

Assessing Decreased Sensation and Increased Sensory Phenomena in Diabetic Polyneuropathies

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Loss of sensation and increased sensory phenomena are major expressions of varieties of diabetic polyneuropathies needing improved assessments for clinical and research purposes. We provide a neurobiological explanation for the apparent paradox between decreased sensation and increased sensory phenomena. Strongly endorsed is the use of the 10-g monofilaments for screening of feet to detect sensation loss, with the goal of improving diabetic management and prevention of foot ulcers and neurogenic arthropathy. We describe improved methods to assess for the kind, severity, and distribution of both large- and small-fiber sensory loss and which approaches and techniques may be useful for conducting therapeutic trials. The abnormality of attributes of nerve conduction may be used to validate the dysfunction of large sensory fibers. The abnormality of epidermal nerve fibers/1 mm may be used as a surrogate measure of small-fiber sensory loss but appear not to correlate closely with severity of pain. Increased sensory phenomena are recognized by the characteristic words patients use to describe them and by the severity and persistence of these symptoms. Tests of tactile and thermal hyperalgesia are additional markers of neural hyperactivity that are useful for diagnosis and disease management. *Diabetes* 62:3677–3686, 2013

Altered sensation (loss or increased sensory phenomena) may be early and prominent manifestations of varieties of polyneuropathy associated with diabetes. These neuropathies may be classified into four major varieties: distal symmetric sensorimotor polyneuropathies (typical and atypical diabetic sensorimotor polyneuropathy [DSPN]); compression and entrapment varieties (median neuropathy at the wrist [carpal tunnel syndrome]); radiculoplexus neuropathies (lumbosacral [Bruns Garland syndrome], thoracic, and cervical); and cranial neuropathies (1–3). Although none of these varieties are uniquely associated with DM, all varieties are more prevalent in diabetes. Underlying mechanisms are different among these varieties (1–3).

Decreased sensation and increased sensory phenomena are not being adequately evaluated in clinical medicine. Possible reasons include the following: 1) methodologies of such assessments are not sufficiently emphasized in training of health care professionals; 2) insufficient time is taken in their evaluation (i.e., to assess kind, severity, and distribution of sensation loss, let alone to assess increased sensory phenomena); 3) reference values are often not available or used; 4) standard techniques of assessment are typically not

used, for example, to assess clinical sensation with cotton wool, disposable stick pins, tuning forks, or other; 5) validated quantitative sensation tests (QSTs) are generally not used; and 6) compensation for such testing is unavailable.

Here we review the neurobiology underlying decreased and increased sensory phenomena occurring in diabetic polyneuropathies (DPNs) and methodologies of their assessment. Especially emphasized in this review are improved methods to screen for sensation loss of feet, with the goal of preventing ulcers and neurogenic arthropathy; use of composite scores of neuropathic signs; computer-assisted (smart) QSTs; nerve conduction (NC) measurements; and counts of intraepidermal nerve fibers as neuropathy end points for therapeutic trials of DPN severity. Also described are measures of increased sensory phenomena.

PRIMARY AND SURROGATE MEASURES TO ASSESS DECREASED SENSATION

Neurobiology and pathology of decreased sensation.

Cutaneous and deep sensations are mediated by superficial and deep topically distributed receptors and nerve fibers. In most patients with peripheral neuropathy, loss of sensation is directly attributable to kind, severity, and distributed loss of these sensory receptors, nerve fibers, or neurons (4–6). Occasionally, loss of sensation occurs without demonstrable loss of sensory units (P.J.D., unpublished data), but this phenomenon has not been observed in DPNs. Pathological damage of sensory units differs among varieties of DPN. Thus, in typical DSPN, pathological degeneration of receptors and nerve fibers begins symmetrically and distally and spreads proximally (7). In compression and entrapment, nerve fiber degeneration begins and is maximal at the site of compression or entrapment. In the radiculoplexus neuropathies, nerve fiber degeneration is multifocal with involvement of nerve roots, spinal ganglia, plexuses, and peripheral nerves (8).

There is a degree of functional specificity of cutaneous and deep receptors and of their sensory nerve fibers (5). Thus, touch-pressure sensation of nonhairy skin is mediated by Meissner corpuscles with small receptive fields, sharp borders, and low thresholds that accommodate rapidly (Fig. 1). Pacinian corpuscles respond to vibratory stimuli and have large receptive fields with sloping borders and low thresholds that accommodate quickly. Cooling receptors are more widely distributed and more frequent than warm receptors. In the feet of some healthy old subjects, warm sensation may not be felt, presumably because there are too few of them with aging. In such old people, the first sensation felt with increasing heat stimuli given by a testing thermode is pain, due to activation of polymodal nociceptors (5,9). By comparison, in most old people, cold stimuli are usually felt as cool pulses before cold pain is felt. Polymodal nociceptors respond to damaging mechanical,

