Consensus Statement

Report and Recommendations of the San Antonio Conference on Diabetic Neuropathy

On 8–10 February 1988, a conference on peripheral neuropathy in diabetes was held in San Antonio, Texas, to review the progress achieved in this field over the past few years. A strong impetus for convening this conference was the recent burst of clinical investigations and trials in diabetic neuropathy and a perception that recent research gains were not widely recognized. The purpose of the conference was to assess the state of knowledge of diabetic neuropathy and to recommend a set of research guidelines for future clinical investigations. In this report, investigation was defined as epidemiological surveys, studies of natural history, and clinical trials of proposed therapies for treatment or prevention of diabetic neuropathy.

The conference was sponsored by the American Diabetes Association and the American Academy of Neurology. The conference format consisted of a panel of 10 experts in the fields of diabetes and peripheral neuropathy who heard 1.5 days of presentations by 23 participants chosen for their expertise in particular aspects of diabetic neuropathy. The participants' presentations were divided into six areas: clinical measures, morphological and biochemical assessment, electrodiagnosis, epidemiology, autonomic nervous system testing, and sensory testing. The panel prepared this report on the conference.

The following operational definition of diabetic peripheral neuropathy was adopted by the conferees:

> *Diabetic neuropathy* is a descriptive term meaning a demonstrable disorder, either clinically evident or subclinical, that occurs in the setting of diabetes mellitus without other causes for peripheral neuropathy. The neuropathic disorder includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system.

Although the term *diabetic neuropathy* subsumes several distinctive neuropathic syndromes, this report focuses on one of them, diabetic polyneuropathy.

GENERAL CONCLUSIONS AND RECOMMENDATIONS

In reviewing the diagnosis and assessment of diabetic neuropathy, the panel was impressed with the large amount of data indicating general concordance among the various methods for detection and measurement of dysfunction. Thus, one major conclusion is that there is an underlying connection among the various abnormalities demonstrated by assessing nerve function. For each category of measurement, compelling evidence supported the validity of various approaches to assessment. Therefore, to fully classify diabetic neuropathy, the panel recommends at least one measure from each of the following categories: clinical symptoms, clinical examination, electrodiagnostic studies (EDX), quantitative sensory testing (QST), and autonomic function testing (AFT). Because various methodologies are employed, each laboratory should standardize these measures by using their own population norms and should report both the absolute data and the relationship of the data to the appropriate normative control population.

The panel also believes that further standardization would be beneficial and recommends that future efforts be directed toward developing common interstudy methodologies. Several multicenter trials have demonstrated the feasibility of standardizing methods among laboratories, and large-scale natural history and epidemiological studies should therefore be encouraged. However, actual implementation of neurological assessment will vary from study to study depending on the question that is addressed. The panel recognizes that in large-scale epidemiological studies a detailed examination of all modalities may not be necessary or feasible. Because the time frame of clinical therapeutic intervention trials tends to be short in relation to the natural history of diabetic neuropathy, there may be a need to use multiple tests to increase the likelihood of detecting significant improvement or deterioration. Therefore, assessment methodology will vary greatly from study to study, but the general principle should be that each assessment requires rigorous review of reliability and precision.

CLINICAL MEASURES

In the last 2 yr, several substantial advances in clinical assessment of diabetic polyneuropathy have been made.

- Careful studies have shown a close correlation between clinical manifestations of diabetic polyneuropathy and neuropathologic abnormalities.
- Several ongoing studies show concordance between clinical dysfunction and objective continuous measures such as EDX, AFT, and QST; nonetheless, each may be abnormal in the absence of clinical correlates. The extent to which early abnormalities in physiologic tests predict the onset and progression of clinical dysfunction remains to be established.
- Clinical instruments appropriate for epidemiological studies and for more detailed staging have been tested for reliability (inter- and intraobserver variability) and validity and have achieved levels acceptable for clinical studies.
- Thoughtful proposals for diagnosing and staging have been promulgated.

