The Rochester Diabetic Neuropathy Study:

Design, criteria for types of neuropathy, selection bias, and reproducibility of neuropathic tests

P.J. Dyck, MD; K.M. Kratz; K.A. Lehman; J.L. Karnes, MS; L.J. Melton III, MD; P.C. O'Brien, PhD; W.J. Litchy, MD; A.J. Windebank, MD; B.E. Smith, MD; P.A. Low, MD; F.J. Service, MD; R.A. Rizza, MD; and B.R. Zimmerman, MD

Article abstract—A cross-sectional survey and subsequent longitudinal study among diabetic residents of Rochester, MN—The Rochester Diabetic Neuropathy Study (RDNS)—is population-based and uses quantitative, validated, and unique end points to detect, classify, and stage neuropathy. Nondiabetic persons, drawn from the same population, serve as controls. For patients 10 to 70 years old, the RDNS cohort is representative of diabetics living in Rochester, MN. We assessed reproducibility of tests used to characterize and quantitate severity of neuropathy in 20 diabetic subjects without neuropathy and with varying severities of neuropathy. Using intraclass correlation coefficient (r_I) as a measure of test reproducibility, we found high r_I (usually 0.9 or better) with small confidence intervals for the Neurologic Disability Score (NDS); weakness subset of NDS (W-NDS); vibratory and cooling detection thresholds (using computer-assisted sensory examination [CASE] IV); compound muscle action potentials; sensory nerve action potentials; and motor nerve conduction velocities. There was good agreement among three trained observors for NDS and the W-NDS.

NEUROLOGY 1991;41:799-807

The magnitude of the health problem represented by diabetic neuropathy is uncertain, with reported frequency of polyneuropathy among diabetics varying from 7% to 80%.[1-3] This variability presumably relates to the use of different tests, cohorts of patients, and minimal criteria for the diagnosis of neuropathy.[4-6] Also, overall prevalence rates of diabetic polyneuropathy (eg, measured by absent ankle reflexes, decreased vibratory sensation, or abnormal nerve conduction) provide too restricted an assessment of disease complications; information on the frequency of neuropathy by types and stages of neuropathy is needed instead. Assessment of morbidity and mortality related to diabetic neuropathy would also be informative.

The course and natural history of various types of diabetic neuropathy have still not been adequately addressed. Even for polyneuropathy, perhaps the most common type of diabetic neuropathy, onset and course are inadequately delineated. Because of the lack of adequate information on the course of diabetic neuropathy, it is not possible to determine the number of patients needed or the optimal duration for clinical trials of improved glycemic control, or use of such agents as aldose reductase inhibitors in prevention or amelioration of diabetic neuropathy. Without such natural history data, it is unclear whether a negative study reflects a lack of an effect or a lack of statistical power.

Putative risk factors for specific types of diabetic neuropathy also remain essentially unexplored. Adequate assessment of such risk factors might suggest novel treatments or generate hypotheses for future research. Even the extensive and important studies by Pirart[7] did not address these needs because the patients were not from a defined population, neuropathy was not characterized by the variety of neuropathic assessments now used, validated neuropathic end points were not used, and neuropathy was not adequately subclassified and staged.

There is a need, therefore, for more comprehensive epidemiologic studies of the prevalence, severity, natural history, and cause of specific types of diabetic neuropathy. The ideal study should (1) include a mixture of patients representative of diabetics in the community (population-based); (2) be prospective; (3) use sensitive and validated end points for detection and characterization of varieties of diabetic neuropathy; (4) use validated minimal criteria for neuropathy; (5) use staging for severity of neuropathy; (6) correct for the frequency of nondiabetic neuropathies; (7) evaluate the appropriate risk factors by using reliable and validated methods

From the Peripheral Neuropathy Center (Dr. Dyck, K.M. Kratz, K.A. Lehman, J.L. Karnes, and Drs. Windebank and Low), the Department of Neurology (Dr. Litchy), the Section of Clinical Epidemiology (Dr. Melton), the Section of Biostatistics (Dr. O'Brien), the Division of Endocrinology, Metabolism and Internal Medicine (Drs. Service, Rizza, and Zimmerman), Mayo Clinic and Mayo Foundation, Rochester, MN, and the Section of Neurology (Dr. Smith) Mayo Clinic Scottsdale, Scottsdale, AZ.

Received September 21, 1990. Accepted for publication in final form November 21, 1990.

Address correspondence and reprint requests to Dr. P.J. Dyck, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

at regular intervals, rather than at times determined by a patient's medical needs; and (8) be designed so that nerve, eye, kidney, and vascular and cardiovascular complications can be compared in the same patients.

The Rochester Diabetic Neuropathy Study (RDNS), which began more than 5 years ago, was designed to meet these criteria. In the present report, we describe the objectives of the RDNS, define minimal criteria for neuropathy, outline the classification and staging approaches used, list the tests performed to assess neuropathy, and assess reproducibility of these tests in a cohort of diabetic patients with and without various degrees of neuropathy. The RDNS cohort is representative of Rochester diabetics, and approaches to characterize and quantify neuropathic manifestations are sufficiently sensitive and reliable that worthwhile insights can be expected from the study. These preliminary data should be useful to others planning new studies by providing information about the choice of assessments, reproducibility of such assessments, and sample size considerations.

Methods. *Selection and recruitment of patients.* Population-based epidemiologic research is possible in Rochester, MN, because medical care is virtually self-contained within the community and is delivered by a defined number of primary-care physicians. Most care is provided by the Mayo Clinic, which has maintained a common medical record system with its two large affiliated hospitals for the past 80 years. This dossier-type medical record contains inpatient and outpatient data and is indexed for retrieval.[8] The medical records of the other medical-care providers in the area who have served the local population are also indexed and retrievable. Thus, all details of the medical care provided to the residents of Olmsted County are available for study.

Using this unique data base, we identified all Rochester residents known to have diabetes mellitus and living within the geographic boundaries of the city on January 1, 1986. Included were the diabetics previously identified by the Rochester Epidemiology Project, those attending Mayo Clinic, Olmsted Medical Group, Saint Marys Hospital, Methodist Hospital, or Olmsted Community Hospital, and participants in lay diabetic organizations. In addition, study coordinators assessed lists of patients who had been admitted to diabetic services to ensure that their names were on the master list. Residents in whom diabetes developed after January 1, 1986, were excluded.

The medical records of these patients (inpatient and outpatient) were then assessed to make an independent judgment that the patient had diabetes mellitus using Diabetes Data Group criteria.[9] If there was any doubt, a diabetologist (F.J.S.) reviewed the medical record to make the judgment. Demographic and risk factors were also collected from these records.

A letter of invitation, approved by the Mayo Clinic Institutional Review Board, was sent to all Rochester diabetic patients. Those who passed the initial screen and agreed to participate signed a consent form.