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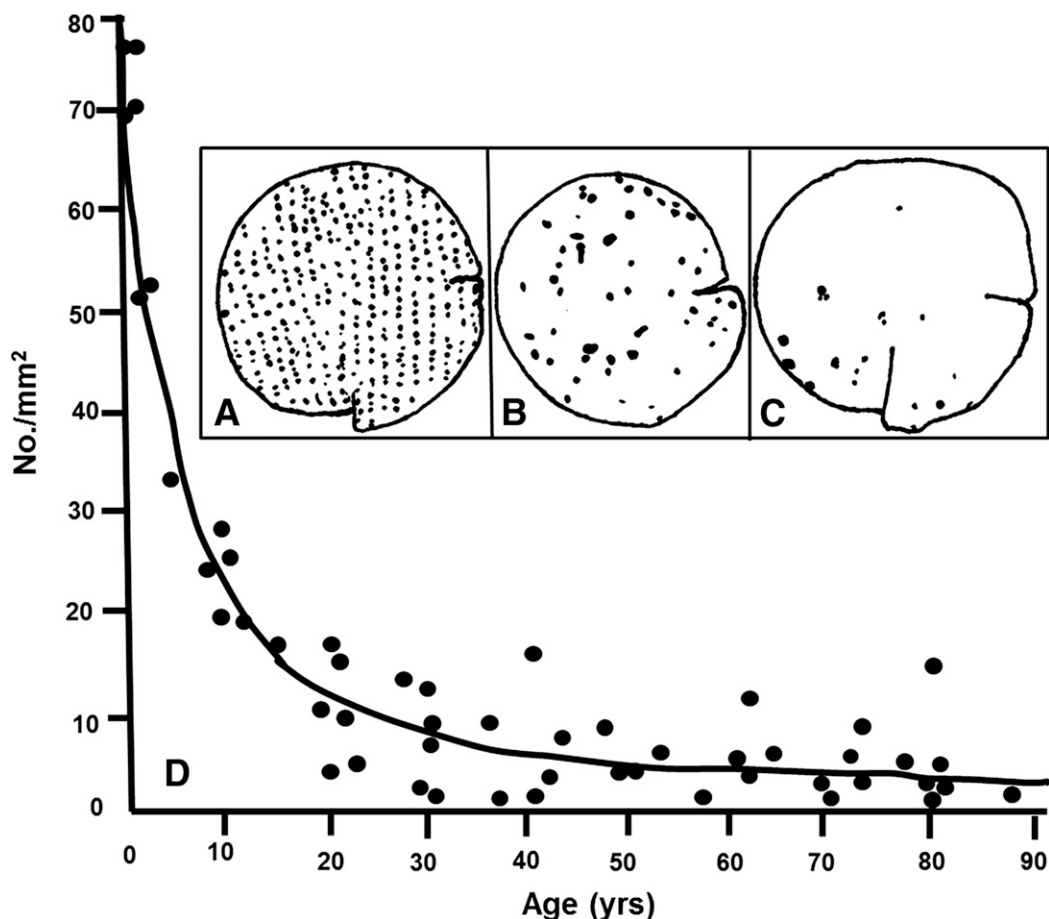


FIG. 1. Density of Meissner corpuscles visualized by the pseudo-cholinesterase reaction in punch biopsy specimens of the skin of the toe of healthy humans to illustrate the influence of age on their density and distribution. Upper insets show Meissner corpuscles in the terminal phalanx of the first toe of a 4-year-old boy (A), 43-year-old man (B), and 76-year-old woman (C). D: Meissner corpuscle density of healthy subjects plotted on the age in years. There is a rapid decrease in density with development (as the surface area increases) and a further decline with aging. (The figure is redrawn from data in Bolton et al. A quantitative study of Meissner's corpuscles in man. *Neurology* 1966;16:1-9.)

chemical, or thermal (i.e., $\geq 46.5^{\circ}\text{C}$) stimuli (causing tissue injury).

Three main patterns of sensation loss mirror the fiber class vulnerability in peripheral nerve disease: selective involvement of large sensory fiber function of touch pressure and vibration (e.g., as found in pseudotabes diabetica and spinocerebellar degeneration); selective involvement of small sensory and often also of autonomic nerve fibers (atypical small-fiber DPN [3], transthyretin amyloid polyneuropathy, hereditary sensory and autonomic neuropathies, and Fabry and Tangier disease); and involvement of both large and small fibers (e.g., typical DSPN and many varieties of other distal symmetric sensorimotor polyneuropathies) (6).

Overview of methods to assess decreased sensation. Characterization of the kind, severity, and distribution of sensation loss is useful and needed for the diagnosis of varieties of polyneuropathies, judging their severity, and monitoring course. Rigorous assessment of sensation loss is especially needed for use in therapeutic trials and for following the clinical course of individual patients on specific therapies. The clinical approaches for doing this are assessment of sensory symptoms (i.e., negative neuropathic sensory symptoms); clinical examination using simple handheld devices (cotton wool, stick pins, and tuning forks); recognition of joint motion; and object recognition and use

of other similar approaches. Simple office or bedside QSTs may help in such bedside assessments.

Surrogate measurements of sensation loss include the following: assessment of attributes of NCs of sensory nerve fibers; morphometric counts of nerve endings (intraepidermal nerve fibers) or of nerve fibers of biopsied sural nerve; and specialized studies (e.g., nerve excitability studies [NES]).

Negative neuropathic sensory symptoms. In questioning patients about sensation loss, it is necessary to make the distinction between sensation loss (negative neuropathic sensory symptoms) and increased sensory phenomena (positive neuropathic sensory symptoms [PNSS]) of "asleepnumbness," "prickling," or varieties of pain, described in more detail in a subsequent section. Negative symptoms are included in the neuropathy symptoms and change score (10) and in other scores (11-13).

Neuropathy signs. Sadly, the clinical assessment of decreased sensation by physicians is generally inadequate because it is not performed or is performed badly. Even expert clinical physicians, specialists in neuromuscular diseases, without pretraining or consensus development, and although showing good test-retest reproducibility, markedly overreported abnormality of neurological signs (including assessment of sensation) in a masked cohort study of patients without and with DSPN (14). When the

study was repeated, asking the same physicians to judge as abnormal only unequivocal abnormality, taking age, sex, and physical fitness into account, proficiency improved remarkably (15). Therefore, physicians should use these more specific approaches in their clinical assessment, and they should be used in the conduct of therapeutic trials.