The panel recommends that

1. Clinical measures of diabetic polyneuropathy are an essential component of both epidemiological and therapeutic studies.
2. Clinical assessment can be tailored to the type of study; rapid, relatively simple measures may be appropriate for some epidemiological studies. Physiologic measures will be useful in most studies, and in clinical trials they may be required to adequately define entry criteria and to monitor progression or improvement.
3. In general, it is advantageous to systematically assess neuropathic signs and symptoms, including sensory, motor, and reflex measures in upper and lower extremities, cranial nerves, and autonomic function.* Such data will provide a complete picture of the neuropathies in the patient population under study and will identify patients whose disorders are known to have substantially different natural histories (e.g., those with proximal asymmetrical motor neuropathies that improve spontaneously). Confounding disorders, including lumbar root disease, significant peripheral vascular disease, and nondiabetic neuropathy, should be systematically excluded.
4. Because clinical measures lack precision, their reliability (inter- and intraobserver variability) and, where necessary, their validity should be ascertained. Reliability is enhanced by choosing dichotomous measures, e.g., the presence or absence of signs and symptoms. It is more reliable to determine whether a tendon reflex is absent than whether it is merely diminished. High degrees of reproducibility are achievable, consistent with those obtained in other neurological disorders.
5. A pretrial observation period including repeated measurements provides a means of reducing intraobserver variability. In multicenter trials, on-site training of data collectors should enhance precision.
6. The incidence and severity of polyneuropathy correlate with duration of disease and age. These factors should be taken into account in selecting patient populations for comparison. The effect of age must also be considered in establishing normative data.

*An excellent description of the relevant physical findings and symptoms can be found in Dyck PJ: Detection, characterization, and staging of polyneuropathy: assessed in diabetics. *Muscle Nerve* 11:21–32, 1988.

MORPHOLOGICAL AND BIOCHEMICAL ASSESSMENT

Biopsy of human sural nerve or fascicle has demonstrated an array of biochemical and morphologic abnormalities. Patterns of fiber loss, diffuse or multifocal, have been assessed and particular features described, e.g., axonal atrophy, nodal swelling, and microvascular change. Basic mechanisms may be studied in humans by this procedure, and correlations of pathological features with the degree of nerve dysfunction and with clinical status have been found. In assessing results, great care should be taken to match for age and duration of diabetes. Biochemical measures should be interpreted in the context of the current metabolic state.

The panel recommends that in the evaluation of human diabetic polyneuropathy, nerve biopsies should only be performed as part of thoughtful, well-designed studies aimed at increasing the understanding of basic etiopathogenesis or the mechanism of action of therapeutic agents. Serial biopsies have a very limited role; whole-nerve biopsy can only be performed twice, and "stump" biopsy at the site of previous sampling carries morphological bias. There is no indication to biopsy nerves in large therapeutic trials.

ELECTRODIAGNOSIS

The electrodiagnostic examination is useful in evaluating various disorders, including mononeuropathy, mononeuritis multiplex, plexopathy, polyradiculopathy, and sensorimotor neuropathy. In a diffuse generalized polyneuropathy, testing a few nerves suffices to indicate the functional state of the peripheral nervous system. In multiple mononeuropathies, affected nerves should be tested to characterize the abnormalities.

In conventional nerve-conduction studies, analyses of action-potential amplitude allow estimates of the total number of active fibers, although an increase in temporal dispersion alone may bias this correlation. Nerve-conduction studies primarily reflect functional status of large myelinated sensory and motor nerve fibers in the upper and lower extremities. Normal results do not rule out neuropathy. Conduction studies have widespread availability and acceptance in the assessment of diabetic neuropathy, particularly in sequential studies.

Electromyography may reveal partial denervation in intrinsic foot muscles as an early sign of diabetic neuropathy. Needle studies also elucidate focal or asymmetric clinical findings not detectable by conduction studies. As the most sensitive indicator of motor axonal degeneration, this technique demonstrates early abnormality in asymptomatic diabetic patients. It also helps document the presence or absence of polyradiculopathy or other peripheral disorders superimposed on diabetic neuropathy.

Thus, a complete electrodiagnostic evaluation, including electromyography, plays an important role in diagnosing diabetic neuropathy. In monitoring the course of the disease, however, conduction studies of selected nerves suffice. When facilities and expertise are available, more sophisticated methods, e.g., near-nerve recording, somatosensory evoked potentials, motor unit count, or measures of refractory periods, may be used.

Reliability of information depends on the accuracy and reproducibility of the raw data. For nerve-conduction studies, sources of error include technical and procedural problems. A proper protocol should include temperature control, accurate measurement of the surface distance as an estimate of the nerve length, and recording of well-defined and artifact-free evoked responses. Other important factors center on qualifications of the electromyographer, procedural consistencies among investigators working at different laboratories in multicenter studies, and development of population-based norms.