The diabetic patients living in Rochester as of January 1, 1986, could be divided into those who enrolled in the RDNS (RDNS cohort) and those who did not (non-RDNS cohort). Because demographic and clinical information was available on both groups of patients (eg, age, sex, type of diabetes, diabetic treatment, and coded medical diagnoses) from the medical record review, it was possible to compare the two cohorts to determine whether the RDNS cohort was representative of Rochester diabetics generally.

Criteria for types of diabetes. Patients in the RDNS cohort were initially classified into those with insulin-dependent diabetes mellitus (IDDM), noninsulin-dependent diabetes mellitus (NIDDM), and other varieties of diabetes mellitus by using an algorithm published earlier.[10] The diagnoses according to this clinical classification were compared with a diagnostic classification based on the C-peptide level at baseline[1] and 6 minutes after a standard glucagon challenge.[2] Basal C peptide was subdivided into the following levels: 1a = <0.2 ng/ml; 1b = ≥ 0.2 but <0.5 ng/ml; and 1c = ≥ 0.5 ng/ml. The change from baseline after a standard glucagon infusion was subdivided as follows: 2a = <0.2 ng/ml; 2b = ≥ 0.2 but <0.5 ng/ml; and 2c = ≥ 0.5 ng/ml. Confirmed cases of IDDM were 1a and 2a; probable cases were 1b and 2a; and uncertain cases were 1b and 2b. NIDDM were 1c and 2b, or 2c, or 1b and 2c.

Assessment of neuropathy. Determination of whether a patient had neuropathy was based on review of the medical record, neurologic tests (assessment of symptoms using the Neuropathy Symptom Score [NSS][11] and the Neuropathy Symptom Profile [NSP][12] described below, neurologic deficits assessed with the Neuropathy Disability Score [NDS][11] described below), nerve conduction (NC) abnormalities, sensory loss assessed with the quantitative sensory examination (QSE),[13,14] and quantitative autonomic examination (QAE).[15,16] (The NSS and NDS were originally called the Neurologic Symptom Score and Neurologic Disability Score.[11]) The minimal criteria for the diagnosis of distal polyneuropathy or proximal asymmetric neuropathy were abnormality (the level defined below) in two or more of NSS or NSP, NDS, NC, QSE, or QAE. If neuropathy was diagnosed, we also determined whether it was due to diabetes mellitus.

Three approaches were used to determine whether a neurologic abnormality was due to diabetes mellitus or to another cause: (1) the patient's history and the medical record were searched; (2) additional tests were performed if needed; and (3) judgments were made as to whether the findings were typical of diabetic neuropathy. Thus, an absent ankle reflex recorded in the medical record since the time of disk surgery was attributed to disk radiculopathy and not to diabetes. When a reason for neurologic findings other than diabetic neuropathy was considered by the examiner, additional neurologic evaluations were performed—eg, magnetic resonance imaging, enzyme tests for varieties of neuropathy, or clinical and electromyographic examination of family members. After ruling out other causes for neuropathy, the type and stage of neuropathy were determined.

The neurologic history and examination (at entry to study) were used for three purposes: (1) as the source from which the NSS and NDS were derived; (2) to help in deciding whether neuropathy, if present, was due to diabetes or another cause; and (3) to classify and stage neuropathy. The approach used in obtaining the history has been described.[11] In brief, volunteered symptoms were recorded, and a checklist was also used to ensure that all motor, sensory, and autonomic symptoms were ascertained. Cross-examination was used to ascertain whether specific symptoms were present. Only symptoms judged to be due to diabetic neuropathy were scored as present in the NSS; symptoms due to age, another neurologic disease, or another neuropathy were not used. In addition, because specificity was preferred over sensitivity, the examiner judged that a symptom was not present unless it was unequivocal. The examiner, therefore, had to judge abnormality considering age, sex, physical fitness, and the occurrence of associated diseases. An NSS of ≥ 1 was considered abnormal.

NSP[12] has been described and validated. Responses greater or equal to the 99th percentile for the neuropathy (N) and subset (weakness [W], sensory [S], and autonomic [A]) scores were considered abnormal.

The neurologic examination needed to derive NDS has been described.[11] In brief, deficits from a predetermined list of evaluations from the conventional neurologic examination were graded. Muscle strength was graded as normal = 0; 25% weak = 1; 50% weak = 2; 75% weak = 3; and 100% weak = 4. Muscle stretch reflexes were graded as normal, 0; decreased, 1; and absent, 2. Sensation was evaluated in index fingers and great toes for light touch-pressure, pinprick, vibratory sense, and joint position sense and graded as normal = 0; decreased = 1; and absent = 2. A summated score (the NDS score) ≥ 2 was considered abnormal.

Before nerve conduction studies were performed, the patients' legs were immersed in warm water at 38 °C for at least 15 minutes. The temperature of the limb was maintained at or above 32 °C during recordings by surface thermistors and infrared lamps. The amplitude (AMP), conduction velocity (CV), and distal latency (DL) of motor fibers of ulnar (UL), median (MED), peroneal (PER), and tibial (TIB) nerves were evaluated by conventional techniques. The sensory nerve action potential amplitude (SNAP), CV, and DL of sensory fibers of MED (stimulated in palm [SNAP-p] and finger [SNAP-f]) and sural (SUR) nerves were also evaluated. Values greater than the 99th percentile were considered abnormal.

The computer assisted sensory examination (CASE) of vibratory (VDT), warming (WDT), and cooling (CDT) detection thresholds was evaluated on the dorsum of the left great toe (VDT) and dorsum of the left foot (CDT) by systems and approaches previously described (CASE III and IV).[13,14] Reference values for site, age, and sex were previously published[14] based on studies of large groups of healthy subjects without neuropathy or disease known to predispose to neuropathy.

The measurement of electrocardiographic R-R interval variability and sweating of the skin of the dorsum of the foot and lateral leg by quantitative sudomotor axon reflex testing (Q-SART) have been described and validated in previous publications.[15,16]

Criteria for neuropathy, diagnosis, and staging. Distal polyneuropathy. Diabetic polyneuropathy[17-21] was diagnosed when (1) neuropathic symptoms and findings (stages 1 to 3, below) were judged to be due to diabetes mellitus; (2) sensory, motor, or autonomic symptoms or signs predominated in the distal segments of lower limbs; (3) findings were symmetric (the NDS for the lower limbs did not vary by more than 3 when NDS was <10, or by more than 25% when NDS was ≥ 10); and (4) abnormality (as defined above) occurred in two or more of NSS or NSP (N, W, S, or A scores), NDS, NC, QSE, or QAE.

Severity of distal polyneuropathy was staged[5,6] as N0 = no polyneuropathy, N1 = asymptomatic polyneuropathy, N2 = symptomatic polyneuropathy, and N3 = disabling neuropathy, by criteria previously published.[6]

Proximal asymmetric neuropathy. In this category, we included varieties called "diabetic amyotrophy," "femoral neuropathy," "sciatic neuropathy," "lumbar" and "sacral" plexopathies, and the more inclusive term "proximal asymmetric neuropathy."[22-26] When both proximal asymmetric and distal symmetric neuropathy were found, the medical record was carefully searched or studies were initiated to determine that the neuropathy was not due to chronic inflammatory demyelinating neuropathy, monoclonal gammopathies of unknown cause, lymphoma, intraspinal tumor, lumbosacral disk or stenosis, pelvic hematoma, abscess, or tumor.