Monofilament screening of foot sensation. Experimental sectioning of posterior spinal roots in cats (16,17) and studies of patients with leprosy (18), inherited sensory neuropathies (19), and diabetes (20–22) have shown that sensation loss is a major risk covariate for limb fractures, plantar ulcers, and neurogenic arthropathy (Charcot joints). In diabetes, these complications cause severe morbidity and high health care costs. Therefore, periodic assessment of the sensation of feet of patients with diabetes with a 10-g monofilament is strongly recommended by health care professionals (23,24). The pathogenesis of foot ulcers and neurogenic arthropathy in diabetes and the rationale underlying periodic testing of foot sensation using monofilaments or other methods of testing have been extensively discussed in the medical literature (12,22,25–38). With detection of loss of sensation and verification of kind, severity, and distribution of this sensory loss and of the underlying variety of DPN, health care providers can formulate a plan to prevent the development of foot complications. Such plans may include management of hyperglycemia, loss of weight, and improved foot care. Because DSPN often develops insidiously and silently (39) (i.e., without PNSS), periodic and regular foot sensation evaluation is strongly recommended.

In a series of trials of a large cohort of diabetic patients, investigators in Toronto, Ontario, Canada assessed the utility of using the 10-g monofilament test for detection of loss of foot sensation and of DPN (12,40,41). They concluded that although there were limitations of its specificity, a simple threshold of ≤ 5 of 8 was predictive of DPN.

Although strongly supporting the use of the 10-g monofilament for this screening purpose, we emphasize that good methods of screening are needed. To provide an accurate and reproducible method of screening, three conditions should be met: 1) a variable degree of impact should be avoided, 2) the mechanical waveform should be standard and reproducible, and 3) response criteria should be defined. To avoid variable impact, the tip of the monofilament should be brought to within 1 or 2 mm of the skin and gently lowered to make contact, and a standard mechanical smooth touch-pressure stimulus should be given. Such a stimulus can be given by bending the monofilament to five-sixths of its extended length and then releasing it slowly over a stimulus period of 1.5–2 s (42) (Fig. 2). With the subject's eyes closed, each of the dorsal phalanges of a foot can be tested sequentially, asking the patient to say "yes" each time the stimulus is felt. The interval between stimuli should be varied from 2 to 5 s so the observer can judge whether responses accurately followed stimuli. If stimuli are correctly identified four or more out of five times, severe sensory loss is unlikely. If the test is abnormal (four or less correct responses or if there is inaccurate timing of responses), sensation loss should be confirmed by a repeat test, more formal QSTing, or other clinical or neurophysiological tests. With confirmation of sensation loss, improved diabetic control (if needed) and increased foot surveillance and care should be instituted.

Computer-assisted QSTs (smart QSTs). Screening of sensation with the 10-g monofilament is not an adequate assessment of the kind, severity, or distribution of

sensation loss, and it is an inadequate criterion for the diagnosis of diabetic sensorimotor polyneuropathy. For diagnosis and characterization of varieties of DPNs, a clinical history and neurological examination is needed. Furthermore, it may be necessary to also assess attributes of NC, QSTs, and autonomic tests. Also, when finding polyneuropathy in a patient with diabetes, other causes of polyneuropathy must be ruled out. To rigorously assess the kind, severity, and distribution of sensation loss for therapeutic trials, the usual physician evaluation may not suffice. It may not be sufficiently standardized, referenced, or monotonic (a consistent trend over time). Ignoring alterations of sensation loss in such evaluations is not a good option because sensation loss is an early and important deficit in major varieties of DPNs. As will be described later, surrogate measures such as attributes of NC and counts of cutaneous receptors, although helpful, do not adequately assess sensation loss. It is thought that computer-assisted (smart) QSTing may meet this need. In a recent proficiency trial of technologists from three medical centers, it was shown that these smart QSTs provided "accurate assessment of sensation loss without intra- or inter-test differences therefore useful for multicenter therapeutic trials" (43). Also, "Smart technology makes possible efficient testing of body surface area sensation loss in symmetric length-dependent sensorimotor polyneuropathy." A recent consensus panel, sponsored by the International Association for the Study of Pain (NeuPSIG) "confirmed the utility of QST for: a) the assessment and monitoring of somatosensory deficits" and for other indications (44).

For the QSTing approach to be suitable for therapeutic trials assessing body surface distribution of large- and small-fiber sensation loss, it must meet high standards. The procedures of QSTing (testing environment, instruction, anatomical sites tested, stimuli, algorithms of testing and finding threshold, reference values, and software control of testing) should be defined, standardized, and efficient. Thus QSTs should be performed in a quiet room free of distraction. Stimuli of large- and small-fiber sensory function should be available for testing. For this purpose, we suggest the use of monofilaments to assess the touch-pressure detection threshold (45) and CASE IVc (WR Medical Electronic, Maplewood, MN) to test heat as pain. Although other tests and systems are commercially available, we report here on approaches that we have developed. Our QSTs assessed for dysfunction of both large- and small-fiber sensory functions using a broad range of stimulus steps from very small to very large, which increase in exponentially increasing steps of magnitude. These tests use validated algorithms of testing and finding threshold and provide reference values and are commercially available (5,42). As shown in Fig. 2, a set of monofilaments A, B, C, - - - I producing -3, -2, -1 - - - 5 ln g stimuli provide exponentially increasing magnitudes of touch pressure suitable for neurosensory testing. For heat as pain (HP)5 (of 1–10) testing, exponentially increasing pyramidal- and trapezoid-shaped heating pulses are used. For touch-pressure threshold, a forced-choice 2:1 stepping algorithm with null stimuli is used. For HP5, the algorithm used is an ascending, nonrepeating stepping algorithm with null stimuli. For both touch pressure detection threshold (TP DT) and HP5 testing, all aspects of testing are preprogrammed, including calculation and printout of results. In testing, the technologist's responsibility is restricted to instructing the patient, management of the test, ensuring that the patient is

