgment, the initial cost would be offset by the lower cost of operation (use of an efficient and reliable test that can be performed by technicians rather than by professionals). The improved characteristic of the stimulus, lack of introduction of extraneous stimuli, use of programmed algorithms, automatic calculation of test results, printout of results, and automatic comparison to previous normative results are added benefits of such systems.

Does altered dysfunction of primary afferent neurons (axons), as evidenced by raised thresholds, indicate the presence of neuropathy? Some investigators consider elevated detection thresholds to reflect metabolic derangement and not neuropathy (2–5). This opinion was based on the following observations: *1*) abnormal thresholds were encountered at anatomic sites without neuropathic symptoms or neurologic findings, e.g., upper limb (3), superior iliac crest (24), and bulbar dermatomes (4,25); *2*) rapid improvement in threshold was reported to follow metabolic correction (24,26,27); and *3*) severity of the sensory abnormality was thought to

TABLE 6
Rate (percentage) of abnormality among different evaluations by number of abnormal evaluations per patient

No. of abnormal evaluations per patient	n	Abnormality (%)					
		NC	VDT	NSS	NDS	CDT	NNSP
6	26	100	100	100	100	100	100
5	27	100	85	93	96	52	74
4	25	92	52	92	76	40	48
3	20	95	50	65	40	30	20
2	20	80	30	33	30	20	5
1	28	50	7	11	4	11	18
0	34	0	0	0	0	0	0

be unrelated to the duration and degree of diabetic control (5). According to this view, functional alterations of nerve fibers were unassociated with neuropathologic abnormality.

Our earlier study (1) and the study presented herein suggest that raised thresholds are associated with fiber loss. The number of diabetics with neuropathologic abnormalities was slightly higher than the number with VDT or CDT abnormality. Earlier studies (1,14,25) and this study also show a strong association between raised detection thresholds and neuropathologic abnormality of the sural nerve. In other studies of neuropathy, raised thresholds were associated with decreased density of sensory receptors in the skin (29,30).

As in our earlier study (1), VDT was abnormal more frequently than CDT. Because vibratory threshold is mediated by large-diameter afferent nerve fibers and cooling is mediated by small-diameter fibers (18,30), this result may suggest that large-diameter fibers are preferentially affected in diabetic neuropathy. However, this conclusion cannot be drawn, because the format and site of the tests were not the same for VDT and CDT. In patients suspected of having neuropathy, it would appear reasonable to evalute both modalities of sensation to characterize abnormalities of large and small myelinated fibers.

ACKNOWLEDGMENTS: We gratefully acknowledge the expert help of Karen Oviatt in proofreading and preparing the manuscript.

This investigation was supported in part by a Peripheral Neuropathy Clinical Center grant from the National Institute of Neurologic and Communicative Diseases and Stroke (NS-14304); a Center grant from the Muscular Dystrophy Association; and the Mayo, Borchard, Upton, and Whirlpool Funds.

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