This type of neuropathy was staged only as N0 = no neuropathy, N2 = symptomatic, or N3 = disabling, because surveillance was not sufficient to allow discrimination between N0 and N1 stages. The separation of N2 from N3 was based on the severity of sensory (pain) or motor symptoms (weakness) by using the staging criteria developed for polyneuropathy.

Autonomic neuropathy. This was diagnosed when there was symptomatic postural hypotension, gastric atony, diarrhea, sphincter loss, or impotence (in men) judged to be due to diabetic neuropathy[27-34] and not to age or another disease. The minimal criteria for diagnosis of these symptoms as autonomic neuropathy are the ones we previously proposed for staging N2 and N3 in diabetic polyneuropathy. If abnormalities of QAE were found without the autonomic symptomatology listed above, this information was used in staging polyneuropathy.

Truncal radiculopathy. This was diagnosed when symptoms and findings implicated single or contiguous thoracic or lumbar 1 and 2 roots, and was judged to be due to diabetes.[21] Symptoms considered to be typical of this type of neuropathy were radicular paresthesia and pain, and electromyographic neurogenic abnormality. Staging into N2 or N3 was on the basis of severity of pain (as described for distal polyneuropathy) and not weakness or autonomic deficit.

Cranial neuropathy. Included here were patients with diplopia due to involvement of cranial nerves III, IV, or VI judged to be due to diabetes mellitus.[35-37] Oculomotor neuropathy was not staged.

Carpal tunnel syndrome (CTS). CTS was diagnosed based on a consideration of symptoms, neurologic findings, symptoms related to conduct of Phalen's test, response to carpal ligament section, and neurophysiologic findings.[35-39] Symptoms considered characteristic of CTS were paresthesia, pain, loss of feeling, or weakness. Paresthesia is intermittent, is localized to the digits, and occurs especially at night. It is brought on by prolonged flexion of the hand at the wrist (as might occur during sleep), prolonged grasping (eg, steering wheel), or by repeated flexion and extension of the hand at the wrist (as in certain occupations). Typically it disappears on straightening the hand at the wrist, as occurs when the arm hangs to the side of the body. Characteristic pain (discomfort) usually is associated with paresthesia, is intermittent, and occurs especially at night. It is located in the wrist or palm of the hand or extends up the arm. It is brought on by the positions and activities described above for paresthesia. Most patients with CTS do not have neurologic findings, but when they do, they consist of sensory loss or muscle weakness, or both, in the distribution of MED from its involvement at the wrist. Phalen's test is done by flexing the hand on the forearm to 90° (or as near to 90° as possible) for 2 minutes. In a positive test, the symptoms of paresthesia or pain, or both, occur during wrist flexion and are relieved with straightening the wrist and allowing the arm to hang by the side. A characteristic therapeutic response to section of the carpal ligament is disappearance or marked improvement of the intermittent paresthesia or pain characteristic of CTS.

The electrophysiologic test results considered to be supportive of CTS are one or more of (1) one or more of (a) MED motor DL >4.4 msec, (b) MED sensory antidromic DL >3.5 msec, or (c) MED sensory palmar DL >2.2 msec, and (d) UL motor DL <3.6 msec and (e) UL sensory palmar <2.3 msec; (2) MED sensory palmar DL minus UL sensory palmar DL >0.5 msec; or (3) conduction block under the carpal ligament by the inching technique.

The criteria chosen for the clinical diagnosis of CTS are given in the table.

Reproducibility of clinical assessments. Reproducibility (test-retest variability) of NSS; NSP (and W, S, and A subsets); NDS (and W, S, and reflexes [R] subsets), VDT, CDT, and WDT; and NC (and various individual and summated attributes) was assessed in 20 diabetic patients chosen by patient coordinators to be without and with various degrees of neuropathy. Three neurologists (P.J.D., A.J.W., and B.E.S.) obtained a second neurologic history and examination of the

Table. Criteria for the diagnosis of carpal tunnel syndrome (CTS)

Paresthesia*	Pain (discomfort)	Phalen's test	Surgical relief	Neurologic findings	Electrophysiologic findings
			Diagnostic of CTS		
+	+	+	+	+	+
+	+	+	+	—	+
+	+	+	NS	—	+
+	+	— or ND	NS	—	+
+	+	+	+	—	— or ND
+	+	+	NS	—	— or ND
—	+	+	+ or NS	—	+
+	—	+	+ or NS	—	+
+	+	— or NS	NS	+	+
			Suspected CTS		
+	—	+	NS	—	— or ND
+	+	—	NS	—	— or ND
—	+	+	NS	—	— or ND
+	—	—	NS	—	+, —, or ND
—	—	—	NS	—	+

* Paresthesia, pain, Phalen's test, surgical relief, neurologic findings, and electrophysiologic findings were considered positive or negative by the criteria outlined in text.
ND Test not done or repeated.
NS No surgery.

same 20 patients 3 to 5 days later. Because these observers examined many patients concurrently and previous medical records were not made available, the details of the previous evaluation were not recalled at the time of the second evaluation. The NSP, NC, VDT, CDT, and WDT were performed by conventional laboratory procedures without personnel apprised that the tests were done to assess reproducibility. The results should reflect the reproducibility typical for patients in the study. QAE was not repeated because previous studies of reproducibility had been performed.

Variability of the patient's neuropathic test scores and test-retest differences were displayed as box-and-whisker figures (showing 25th, 50th, and 75th percentile values and ranges). We used the intraclass correlation coefficient (r_I)[40] to measure reproducibility. Specifically, let X_{ij} represent the j^{th} observation on the i^{th} person for a given test procedure ($j = 1, 2$; $i = 1, \ldots, n$). The model is

$$X_{ij} = \pi_i + \eta_{ij}$$

where π_i is the true value for patient i and η_{ij} is the measurement error in assessing π_i. The variance among X_{ij} thus consists of two components: among-subject variance (σ_π^2) and experimental error (σ_η^2), so that

$$\mathrm{Var}(X_{ij}) = \sigma_\pi^2 + \sigma_\eta^2.$$

The intraclass correlation coefficient is defined as the proportion of this variance attributable to variability among subjects, ranging from 0 (all variability is experimental error) to 1 (no experimental error):

$$r_I = \sigma_\pi^2/\sigma_\pi^2 + \sigma_\eta^2.$$

The components σ_π^2 and σ_η^2 have been estimated by analysis of variance. In addition to the desirable aspects of placing experimental error in relation to variability among subjects, r_I has the additional desirable property of being unit-free, thus enabling a direct comparison of the different methods. Confidence intervals for r_I have been obtained with the methodology used by Searle.[41]

Results. *Selection bias.* Considering diabetics of all ages, the RDNS cohort (378 patients) did not differ from the nonparticipants (490 patients) in the community with respect to sex, therapy (insulin, oral agents, or no treatment), duration, or type of diabetes (as assessed from the medical record). Comorbidity was less common. Among the 30 medical disorders evaluated, stroke (2% and 7%, $p < 0.001$), congestive heart failure (2% and 9%, $p < 0.001$), ischemic leg ulcer (3% and 7%, $p = 0.003$), cataract (8% and 15%, $p = 0.002$), and macular degeneration (2% and 4%, $p = 0.03$) were significantly less frequent in the cohort than in nonparticipants.