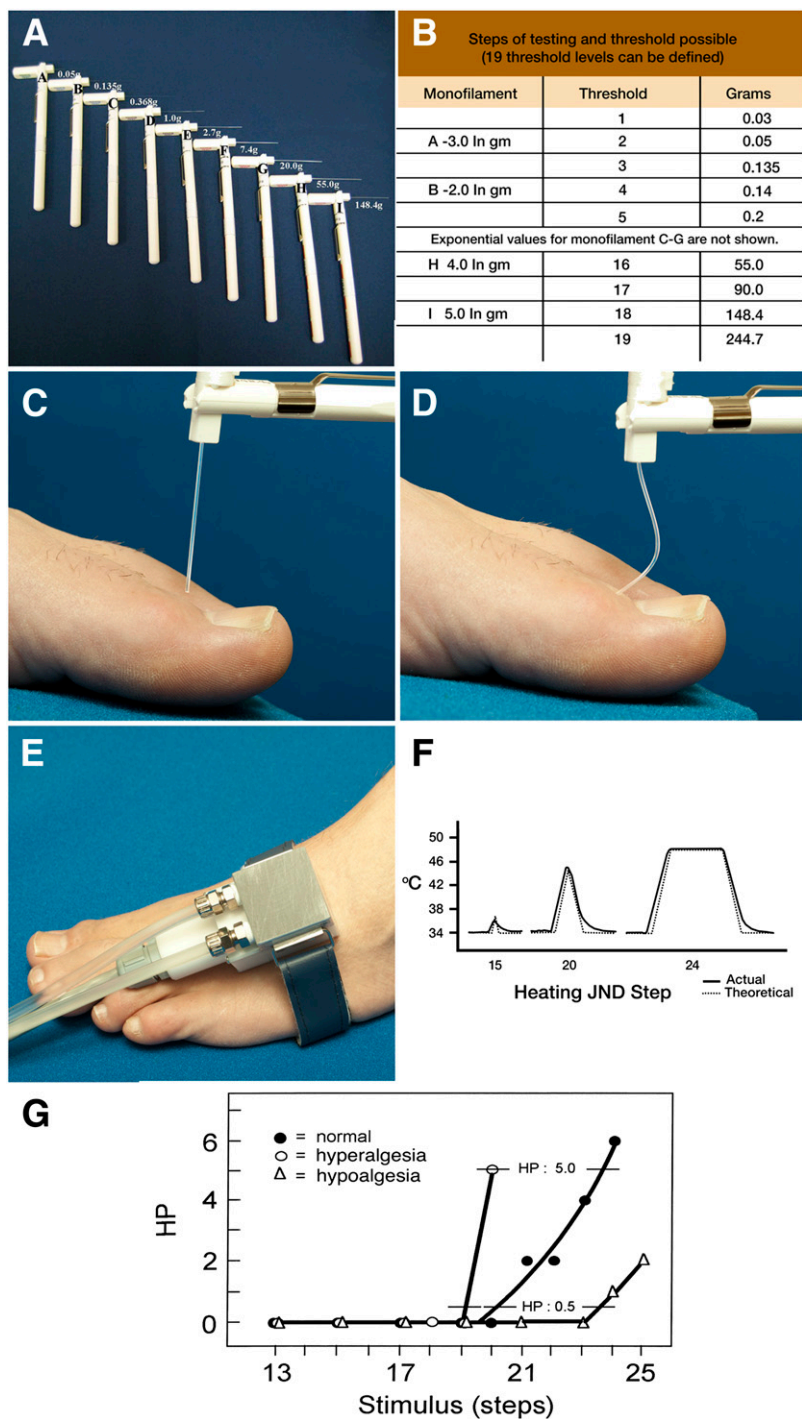


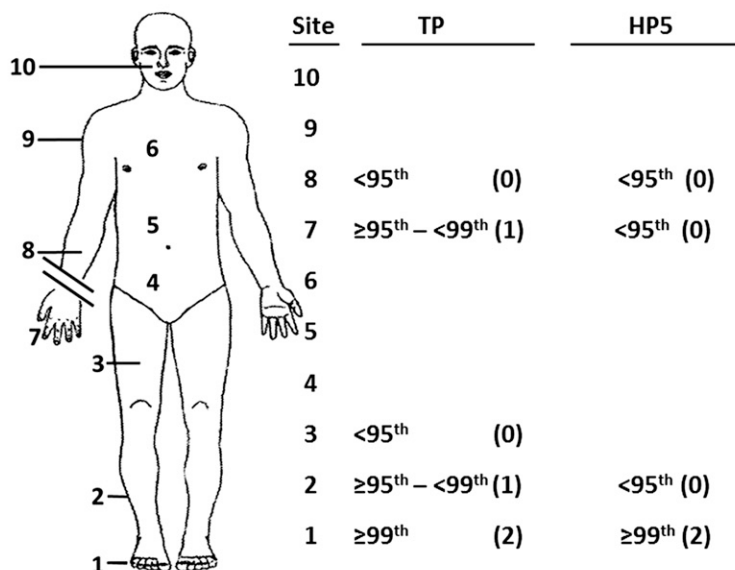
FIG. 2. Illustrated are graded Dyck monofilaments, a modification of Semmes Weinstein monofilaments (North Coast Medical, Inc., Morgan Hill, CA) used in quantitative testing of touch-pressure sensation, altered to provide exponential increases of force suitable for neurosensory testing. Monofilaments A, B, C - - - I shown in A and B provide static loads that increase exponentially from $-3 \ln g$ to $5 \ln g$. In monofilament testing, to avoid a variable degree of impact, the monofilaments should first be brought to within 1 or 2 mm of the skin (C), gently lowered to make contact with the skin and bent to five-sixths of its extended length (D), and then slowly released, with the entire stimulus event taking 1.5–2 s. If null stimuli are used (e.g., in 2:1 alternative forced-choice testing), the observer should go through all the motions of stimuli testing but without making contact with the skin. E: The CASE IVc thermode is shown for evaluation of cooling and heat as pain threshold testing. The thermoelectric technology used allows giving of pyramidal- and trapezoid-shaped thermal stimuli (F). The CASE IVc system is manufactured by WR Medical Electronics. Typical patterns of hyperalgesia, normal response, and hypoalgesia using the CASE IVc system are shown in G. (The panels are reformatted from P.J.D.'s previous publications.) HP, heat as pain; JND, just noticeable difference.