Nerve-conduction studies reveal abnormalities in some diabetic patients without neurological symptoms or signs. In patients with clinical deficits, evoked-response amplitude generally correlates with functional impairment, the latter resulting primarily from either axonal degeneration or conduction block. The severity of clinical neurological deficits correlates with the number and magnitude of nerve-conduction abnormalities.

Although different components of the electrodiagnostic examination relate to different neurophysiologic aspects of peripheral nerve function, most nerve-conduction measurements significantly correlate with each other in a large group of diabetic subjects. Individual sensory-summary variables correlate significantly with each other and with most motor-summary variables. Similarly, motor-summary variables, excluding amplitude measures, correlate significantly with each other.

In the case of minimal symptoms or signs, evaluation is directed toward the most susceptible nerves. Distal lower-extremity responses are more commonly abnormal than upper-extremity responses, and sensory abnormalities are more frequent than motor abnormalities. Conversely, absent lower-extremity responses provide no information about possible demyelination or subsequent progression or improvement; in this case, nerves that are less involved should be studied.

The panel recommends that

1. The preferred protocol should specify uniform techniques to be used. If this is not possible, the data can be normalized for interlaboratory comparisons. One statistical technique expresses each component of the motor and sensory conduction examination as a percentage of the laboratory mean value of the normal population or in terms of standard-deviation intervals from normal mean values.
2. In epidemiologic protocols, electrodiagnostic studies of one or two nerves may suffice. Monitoring improvement or deterioration in clinical trials will usually require a more extensive battery of electrodiagnostic measures consisting of motor and sensory nerve–conduction studies in the upper and lower limbs.
3. Both epidemiological and clinical tests should include measurement of amplitude and latency at each site of stimulation and calculation of segmental conduction velocity, as well as F wave latency. Table 1 illustrates such a protocol.

EPIDEMIOLOGICAL STUDIES

The epidemiological studies of diabetic neuropathy are concerned with three questions: *1*) Who gets diabetic neuropathy? Descriptive epidemiology includes the measurement of incidence and prevalence. *2*) Why do they get it? Analytical epidemiology includes the measurement of host-genetic factors and environmental determinants. *3*) What are the best approaches to prevention or treatment? Experimental epidemiology can be subdivided into natural experiments, such as the comparison of neuropathy incidence among patients with diabetes in different cultures, and randomized clinical trials.

Epidemiological studies, by definition, always have numerators and denominators and rates. Proper classification of individuals into cases and controls and precise measurement of specific risk factors are essential.

Epidemiological tools should be *1*) simple and safe; *2*) characterized by small within- versus between-individual variation; *3*) accurate, highly sensitive, and specific when compared to a defined gold standard; and *4*) free of bias.

Epidemiological tools depend on the questions to be answered and the method for classifying cases and noncases, i.e., the gold standard for a specific study. Epidemiological research will improve as the measurement tools improve and become more standardized. It is especially important that results are comparable across as well as within studies and also over time, because variations among different populations and changes over time are critical for generating etiological hypotheses.

The study of etiology usually requires a measurement of incidence. Therapeutic trials are also often best conducted in recently diagnosed, i.e., incident, cases. Reliable ascertainment of incidence requires more refined measuring instruments than does the ascertainment of prevalence.

TABLE 1
Sample protocol for electrodiagnostic tests

Motor nerve–conduction studies
Unilateral studies of either ulnar or median nerve including F waves in the upper limb
Unilateral studies of peroneal nerve including F wave in the lower limb
Measurement of muscle-action potential amplitude and latency at each site of stimulation and calculation of segmental conduction velocity
Sensory nerve–conduction studies
Unilateral studies of either ulnar or median nerve in the upper limb
Unilateral studies of either medial plantar or sural nerve in the lower limb
Measurement of nerve-action potential amplitude and latency at each site of stimulation and calculation of segmental conduction velocity
Studies of additional nerves may be necessary to characterize abnormalities based on the distribution of clinical symptoms or signs

Epidemiological studies also attempt to quantify the degree of neuropathy and the associated symptomology and disability. In quantifying the extent of neuropathy, all patients with neuropathy become the denominator and the extent of disease becomes the numerator. The ability to discriminate between stages of diabetic neuropathy depends primarily on the within-individual variations. An instrument could be very accurate but have substantial within-individual variability, resulting in substantial misclassification. A major consequence of within-individual variation is regression to the mean, a phenomenon that occurs with practically all measurements. The effect of within-individual variability can be reduced by repeat measurements in the same individual over time and by selecting larger differences among categories for grouping individuals.