Among patients less than 70 years old, there were no comorbidity differences between the RDNS and non-RDNS cohorts, and none of the various medical conditions was significantly less prevalent in the RDNS compared with the non-RDNS patients.

Criteria for types of diabetes mellitus. By use of the clinical algorithm, 98 (26%) of the 378 patients in the RDNS cohort were IDDM and 280 (74%) were NIDDM. Of the 334 patients evaluated for C-peptide responsiveness (chemical criterion) 82 (25%) were IDDM and 252 (75%) were NIDDM. Of the 334 patients evaluated by both clinical and chemical criteria, 79 (24%) were IDDM and 255 (76%) were NIDDM by clinical criteria.

In 89% of patients there was agreement between clinical and chemical criteria for diabetes type. Seventeen (5%) patients were IDDM by clinical criteria and NIDDM by chemical criteria. Twenty (6%) patients who were NIDDM by clinical criteria were IDDM by chemical criteria. We interpret these findings as showing a high degree of concordance between clinical and chemical criteria.

Reproducibility of neuropathic evaluation results.

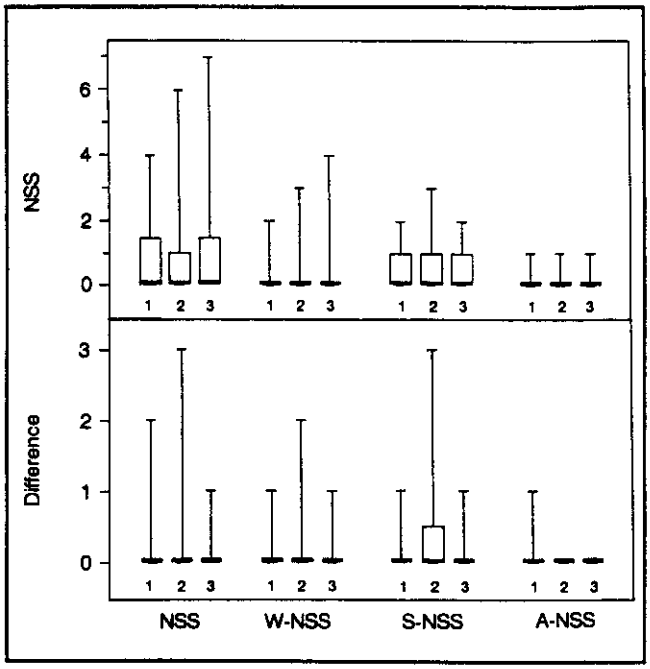

Figure 1. (Upper) Box-and-whisker plots show the 25th, 50th, and 75th percentile values and ranges of the Neuropathy Symptom Score (NSS) and subsets (W = weakness, S = sensory, and A = autonomic) from 20 diabetic patients without and with varying severity of neuropathy who were used to study test reproducibility. There are differences in the distribution of NSS scores among the three observers. (Lower) Test-retest difference in NSS scores.

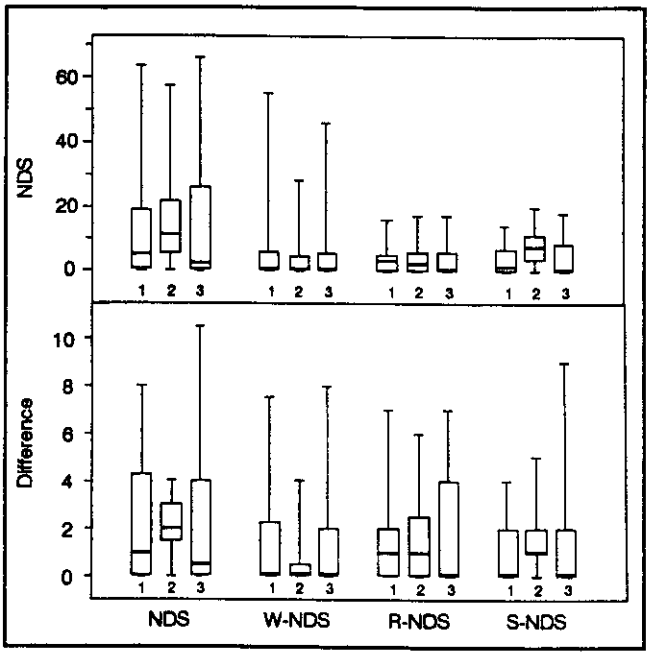

Figure 2. (Upper) Box-and-whisker plots show the 25th, 50th, and 75th percentile values and ranges of the Neuropathy Disability Score (NDS) and its subsets (W = weakness, S = sensation, and R = reflexes) in 20 diabetic patients chosen for reproducibility studies. (Lower) Test-retest variability for observers 1, 2, and 3 and for subsets of NDS.

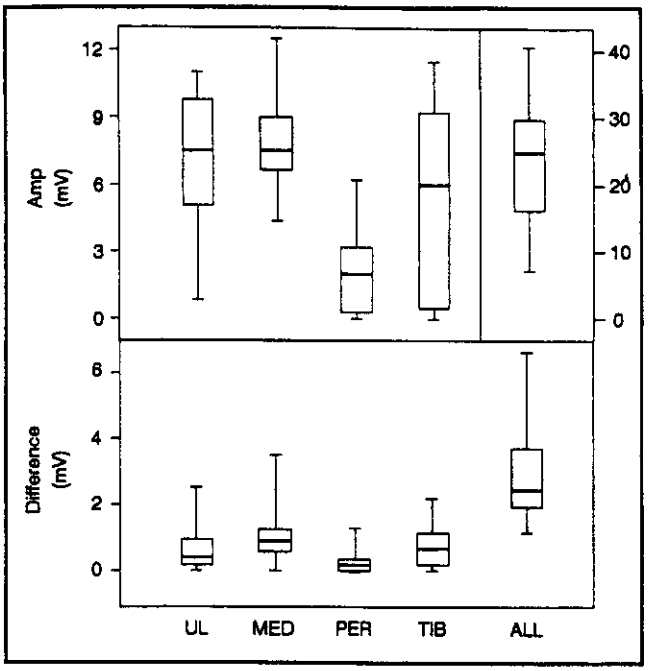

Figure 3. (Upper) Box-and-whisker distribution plots (described in legend for figure 1) for the compound muscle action potential of ulnar (UL), median (MED), peroneal (PER), tibial (TIB), and combined (ALL) nerves for 20 diabetics chosen for reproducibility studies. (Lower) Test-retest variability in the same nerves.