alert and responsive, correctly entering patient responses, and printing out test results.

In testing for and estimating the body surface distribution of sensation loss in a condition like DSPN, the knowledge that the disease process is symmetrical and length

dependent is used to limit the amount of testing needed to a minimum. The approach used to estimate decreased sensation in DSPN is briefly described and illustrated in Fig. 3. The computer software that performed body surface QSTing was developed by P.J.D. and programmed for personal

Smart QST of Body Sites (smart QST_{BS 20} TP and HP5) for Symmetrical Length-dependent Sensorimotor Polyneuropathy Case of DSPN



System Components

- Monofilament A, B, C --- I; -1, -2, -3 --- 5 In gms and 2:1 forced-choice stepping with null stimuli algorithm.
- CASE IVc heat as pain of threshold (HP0.5) and HP5.
- Percentile reference values < 95th = 0 points; ≥ 95th - < 99th = 1 point; and ≥ 99th = 2 points for sites 1 – 10.
- Computer algorithm for testing touch pressure, HP5 and for estimating sensation threshold decrease which is symmetrical and length-dependent, i.e., from testing only one side and testing from borderline to abnormal or to normal. Exact thresholds < 95th or ≥ 99th are not estimated to save time.
- Computer algorithms: 1) interactive algorithm to estimate threshold, 2) testing only contiguous sites which are normal, borderline decreased or decreased and 3) estimation of QST_{BS 20} TP and HP5 as NIS points or % of max.

Test Performance and Interpretation

- In this patient with DSPN: from evaluation of 5 unilateral sites, QST_{BS 20} TP and HP5 was estimated in ~ 90 minutes.
- Results: QST_{BS 20} TP and HP5; 6 of 80 NIS points = 7.5% of max
 QST_{BS 20} TP, 4 of 40 points = 5% of max
 QST_{BS 20} HP5, 2 of 40 points = 2.5% of max

FIG. 3. This figure outlines the methodology and steps used to estimate sensation loss of predetermined standard cutaneous fields of the body's surface area to estimate sensation loss of large and small sensory fibers in symmetrical length-dependent sensorimotor polyneuropathy (e.g., DSPN) and other sensorimotor polyneuropathies (e.g., familial amyloid polyneuropathy). The approaches were developed by P.J.D. and then were programmed for CASE IVc by WR Medical Electronics. The 95th and 99th percentile values for touch pressure and HP5 for each of the 10 sites were provided by P.J.D. and colleagues. As described in the text, the algorithm is designed to test only one side of the body (because the pathological process is assumed to be symmetrical); not continuing testing when thresholds are found to be <95th or >99th percentile; and testing only lateral leg and forearm sites and only a few additional sites depending on length dependence of sensation loss. Most aspects of testing (finding the threshold, comparing the results to reference values, selecting a subsequent site to be tested, and printout of results) are automated (smart QSTing). TP, touch pressure.

computer or CASE IVc use by WR Medical Electronics. The body surface QSTing approach provides instruction for which monofilaments are to be tested, the order of stimulus and null stimulus to be given, and even the order of anatomical sites to be tested. Thus, of the 20 selected anatomical sites that are used to represent the body surface area, it may be possible to estimate sensation loss from the evaluation of as few as four sites and only a slightly larger number of sites in more severe sensory loss. A similar approach to that for the entire body can be used to estimate sensation loss of a limb (e.g., in diabetic lumbosacral radiculoplexus neuropathy [DLRPN] [Bruns Garland syndrome]).

NCs: surrogate measure of sensation loss. NC studies (NCS) and needle electromyography are sensitive, objective, and quantitative indicators useful for the diagnosis and characterization of varieties of polyneuropathy (e.g., of neuropathies associated with diabetes) (1,2,46). They are among the most objective and quantitative early indicators of typical DSPN and therefore useful as diagnostic tools of DSPN (47–50). Among the attributes of NCs, peroneal conduction velocity and sural sensory nerve action potential amplitude expressed as percentiles and corrected for applicable variables of age and anthropomorphic variables are especially sensitive indicators of DSPN (51–53).

In contrast to their good qualities for detection of DSPN, attributes of NC are only weak measures of neuropathy severity. Thus, they provide only limited information about the kind, severity, and distribution of muscle weakness and kind and distribution of sensory loss and of autonomic deficits. In addition, sural sensory nerve action potentials have a strong floor effect, a serious deficit for conducting therapeutic trials.

Epidermal nerve fibers: a surrogate measure of sensation loss. Counts of nerve endings and fibers. Sensory impairment in DSPN is characterized by dysfunction of small- (A δ and C) and larger-diameter (A α β) nerve fibers. Large myelinated sensory fibers, except for their cutaneous receptors, can be evaluated by NCs. QSTs measure both large- and small-fiber sensory function but do not localize dysfunction to either the central or peripheral sensory nervous system. The advent of punch skin biopsy analysis of cutaneous nerve terminals has provided an additional tool for diagnosis of DSPN and its monitoring in clinical trials (54–58).