The panel recommends that before any instrument is used in a study of diabetic neuropathy, *1*) the within- and between-individual variability should be defined, *2*) the sensitivity and specificity in relation to the defined gold standard for the study should be determined, *3*) the distribution of the parameters in the study population should be estimated, and *4*) any biases related to the characteristics of the population and the method of measurement (e.g., ethnic or educational differences, age, sex, and whether the observer is blinded or not blinded to the measurement) should be identified.

AUTONOMIC NERVOUS SYSTEM FUNCTION

Diabetic autonomic neuropathy may manifest as dysfunction of several different organ systems, e.g., cardiovascular, gastrointestinal, genitourinary, sudomotor, and ocular. The symptoms are important in individual patients but difficult to evaluate and quantitate because they are often nonspecific.

Several objective measurements of autonomic function have been developed. These tests measure end-organ responses to activation of neural reflex arcs. They can be influenced by end-organ failure, intercurrent illness, drugs, and age. They may be classified in the following manner.

Noninvasive tests. These are suitable for routine screening for autonomic dysfunction or for monitoring the progress of autonomic neuropathy. When performed in a carefully controlled manner, the following tests have been validated and shown to be reliable and reproducible, to correlate with each other and with tests of peripheral somatic nerve function, and to have prognostic value.

1. Tests of heart-rate control (mainly parasympathetic). Heart-rate response to
   a. Valsalva maneuver
   b. Deep breathing
   c. Standing
2. Tests of blood pressure control (mainly sympathetic). Blood pressure response to
   a. Standing or tilting
   b. Sustained handgrip
3. Tests of sudomotor control, i.e.,
   a. Temperature-induced sweating
   b. Chemically induced sweating (e.g., acetylcholine or pilocarpine)

Measures of autonomic function particularly lend themselves to a staging system because there is a hierarchy of levels of sensitivity of these measures. For example, an abnormality of heart-rate variability alone may be the earliest stage, an abnormality of Valsalva response may define an intermediate stage, and the presence of postural hypotension may define a more severe stage.

Invasive tests of cardiovascular function, gastrointestinal motility, and bladder function. These are not suitable for routine screening or for monitoring progress.

Other biochemical, physiological, and pharmacological studies. Although useful, they may not be generally available. They include skin vasomotor reflexes, plasma norepinephrine response to standing, pupillometry, and pancreatic polypeptide response to hypoglycemia or a meal.

The panel recommends that

1. Symptoms possibly reflecting autonomic neuropathy should not, by themselves, be considered markers for its presence.
2. Noninvasive validated measures of autonomic neural reflexes should be used as specific markers of autonomic neuropathy if end-organ failure is carefully ruled out and other important factors, such as concomitant illness, drug use, and age, are taken into account. An abnormality of more than one test on more than one occasion is desirable to establish the presence of autonomic dysfunction.
3. Independent tests of both parasympathetic and sympathetic function should be performed.
4. A battery of quantitative measures of autonomic reflexes should be used to monitor improvement or deterioration of autonomic nerve function, although their utility for monitoring patients over time has not clearly been established.

SENSORY SYSTEM TESTING

Various approaches are available to detect and measure abnormalities in somatosensory function. Most evaluate subjective attributes of sensations evoked by natural stimulation of cutaneous receptors. Thus, they are psychophysical somatosensory tests that provide information on the function of entire afferent pathways, from receptor to brain. Such tests should not be construed as specific probes for primary afferent units, e.g., for detection or measurement of peripheral neuropathy. Some of the probes used to evaluate somatosensory status explore neurosecretory function in primary sensory units rather than psychophysical function.

The incorporation of new quantitative probes in the study of somatosensory function is timely for several reasons. *1*) They are highly sensitive, acceptably reproducible, and noninvasive. *2*) They explore a broad range of somatosensory submodalities thus indirectly revealing the status of a range of primary cutaneous sensory nerve fibers. In doing so, these tests examine the function of nerve fibers not easily accessible to electrophysiological evaluation. *3*) The psychophysical types of sensory system tests can document and measure a parameter of disorder that no other test, including nerve biopsy, can explore, i.e., hyperalgesia. Hyperalgesia is an aberration of somatosensory function whereby weak natural stimuli abnormally elicit a painful response. It is the

only example of a measurable positive sensory phenomenon; all other tests only explore deficit of function.