Figures 1 through 3 present the distribution of test results in box-and-whisker figures for the 20 diabetic patients and the difference between the first and second evaluation for (1) NSS and subsets (figure 1); (2) NDS and subsets (figure 2); and (3) compound muscle action potentials (CMAP) (figure 3). Similar data were graphed for NSP and subsets, motor nerve conduction velocity (MNCV), and sensory nerve action potentials and are available on written request. The data show that there was a reasonable mixture of patients without neuropathy and with various severities of neuropathies. With the NDS as an indication of severity of neuropathy and minimal criteria for neuropathy of two or more points, more than 15 patients had neuropathy. Some patients had severe neuropathy with NDS values at approximately 60 points. The choice of the 20 patients appears to have provided a suitable range of severities on which to test reproducibility.

These graphs also illustrate variability among observers. Although the distributions of test results for the NSS and NDS show differences, they are similar. The graphs may also be used to look for test-retest differences between two evaluations.

Use of the r_I provided the most information about reproducibility within and among observers and tests. NSS (and subsets) reproducibility as measured by r_I was high in most cases: greater than 0.9 six of 12 times and greater than 0.75 eleven of 12 times (figure 4). For confidence intervals, statistically significant differences were observed among observers 2 and 3 for weakness and between observers 1 or 2 and 3 for autonomic symptoms. For NSP, the intraclass correlation

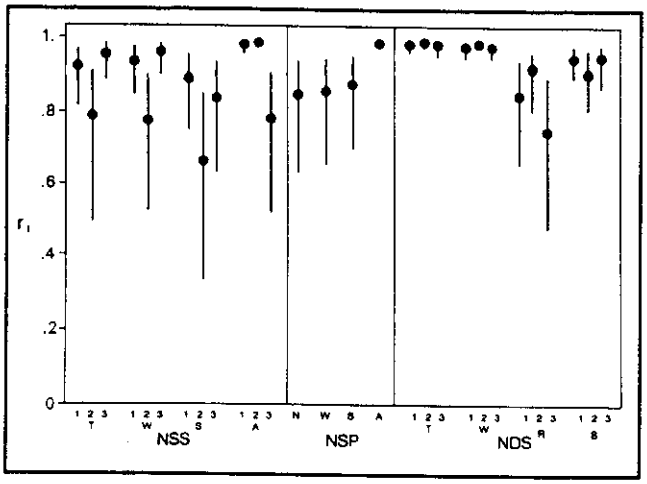

Figure 4. The test-retest intraclass correlation coefficient and confidence intervals (95%) for Neuropathy Symptom Score (NSS): total (T), weakness (W), sensory (S), and autonomic (A) subsets and observers 1, 2, and 3; Neuropathy Symptom Profile (NSP): neuropathy (N), and weakness (W), sensory (S), and autonomic (A) subsets; and Neuropathy Disability Score (NDS): total (T), weakness (W), reflex (R), and sensory (S) subsets. The test-retest correlation coefficients for NSS were often high, especially for observers 1 and 3. Sometimes a significant difference was found among observers, eg, between observers 2 and 3 for W and between observer 1 or 2 and observer 3. Note the high correlation coefficient and low confidence intervals for NDS and NDS-W.

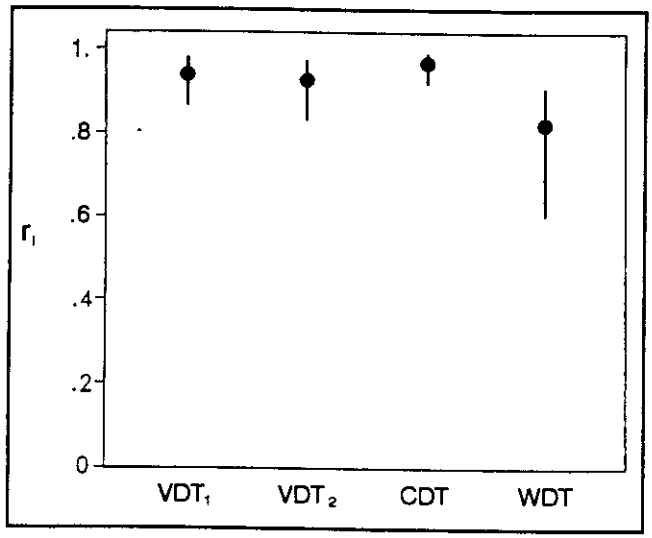

Figure 5. Test-retest intraclass correlation coefficients and confidence intervals (95%) for vibratory (VDT_1; levels just noticeable difference [JND] of testing) and VDT_2 (normal deviate), cooling (CDT; JND levels of testing), and warming (WDT) detection thresholds.

coefficient was greater than 0.8 for all four scales. The confidence intervals were not significantly different among N, W, and S scales, but each of these differed significantly from the A scale (figure 4).

The r_I for NDS and W-NDS was >0.95 for each of the three observers and the confidence intervals were

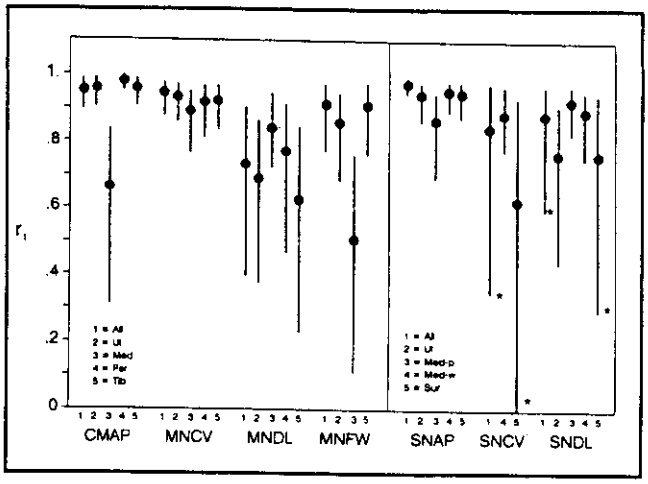

Figure 6. Test-retest intraclass correlation coefficient and confidence intervals (95%) for compound muscle action potential (CMAP), motor nerve conduction velocity (MNCV), motor nerve distal latency (MNDL), motor nerve F waves (MNFW), sensory nerve action potential (SNAP), sensory nerve conduction velocity (SNCV), and sensory nerve distal latency (SNDL) for nerves 1 through 5, as identified on the graph. By the criteria of a high correlation coefficient and small confidence intervals among attributes of nerve conduction, CMAP and SNAP performed best.

small. By comparison, the S-NDS and R-NDS had smaller r_I values and much larger confidence intervals. The confidence intervals of S-NDS or R-NDS sometimes were significantly different from those of NDS or W-NDS.