Various cutaneous sensory structures (epidermal nerve fibers [ENFs], the subepidermal nerve fiber plexus, and Meissner corpuscles) have been considered as markers of DSPN (54,55,59–61). Among these, quantification of ENF density (ENFD) has been most extensively studied in DSPN (54,62–64).

The study of small-fiber neuropathy (SFN) in diabetes typically involves two to three 3-mm biopsies (commonly the distal leg, distal thigh, and proximal thigh) to demonstrate small-fiber pathology and its distribution (54,56,57,62–64). In most diabetic patients, skin biopsies can be accomplished with a minimal complication rate.

Harvested biopsies are fixed in 2% periodate, lysine, paraformaldehyde, or Zamboni's fixative, cryoprotected, and sectioned on a sliding freezing microtome, usually at 50 μ m thickness, to demonstrate the arborization of ENFs (54–58).

The ENFD technique involves immunohistochemistry with polyclonal antibodies to the panaxonal marker protein gene product 9.5 using a light microscopic peroxidase

approach or immunofluorescence (54–58). For clinical diagnosis and therapeutic trials, light microscopy is most widely used. Immunofluorescence/confocal microscopy is especially useful for multi-labeling of cutaneous nerve fibers in the research setting. ENFD is quantitated as the number of fibers crossing the dermal-epidermal junction per millimeter as visualized under high-power light microscopy, by a manual rater, or via nerve fiber tracing systems using confocal microscopy (54–58).

Normative ENFD data are most extensive for the distal leg. Studies suggest a modest effect of age and sex, but not weight or height, on ENFD (61,62). Typically, three to five nonadjacent sections have been used for light microscopic estimation of ENFD (56–58,61). Engelstad et al. (62) have highlighted the importance of confidence intervals to determine an adequate number of sections for accurate estimation of ENFD.

In health, the epidermis and dermis contain a rich network of fibers. ENFs are fine, 0.5–1- μ m-diameter, unmyelinated structures that comprise the sensory endings of A δ and C fibers. They arise from a subepidermal nerve fiber plexus and extend to all layers of the epidermis, coursing relatively perpendicular to the surface of the skin, with a simple branching configuration (55–58).

Quantification of ENFD is widely used in the diagnosis of SFN (54–58). Length-dependent reductions in ENFD occur in diabetic cohorts without clinical neuropathy compared with control subjects, with further decreases in those with clinical DSPN (54,63,64). Reductions in distal leg ENFD may be seen when NCs are in a normal range (63). The converse also occurs, supporting the complementary nature of ENFD and NC in the characterization of DSPN (62) (Fig. 4).

In the clinic, skin biopsy can aid the diagnostic confirmation of DSPN, in patients with sensory complaints or neuropathic pain and normal NC. Although reductions in ENFD provide evidence of small nerve fiber pathology and confer an increased risk of neuropathic pain, they are only weakly associated with neuropathic pain intensity (65). Skin biopsy is presently primarily a tool to confirm SFN and measure its severity and progression, but only rarely discloses an etiology for SFN (e.g., amyloid or vasculitis) (58).

Skin biopsy has also been applied as an outcome measure in DSPN clinical trials. ENFD has been used to suggest beneficial effects of pancreatic transplantation on DSPN in type 1 diabetes and diet/exercise in adult-onset glucose dysmetabolism (66,67). These observations require confirmation.

Beyond reductions in ENFD, cutaneous nerve terminals may show morphological changes in DSPN (54–58). Thus, ENFs may show focal axonal swellings and alterations in orientation, branching, and distribution within the epidermis. Among these, axon swellings, which may reflect a predegenerative state of ENF, have received the most attention (68–70). These parameters show increases in SFN that may precede reductions in ENFD; however, their quantification is challenging and, as yet, none have been incorporated in clinical trials.

Additional immunohistochemical markers of cutaneous nerve fibers (beyond protein gene product 9.5) have been used in neuropathic states. Thus, ENF may be labeled with antibodies to the capsaicin receptor (TRPV1), neuropeptides (substance P and CGRP), GAP43 (a marker of regeneration), and Tuj1 (a cytoskeletal protein), among others (71–73). Further studies are needed to determine whether