Current drawbacks of the more sophisticated and quantitative tests are the incomplete degree of standardization or validation and the expense and bulk of the instruments used.

The following are examples of QST.

Vibration sense. Repetitive mechanical indentation of the skin delivered at prescribed frequency and amplitude through automated instruments is a widely used, sensitive, and reproducible test for afferent systems served by peripheral myelinated fibers of large caliber. Deficit in this function tends to correlate with, but often precedes development of, abnormality in tendon reflexes, light touch, and position sense. Abnormality in this function does not necessarily mean that the lesion resides in the peripheral nervous system.

Thermoreception. Detection of thresholds for cold and warm sensations has gained acceptance in the evaluation of afferent functions served by small-caliber myelinated and unmyelinated fibers at the peripheral nerve level. Abnormalities in cold and/or warm thresholds may constitute the earliest evidence of neurological deficit. Abnormality in thermoreception does not necessarily indicate a peripheral nervous system disorder. Conversely, normality does not exclude large-fiber neuropathy.

Nociception. Evaluation of the psychophysical function of nociceptor systems at threshold levels is conveniently pursued by controlled, measured, local administration of warm or cold transients through contact thermodes. The test can be performed as an extension of thermoreception testing. Thermal-pain thresholds provide unique insights into the function of somatosensory pathways served by unmyelinated fibers, the most abundant peripheral nerve units. Evaluation of the status of warm specific pathways cannot be used to draw conclusions about nociceptor fibers. Documentation of hyperalgesia can be achieved through determination of a unique reduction of nociceptor threshold.

Antidromic vasodilation. A flare induced by antidromic activation of neurosecretion in unmyelinated nociceptor terminals can be elicited by chemical stimulation of the skin and can be measured quantitatively. This is the only noninvasive test available that specifically probes the status of the primary unmyelinated nociceptor units themselves rather than the pathway as a whole. Therefore, abnormality is diagnostic of neuropathic involvement of unmyelinated nociceptor fibers.

The panel recommends that quantitative testing of the spectrum of sensory systems be included in the evaluation of diabetic polyneuropathy.

CLASSIFICATION OF DIABETIC POLYNEUROPATHY

As part of the panel deliberations, a classification intended purely for research purposes was devised (Table 2). The purpose of the classification is to facilitate categorization of patients with diabetes by employing either clinical criteria alone or clinical and physiological criteria. Clinical criteria should include a validated questionnaire or interview technique for detecting neuropathic symptoms and a neurological examination, with both measures performed and scored quantitatively in a standardized manner (see CLINICAL MEASURES). In Table 2, Class I refers to patients without demonstrable signs or symptoms, and Class II refers to those with symptoms, signs, or both. For investigators not using physiological tests, further classification within this scheme cannot be made. Subclasses of polyneuropathy are defined by physiological tests, including EDX, QST, and AFT.

TABLE 2
Research classification of diabetic polyneuropathy

	Clinical assessments		
	Symptom score	Neurological examination score	Abnormal physiological tests
Class I			
A	0	0	0 *or* AFT or QST
B	0	0	EDX *or* AFT and QST
C	0	0	EDX *and* either AFT or QST or both
Class II			
A	+	0	0 *or* AFT or QST
B	0 or +	+	EDX *or* AFT and QST
C	0 or +	+	EDX *and* either AFT
	+	0 or +	or QST or both

+, Abnormal result; 0, normal result.
AFT, autonomic function testing; EDX, electrodiagnosis; QST, quantitative sensory testing.

The intent behind this classification is to group diabetic patients with polyneuropathy or without demonstrable polyneuropathy into definable categories for research purposes. The classification is not intended to stage diabetic polyneuropathy or to provide a grading scale of severity. Although this report does not propose an approach to staging diabetic polyneuropathy, Dyck* has recently put forward a four-step staging proposal. The panel encourages further data acquisition for the development of staging methods.

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*Dyck PJ: Detection, characterization, and staging of polyneuropathy: assessed in diabetics. *Muscle Nerve* 11:21–32, 1988.