The r_I for VDT_1 (by just noticeable differences [JND] steps of stimulus intensity), VDT_2 (normal deviate), and CDT (by JND steps) was >0.9 (figure 5). The r_I for WDT was slightly more than 0.8 and its confidence interval was significantly different from that of CDT. By the criteria of high r_I and small confidence interval, among attributes of nerve conduction, CMAP, MNCV, and SNAP were best (figure 6). Among CMAP, MED CMAP did not perform as well as the others, with confidence intervals significantly worse than those of ΣCMAP and PER CMAP. Among SNAP, median SNAP-p was significantly different from ΣSNAP. By the criteria of reproducibility, NDS, VDT, CDT, ΣCMAP, and ΣSNAP show high degrees of reproducibility. By contrast, assessment of symptoms by NSS or NSP did not show the same degree of reproducibility. Significant differences were not found between the reproducibility of NDS or W-NDS among observers. For NSS, significant differences in reproducibility of assessing weakness and autonomic symptoms were encountered among observers. This is of note because these observers worked together closely, used the same grading approaches in their practices, and had agreement on grading approaches before the study was initiated.

Discussion. Melton and Dyck[1] reviewed epidemiologic information about diabetic neuropathy and commented on the factors responsible for the "generally poor qual-

ity of the data" particularly as related to mortality, morbidity, public health cost, and prevalence. They noted that, based on death certificate data, diabetic neuropathy "appears to contribute little to morbidity." They pointed out, however, that such data are notoriously poor and probably would not reflect the possible role of disorders such as autonomic neuropathy on sudden death.[42] There is no reliable information on morbidity, epidemiologic data being essentially limited to estimates of the frequency of diabetic neuropathy. The influence of neuropathy on symptomatology also remains unevaluated. The public health costs that can be attributed to diabetic neuropathy remain unestimated. It is, therefore, difficult for investigators, health agencies, or pharmaceutical houses to know how to set research priorities and allocate resources.

The high variability (5% to 80%) in the reported frequency of diabetic neuropathy probably relates mainly to different cohorts of diabetics studied, use of different neuropathic end-point evaluations, different criteria for abnormality of these end points, and different minimal criteria for neuropathy. For example, considerable variability occurs among cohorts selected by their attendance at public hospital diabetic clinics,[7] referral to tertiary care centers, referral for a specialized evaluation (eg, electromyographic evaluation),[43] or entry into a controlled clinical trial[44] or retrospective population-based studies.[45-47]

A major difference in reported frequency of neuropathy might relate to different evaluative procedures used (clinical examination only, nerve conduction, QSE, or QAE), different levels of test abnormality (eg, an arbitrary level or a percentile response considering test, site, age, and sex and based on comprehensive studies of controls), and minimal criteria for the diagnosis of neuropathy (eg, absent ankle reflexes and vibratory abnormality at ankle, diagnosis of neuropathy by a neurologist, or two or more abnormalities among NSS or NSP, NDS, NC, QSE, or QAE).

Nonetheless, earlier studies[7,17-19,48,49] provided several insights: (1) manifestations of neuropathy are usually not revealed at the time of diagnosis of diabetes mellitus and may take many years to develop; (2) the percentage of patients showing manifestations of polyneuropathy, such as decreased ankle reflexes or decreased vibratory sensation at the malleolus or altered nerve conduction, increases with duration of diabetes mellitus; (3) diabetic polyneuropathy occurs in both IDDM and NIDDM; and (4) among diabetic patients, neuropathy is associated with complications such as retinopathy and nephropathy.

This study has several important features which should allow more comprehensive study of diabetic neuropathy: (1) patients are evaluated at baseline and then at periodic preset dates, and not only when the patient seeks help because of sickness; (2) the evaluative procedures and risk factors used are predetermined and more comprehensive; (3) defined criteria for abnormality based on unique methods and adequate controls are used; and (4) risk factors are serially evaluated. In addition, medical records covering the patients' entire residence in the community are scanned to identify preceding episodes of neuropathy, comorbidity, and other important aspects of natural history. Thus, the study exploits the special medical care and recording facility provided by the Mayo Clinic for more than 80 years. The RDNS combines the strengths of the population-based but retrospective Rochester Epidemiology Project and those of a prospective study in which patients are assessed cross-sectionally and then followed longitudinally.

In addition to describing the aims and design of the RDNS, the present report (1) compares the results of clinical and chemical algorithms for the separation of IDDM and NIDDM, (2) assesses selection bias of patients entering the RDNS, and (3) assesses the variability of clinical end-point evaluation among and within observers and tests.

There was good agreement (89%) for diagnoses of IDDM or NIDDM by the clinical and the chemical algorithm. Because production of insulin is thought to be a fundamental difference between IDDM and NIDDM, we have chosen simply to use the chemical criteria to make the distinction. The issue of use of the C-peptide response to glucagon in separating IDDM and NIDDM has been studied by others.[50-53]

The strength of a population-based study is that it provides representative information about the given population that may then be compared with and extrapolated to more general populations. In the conduct of such studies, it is generally impossible (because of expense or refusal of patients) to have all patients enrolled. Actually, it is unnecessary for all to be enrolled, provided the cohort studied is representative of the overall group and is sufficiently characterized and large enough to make extrapolation to the general population possible. The RDNS includes approximately 38% of all Rochester diabetics, and the comprehensive and integrated nature of the medical record system in Rochester allowed us to assess the representativeness of study subjects compared with those diabetics who did not enroll. Considering the entire cohort of 378 patients, we underrecruited patients less than 10 and more than 70 years old. Among patients 10 to 70 years old, however, only slight biases (to be reported in detail elsewhere) in selection occurred, and the biases were ones not known to influence diabetic complications. We conclude that the RDNS is representative of Rochester diabetics and should provide a reasonable cohort on which to base conclusions about the cause and natural history of diabetic neuropathy.

We previously reported on approaches that might be used to assess for neuropathic symptoms and deficits in diabetic neuropathy. Abnormality of NSS and NDS was based on judgments of neurologists[5,6,11] recognizing that neuropathic symptoms and deficits may occur in old age. Normative values have been reported for attributes of NC,[5] QSE,[13] and QAE.[16] In a study of approximately 180 diabetics with and without neuropathy, we showed[5] that the level of abnormality of one neuropathic evaluation, such as those used here, was usually significantly associated with the result of another neuropathic evaluation, but the specific results of one test did not predict precisely those of another. We also

reported[54] minimal criteria for the diagnosis of diabetic neuropathy and showed that such criteria result in approximately the same separation of diabetic patients with and without neuropathy as did a quantitative neuropathologic index of neuropathy. A staging approach for diabetic neuropathy has been proposed.[6] A consensus group recommended that, for research purposes, symptoms, deficits, nerve conduction, quantitative sensory examination, and quantitative autonomic examination should be used.[55]

Several approaches have been introduced to assess symptoms and neuropathic deficits in peripheral nerve injuries[56] and in polyneuropathy.[57] Although quantitation of neuropathic symptoms and deficits has been used in controlled clinical trials,[58] it has not been extensively applied in epidemiologic studies. From our earlier studies[5,6] in diabetics, we know that these clinical measurements can be used to set minimal criteria and stage severity of neuropathy. We found[5] that severity of NSS, NSP, or NDS is significantly associated with severity of neuropathy as assessed by nerve conduction or quantitative sensory examination.