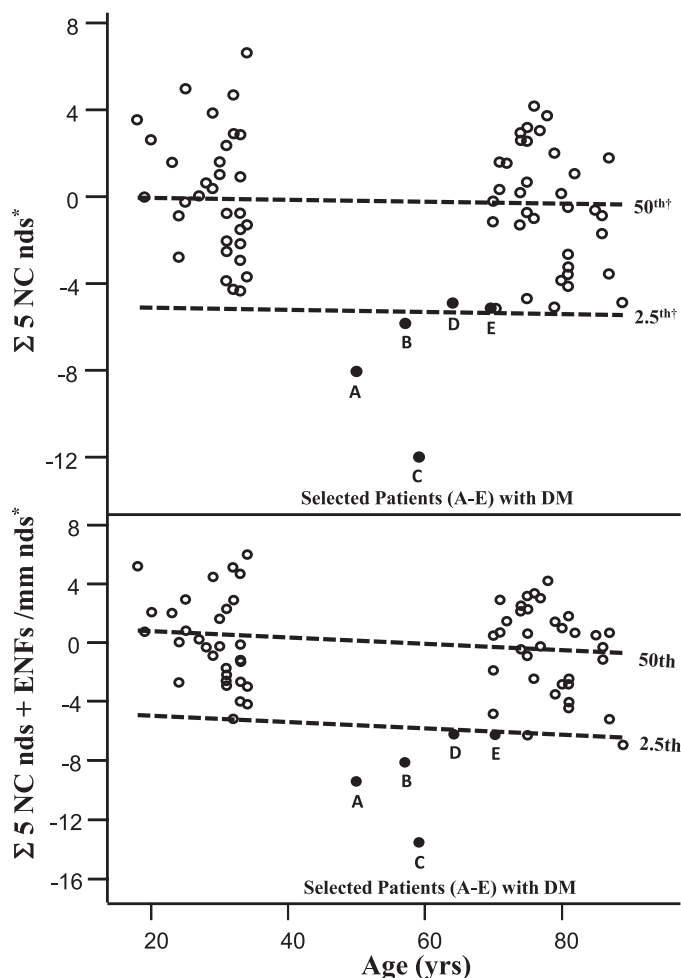


FIG. 4. The *top* figure provides composite NC normal deviate score (nds) values (from percentiles) of healthy subjects (open circles) and five patients with diabetes (DM) and borderline and abnormal values (solid circles). In the *bottom* figure, the combined normal deviate values of the composite NC score normal deviate values of ENFs/1 mm of the same healthy subjects and diabetic patients are shown. A 50th and 2.5th percentile line is shown for both *top* and *bottom* figures. Estimating abnormality using both NC (large-fiber function) and ENFs/1 mm as compared with use of only NC appears not to have altered the pattern of abnormality a great deal, but patients D and E, who were low normal by NC criteria, are just abnormal when assessed by both NC and ENFs/1 mm. *Abnormality is in the lower tail; †based on $n = 330$ Rochester Diabetic Neuropathy Study of Healthy Subjects. (Data are from Engelstad et al. ENFs – confidence intervals and continuous measures with NC. *Neurology* 2012;79:2187–2193.)

these markers have the utility to demonstrate selective involvement of subpopulations of cutaneous nerve fibers in DSPN.

Composite measures of neuropathy signs, sensation loss, and surrogate measures (e.g., Neuropathy Impairment Score + 7). For an overall assessment of neuropathy impairment, we summed the abnormality of neuropathic signs (Neuropathy Impairment Score [NIS]) with seven nerve test abnormalities (NIS + 7). This composite score has been extensively used in both cohort studies and therapeutic trials of DSPN and is also being used in transthyretin amyloid polyneuropathy trials. In NIS + 7, the weakness of representative muscle groups are scored from 1 (25% weak) to 4 (paralyzed) for a total of 192 points. Muscle stretch reflexes are scored from 1 (decreased) to 2 (absent) for a maximum score of 20 points.

Physician assessment of sensation of feet and hands is scored for touch pressure, vibration, pin-prick, and joint motion, and each is graded as decreased (1 point) or absent (2 points) for a total score of 32 points. For the seven tests (five attributes of NCs, vibratory detection threshold, and heart rate decrease with deep breathing), the maximal score of each test is 3.72 normal deviates from percentiles (nds). The maximum NIS + 7 score, therefore, is 270 points and normal deviates. In modified NIS + 7, the body distribution of sensation loss replaces the assessment of vibration detection threshold in NIS + 7.

NES: a surrogate measure of sensation loss. Recently there has been a rebirth in the field of NES (74). The apparatus necessary to perform NES is similar to conventional NCS; however, the information supplied is very different. NCS quantify the amplitude of a response to nerve stimulation and assess the velocity of action potentials along the nerve. NES assess the excitability of a nerve directly under the stimulating electrode, which leads to inferences about the resting membrane potential and the state of ion conductances. Like NCS, NES study only large myelinated fibers. Although NES have not entered standard clinical practice, they have provided valuable insights about the pathophysiology of human neuropathies, including those caused by diabetes.

Krishnan and Kiernan (75) used NES in patients with symptomatic typical DSPN. The altered excitability detected points toward a depolarized resting membrane potential and decreased density of voltage-gated sodium channels in diabetic neuropathy. A subsequent study further argued for deficiency in the sodium-potassium ATPase pump, possibly explaining the depolarized resting membrane potential. More recently, NES have been used as a biomarker for presymptomatic diabetic neuropathy. Although needing critical confirmation, some initial studies (76,77) demonstrate subtle changes in nerve excitability prior to the onset of diabetic neuropathy, as determined by either NCS or symptoms. The utility of NES as a biomarker for presymptomatic diabetic neuropathy is provocative and will need to be tested further in larger prospective studies.

METHODS FOR ASSESSMENT OF ABNORMAL SENSORY PHENOMENA: PNSS, TACTILE AND THERMAL HYPERALGESIA, AND ECTOPIC IMPULSE GENERATION

Neurobiology of PNSS. After partial injury of sensory nerves, patients frequently report not only loss but also increased abnormal sensory phenomena (PNSS) (78–81). These symptoms may occur spontaneously or be induced or increased by contact, compression, or thermal stimuli. Wall and Gutnick (82), using single fiber electrophysiological recordings in a rat neuroma model, observed excessive ectopic impulse generation from the neuroma and inferred that this was arising from small damaged or regenerating fibers. They surmised further that a degree of hyperesthesia (or hyperalgesia) was associated with these increased nerve impulses because rats would gnaw at the denervated foot, causing autotomy (83). Electrophysiological recording from groups of small sensory nerve fibers in human nerve disease has provided further evidence that excessive ectopic impulse generation is implicated in PNSS and in the phenomena of hyperesthesia (hyperalgesia) occurring spontaneously or stimulus induced. It is also likely that peripheral nerve injury may induce central