The reproducibility of NSS, NSP, or NDS (and their subsets) has not previously been assessed. The three observers in our study were from the same medical institution, worked together in a peripheral neuropathy center, and agreed on grading criteria before beginning the study. The results, therefore, might be different (worse) when neurologists are recruited from different institutions and participate without pretraining. Even using trained observers, significant differences among observers were found for some subsets of NSS. The NDS, on the other hand, was scored similarly among observers. Reproducibility was high, with small confidence intervals for NDS and W-NDS. Among NDS subsets, the worst reproducibility was for S-NDS. An intermediate level of reproducibility was achieved for R-NDS.

This study focused on what tests should be used in controlled clinical and epidemiologic trials. The results were needed for the evaluation of RDNS data, but they may be used in the design of other trials. We suggest that for such trials one does want an overall assessment of motor, sensory, and autonomic symptoms and neurologic deficits and a classification of type of neuropathy. We suggest that this overall assessment can be made by use of NSS (or NSP), NDS, NC, QSE, and QAE and by our staging approach. The choice of test or subset of the test depends on how sensitive, reliable, and reproducible it is.

In this study we have addressed the reproducibility of tests in routine use as they are done in our practice. Using these routine approaches, we found that the overall reproducibility of NDS and of W-NDS was high and not different among the three observers involved. Summated (UL, MED, PER, and TIB) CMAP and CMAP of UL, PER, or TIB nerves and summated SNAP (UL, MED-W, and SUR) of UL, MED-W, and SUR also were reproducible. Among sensory evaluations, SNAP, VDT, and CDT were most reproducible. Although motor nerve conduction velocities were quite reproducible also, sensory conduction velocities were not. It is not surprising that the assessment of symptoms was not very reproducible and that significant differences in judging symptoms occur even among neurologists who work together and agree on grading criteria.

The difference in reproducibility in assessment of symptoms among observers has implications for future studies: one might want to use only observers who have low reproducibility. Another alternative is to use the NSP, a test that does not use observers. The high reproducibility of NDS, VDT, CDT, CMAP, and SNAP is important. These tests are direct measures of neuropathic deficit. NDS is an overall assessment of muscle weakness, reflex abnormality, and sensory loss. VDT has been shown to relate to loss of large-diameter sensory fibers, and CDT of small-diameter sensory fibers.[59,60] In humans, decrease of CMAP and SNAP relates to decrease in number of largest motor and sensory fibers directly. The tests reflect actual changes in peripheral nerves in diabetic neuropathy. Because of their good reproducibility and because they measure neurologic deficits directly, they will be the ones emphasized in the RDNS and can be recommended for controlled clinical and epidemiologic trials.

References

1. Melton LJ, Dyck PJ. Epidemiology. In: Dyck PJ, Thomas PK, Asbury A, Winegrad AI, Porte D, eds. Diabetic neuropathy. Philadelphia: WB Saunders, 1987:27-35.
2. Palumbo PJ, Elveback LR, Whisnant JP. Neurologic complications of diabetes mellitus: transient ischemic attack, stroke, and peripheral neuropathy. Adv Neurol 1978;19:593-602.
3. Thomas PK, Eliasson SG. Diabetic neuropathy. In: Dyck PJ, Thomas PK, Asbury A, Winegrad A, Porte D, eds. Diabetic neuropathy. Philadelphia: WB Saunders, 1987:1773-1810.
4. Dyck PJ, Karnes J, O'Brien PC. Diagnosis, staging, and classification of diabetic neuropathy and associations with other complications. In: Dyck PJ, Thomas PK, Asbury A, Winegrad A, Porte D, eds. Diabetic neuropathy. Philadelphia: WB Saunders, 1987:36-44
5. Dyck PJ, Bushek W, Litchy WJ. Vibratory and cooling detection thresholds compared with other tests in diagnosing and staging diabetic neuropthy. Diabetes Care 1987;10:432-440.
6. Dyck PJ. Detection, characterization, and staging of polyneuropathy: assessed in diabetics. Muscle Nerve 1988;11:21-32.
7. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973. Diabetes Care 1978;1:168-188.
8. Kurland LT, Molgaard CH. The patient record in epidemiology. Sci Am 1981;245:54-63.
9. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979;28:1039-1057.
10. Dyck PJ, Karnes JL, Daube J, O'Brien P, Service FJ. Clinical and neuropathological criteria for the diagnosis and staging of diabetic polyneuropathy. Brain 1985;108:861-880.
11. Dyck PJ, Sherman WR, Hallcher LM, et al. Human diabetic endoneurial sorbital, fructose, and *myo*-inositol related to sural nerve morphometry. Ann Neurol 1980;8:590-596.
12. Dyck PJ, Karnes J, O'Brien PC, Swanson CJ. Neuropathy symptom profile in health, motor neuron disease, diabetic neuropathy, and amyloidosis. Neurology 1986;36:1300-1308.
13. Dyck PJ, Karnes J, O'Brien PC, Zimmerman IR. Detection thresholds of cutaneous sensation in humans. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R, eds. Peripheral neuropathy. Philadelphia: WB Saunders, 1984:1103-1138.
14. Dyck PJ, Karnes J, O'Brien PC. Detection thresholds of cutaneous sensation. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R, eds. Peripheral neuropathy. Philadelphia: WB Saunders, 1984:107-121.

15. Low PA. Quantitation of autonomic responses. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R, eds. Peripheral neuropathy. Philadelphia: WB Saunders, 1984:1139-1166.
16. Low PA, Fealey RD. Sudomotor neuropathy. In: Dyck PJ, Thomas PK, Asbury A, Winegrad AI, Porte D, eds. Diabetic neuropathy. Philadelphia: WB Saunders, 1987:140-145.
17. Rundles RW. Diabetic neuropathy: general review with report of 125 cases. Medicine 1945;24:111-121.
18. Martin MM. Diabetic neuropathy. A clinical study of 150 cases. Brain 1953;76:594-603.
19. Fagerberg S-E. Diabetic neuropathy. A clinical and histological study on the significance of vascular affections. Acta Med Scand 1959;164 (suppl 345):1-97.
20. Mulder DW, Lambert EH, Bastron JA, and Sprague RG. The neuropathies associated with diabetes mellitus: a clinical and electromyographic study of 103 unselected diabetic patients. Neurology 1961;11:275-284.
21. Thomas PK, Eliasson SG. Diabetic neuropathy. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R, eds. Peripheral neuropathy. Philadelphia: WB Saunders, 1984:1773-1810.
22. Bruns L. Uber neuritische Lahmungen beim Diabetes Mellitus. Berl Klin Wochenschr 1890;27:509-521.
23. Garland H. Diabetic amyotrophy. Br Med J 1955;2:1287-1296.
24. Calverley JR, Mulder DW. Femoral neuropathy. Neurology 1960;10:963-971.
25. Asbury AK. Proximal diabetic neuropathy. Ann Neurol 1977;2:179-190.
26. Raff MC, Sangalang V, Asbury AK. Ischemic mononeuropathy multiplex associated with diabetes mellitus. Arch Neurol 1968;18:487-493.
27. Hreidarsson AB. Pupil motility in long-term diabetes. Diabetologia 1979;17;145-150.
28. Mandelstam P, Lieber A. Esophageal dysfunction in diabetic neuropathy-gastroenteropathy. JAMA 1967;201:582-586.
29. Martin MM. Involvement of autonomic nerve fibres in diabetic neuropathy. Lancet 1953;1:560-571.
30. Fagerberg S-E, Kock NG, Petersen I, Stener I. Urinary bladder disturbances in diabetes. Scand J Urol Nephrol 1967;1:19-28.
31. Ellenberg M. Impotence in diabetes: the neurologic factor. Ann Intern Med 1971;75:213-219.
32. Low PA, Zimmerman BA, Dyck PJ. Comparison of distal sympathetic with vagal function in diabetic neuropathy. Muscle Nerve 1986;9:592-596.
33. Pfeifer MA, Weinberg CR, Cook DL, et al. Autonomic neural dysfunction in recently diagnosed diabetic subjects. Diabetes Care 1984;7:447-453.
34. Bradley WE, ed. Aspects of diabetic autonomic neuropathy. Ann Intern Med 1980;92(suppl 2):1-342.
35. Dreyfus PM, Hakim S, Adams RD. Diabetic ophthalmoplegia. Arch Neurol Psychiat 1957;77:337-349.
36. Asbury AK, Aldredge H, Hershberg R, Fisher CM. Oculomotor palsy in diabetes mellitus: a clinico-pathological study. Brain 1970;93:555-561.
37. Rucker CW. The causes of paralysis of the third, fourth, and sixth cranial nerves. Am J Ophthalmol 1966;61:1293-1302.
38. Stewart JD, Aguayo AJ. Compression and entrapment neuropathies. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R, eds. Peripheral neuropathy. Philadelphia: WB Saunders, 1984:1435-1457.
39. Kimura J. Nerve conduction and electromyography. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R, eds. Peripheral neuropathy. Philadelphia: WB Saunders, 1984:919-966.
40. Winer BJ. Statistical principles in experimental design, 2nd ed. New York: McGraw-Hill, 1972:283-289.
41. Searle SR. Linear models. New York: Wiley, 1971.
42. Ewing DJ, Campbell IW, Clarke BF. Mortality in diabetic autonomic neuropathy. Lancet 1976;1:601-603.
43. Montagne A, Buchthal F. Electrophysiological studies in diabetic neuropathy. J Neurol Neurosurg Psychiatry 1970;33:442-452.
44. DCCT Research Group. The diabetes control and complications trial (DCCT): design and methodologic considerations for the feasibility phase. Diabetes 1986;35:530-545.
45. Palumbo PJ, Elveback LR, Chu C-P, Connolly DC, Kurland LT. Diabetes mellitus: incidence, prevalence, survivorship, and causes of death in Rochester, Minnesota, 1945-1970. Diabetes 1976;25:566-577.
46. Melton LJ, Ochi JW, Palumbo PJ, Chu C-P. Sources of disparity in the spectrum of diabetes mellitus at incidence and prevalence. Diabetes 1983;6:427-431.
47. Ochi JW, Melton LJ, Palumbo PJ, Chu C-P. A population-based study of diabetes mortality. Diabetes Care 1985;8:224-229.
48. Palumbo PJ, Elveback LR, Whisnant JP. Neurologic complications of diabetic mellitus: transient ischemic attack, stroke, and peripheral neuropathy. In: Schoenberg BS, ed. Advances in neurology, vol 19. Neuroepidemiology: a tribute to Bruce Schoenberg. New York: Raven Press, 1978;19:593.
49. Jordan WR. Neuritis manifestations in diabetes mellitus. Arch Intern Med 1936;57:307-366.
50. Gjessing HJ, Matzen LE, Faber OK, Froland A. Fasting plasma C-peptide, glucagon stimulated plasma C-peptide, and urinary C-peptide in relation to clinical type of diabetes. Diabetologia 1989;32:305-311.
51. Snorgaard L, Hasselstrom K, Lumholtz IB, Thorsteinsson O, Siersbaek-Nielsen K. Insulin/C-peptide response to intravenous glucagon. A dose-response study in normal and non-insulin-dependent diabetic subjects. Acta Endocrinol (Copenh) 1988;117:109-115.
52. Jayyab AK, Heding LG, Cyzsyk A, Malczewski B, Krolewski AS. Serum C-peptide and IRI levels after administration of glucagon and glucose in non-insulin-dependent diabetics. Horm Metab Res 1982;14:112-116.
53. Mirel RD, Ginsberg-Fellner F, Horwitz DL, Rayfield EJ. C-peptide reserve in insulin-dependent diabetics: comparative responses to glucose, glucagon, and tolbutamide. Diabetologia 1980;19:183-188.
54. Dyck PJ, Windebank A, Yasuda H, Service FJ, Rizza R, Zimmerman B. Diabetic neuropathy. In: Vranic M, Hollenberg CH, Steiner G, eds. Comparison of type I and type II diabetes. New York: Plenum, 1985:305-320.
55. American Diabetes Association Consensus Statement. Diabetes Care 1988;11:592.
56. Medical Research Council. Aids to the examination of the peripheral nervous system, memorandum No. 45, London, Her Majesty's Stationery Office by the White Ross Press, 1975.
57. Hughes RAC, Newsom-Davis JM, Perkin GD, Pierce JM. Controlled trial of prednisolone in acute polyneuropathy. Lancet 1978;2:750.
58. Dyck PJ, Daube J, O'Brien P, et al. Plasma exchange in chronic inflammatory demyelinating polyradiculoneuropathy. N Engl J Med 1986;314:461-465.
59. Dyck PJ, Karnes J, O'Brien PC, Zimmerman IR. Detection thresholds of cutaneous sensation in humans. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R, eds. Peripheral neuropathy. Philadelphia: WB Saunders, 1984:1103-1138.
60. Lambert EH, Dyck PJ. Compound action potentials of sural nerve in vitro in peripheral neuropathy. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R, eds. Peripheral neuropathy. Philadelphia: WB Saunders, 1984:1030-1044.

Reprinted from NEUROLOGY, Volume 41, Number 6, June 1991