nervous system alteration modulating sensory events (84). Abnormality of voltage-gated channel function has increasingly been implicated in the pain experience (85–88). Also, proinflammatory cytokines (e.g., tumor necrosis factor- α , interleukins, and other pain peptides) and central nervous system dysfunction may also be involved in the initiation or maintenance of spontaneous or stimulus-induced hyperesthesia (hyperalgesia). Thus, minute injections of nerve growth factor (NGF) were shown to decrease the threshold of tactile, pressure, or thermal hyperalgesia and increase the steepness of the stimulus response slope of the pain response from giving increasingly stronger thermal heat pulses (HP5–0.5 [of 1–10]) (Fig. 5). The hyperesthesia (hyperalgesia) persisted for several weeks (89). A recent study has shown that methylglyoxal modification of Na_v 1.8 facilitates nociceptive neuron firing and causes hyperalgesia in a model of experimental diabetic neuropathy, thus raising the possibility of pharmacological modification of spontaneous or induced hyperalgesia (90).

PNSS. PNSS are the characteristic and unique reports of the subjective sensory symptoms experienced by patients with peripheral nerve injury or sensory polyneuropathy.

They are spontaneous or stimulus-induced sensations recognized by the descriptive words patients use to describe them, by stimuli which elicit them, and by their typical anatomical distribution. Thus, English-speaking patients may describe PNSS using expressions like “numb-asleep” feelings, the sensation after “lying too long on an arm,” or “insects crawling over the skin;” a feeling of “tightness or thickness;” and “prickling” or “jabbing, stabbing, burning, deep aching, or constricting pain” and by other expressions. The conclusion that the descriptors are PNSS is strengthened when the symptoms occur in an anatomical distribution typical of known patterns of polyneuropathy (e.g., multiple mononeuropathy, radiculoplexus neuropathies, distal symmetric length-dependent polyneuropathies, and others). It is further strengthened when tactile or thermal hyperalgesia in the affected cutaneous areas can be demonstrated.

For purposes of recording the body surface distribution of spontaneously occurring positive neuropathic symptoms, a cartoon of the outline of a body (as shown in Fig. 2) may be used.

CONCLUSIONS

Herein, we reviewed the somewhat paradoxical phenomena of decreased and increased sensory phenomena, which may be early and prominent features of DPNs. In this review, we emphasize the quantitative assessment of these disparate phenomena. For screening of foot sensation using the 10-g monofilament, we suggest the following: a standard approach to avoid impact, give standardized stimuli and judge abnormality by defined criteria. For therapeutic trials, improvement of the assessment of clinical sensation loss can be achieved by the clinical use of “unequivocally abnormal” signs, taking age, sex, and physical variables into account, or the use of computer-assisted (smart) QSTs of body surface area of touch pressure and heat as pain 5 (of 1–10), a recently introduced evaluation. Abnormalities of NC and ENF counts are good diagnostic surrogate measures of sensation loss but may have floor (ceiling) effects for therapeutic trials and may have other limitations (i.e., insufficiently representing distributed sensory loss). Increased and abnormal sensory phenomena are assessed by tallying the kind, severity, and distribution of PNSS and by assessment of tactile and thermal hyperalgesia using QSTing approaches.

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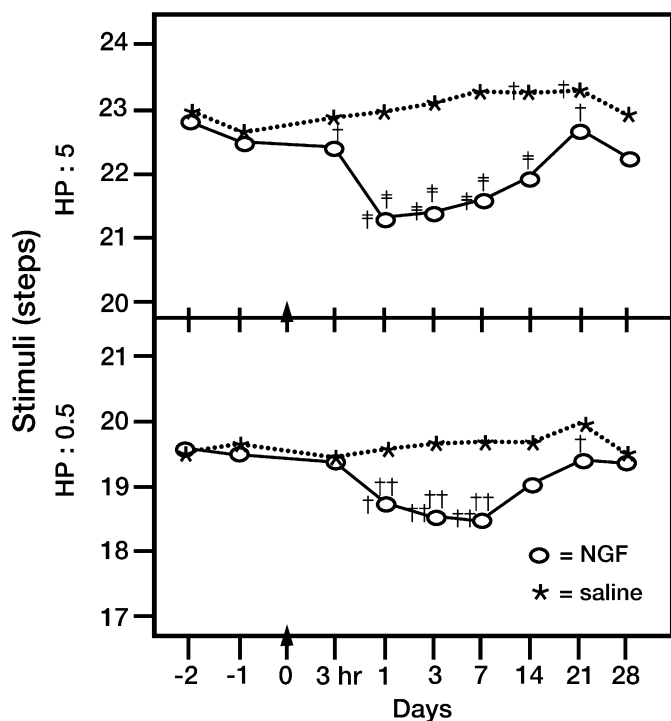


FIG. 5. Plotted are the HP thresholds (HP5 and HP0.5 using the CASE IVb system) at various times (days) before and after intracutaneous injections of minute amounts of NGF (open circles) into the skin of the volar forearm of healthy subjects as compared with injection of the contralateral forearm with saline. Subjects and observers were masked as to which side was injected with NGF. Sixteen healthy subjects were assessed over a period of 28 days. A significant decrease in HP0.5 and HP5 followed NGF injection, and this was significant for HP5 for all periods between 3 h and 21 days after NGF injection; for HP0.5, significant thermal hyperalgesia was found for 1, 3, and 7 days after injection. The data provide convincing evidence that the methodology used in CASE IVc is a useful methodology for the demonstration of thermal hyperalgesia. In this study, mechanical hyperalgesia was also demonstrated. (Data are from Dyck et al. Intradermal recombinant human NGF induces pressure allodynia and lowered heat-pain threshold in humans. *Neurology* 1997;48:501–505.) †, ††Statistically significant differences in the heat pain responses at the time interval shown.

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