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Quantitative Sensory Testing: Methodology, Applications, and Future Directions

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Summary: Quantitative sensory testing (QST) is based on well-developed psychophysical methods that define not only the stimulus (type, characteristics, quantity, presentation, testing format, and environment) but also the response (form and analysis). With the availability of personal computers, transducers, electronic circuitry, and specially written software, it became possible to develop systems that delivered physical stimuli with waveforms that were precisely defined, quantitated, and graded over a broad range of magnitudes, and capable of eliciting unitary sensations. Specific algorithms of testing and finding threshold could now be programmed for exact and sequential error-free testing. Results could also be efficiently and accurately printed out and compared with normal values with consideration of modality, site, gender, height, and weight. QST's main application is in quantifying modality-specific detection thresholds (and some suprathresholds also) in health (by site, side, development, aging, and other) and in disease (involving sensory receptors, nerve fibers, central nervous system tracts, or cerebral association areas), allowing it to play the unique role of standardizing the clinical examination. Used to identify modality-specific sensory loss it can, for example, be correlated with the compound action potential of sural nerve in vitro and with the number and sizes of fibers. In detecting patterns of sensory abnormality, it can also suggest the presence of specific diseases and be used to follow the course of sensory loss. Finally, because it is the best approach to detect, characterize, and quantitate sensory abnormality, it is useful both in epidemiologic and controlled clinical trials. Although our review focuses especially on the approaches and system we have developed, other systems using standardized approaches are available allowing the evaluation of vibratory (VDT), cooling (CDT), and warming (WDT) detection thresholds and visual analog scaling of heat pain (HP VAS). **Key Words:** Sensation—Nerve fibers—Sensory thresholds—Quantitative sensory testing—Psychophysics.

The clinical evaluation of sensation plays an important part in the neurologic examination. Using simple handheld tools (pin, cotton, tuning fork, etc.) the examiner assesses whether light touch, pin-prick, vibration, joint position, and motion are felt normally or not. Judgments are then made about decreased sensation or hypersensitivity, both helpful in differential diagnosis. Typically, the examiner recognizes abnormality by comparing affected with unaffected areas, with homologous regions, or simply comparing results with what is thought to be normal considering modality, site, age, and gender. From this and other information, inferences are made about attributing

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abnormality to dysfunction in cerebral association areas, fiber tracts, or peripheral nerve fibers. Judgments are also made about whether the process is focal or in a sensory system, and about which pathologic process might be responsible. Although this clinical approach is useful for the detection of some focal lesions of brain, spinal cord, and nerve, for some purposes it has major shortcomings. Stimuli with precisely defined waveforms cannot be given reproducibly, the algorithm of testing is not standardized, the responses are not defined or recorded, and results are not adequately compared with normal results considering modality, site, age, sex, and other variables. As a result, bedside approaches can do little better than detect sensory loss and perhaps altered sensation among regions. They are not adequate for reliably determining threshold for specific modalities at given sites or for reliably evaluating heightened or lowered responses using standardized and statistical approaches. For the reliable evaluation of sensory threshold. for assessing hypersensitivity, and for use in epidemiologic and controlled clinical trials, quantitative sensory testing is needed.

Quantitative sensory testing (QST), based in psychophysics, attempts to specify all events of sensory testing and the method of responding. Its main goal is to provide standardized and quantitated stimuli, using appropriate approaches, with a view to quantitating detection or estimating a level of response. Because the manner in which a subject responds to a stimulus, as well as the method of stimulus delivery, can influence this response, both are explicitly addressed. With the development of various stimulus delivery algorithms, as well as response paradigms, QST techniques have been verified and their adaptation for use both in human and animal experimental studies (Maurissen, 1988; O'Brien et al., 1989) has established the field of quantitative sensory testing.

Despite the improvements offered by QST approaches, two reservations can be raised. The first is the need for subject interaction. By its very nature, QST is subjective and not objective as are other forms of sensory testing (e.g., sensory nerve conduction studies), which do not require active patient participation. Clearly, these two forms of testing are different, yet each is valid in its own way. Unlike sensory nerve conduction velocity (NCV), QST attempts to assess the subject's response to quantified naturally occurring stimuli that are modality specific (cool, warm, cold; heat pain) as well as evaluating subjective alterations in sensation (e.g., hypersensitivity). [QST capability of evaluating small and unmyelinated nerve fiber function is not applicable to autonomic nervous system (ANS) evaluation. Such ANS testing methodology has been the subject of recent reviews (Low, 1993; Schondorf, 1993)]. If any skepticism remains about the validity of QST, the reader should consider the case of visual and auditory function. Here, a variety of psychophysical tests are used daily for the study of physiology as well as the detection, characterization, and follow-up of disease. Despite the availability of electrophysiologic studies for retina and cochlea, they are not nearly as important or practical as psychophysical tests. The second concern about QST is that it tests the entire somatosensory pathway and its association areas. One may ask how such an approach could be applied to the detection of an abnormality at a specific level, e.g., receptors, peripheral nerve fibers, and so on. QST is not meant to provide this kind of localization. Such information is generally provided by other evaluative procedures.

Despite our inclusion of examples that demonstrate QST's usefulness when applied to various clinical conditions, this is not the primary focus of our review. Rather, we will direct our attention to the requirements that allow the development and validation of a specific sensory test. As emphasized in a recent consensus report (Peripheral Neuropathy Association, 1993), several areas need to be addressed. These include the necessity for a defined stimulus that is appropriate to the modality of sensation tested, invariant over a broad range of magnitudes, and quantifiable. A testing algorithm that is validated both in subjects and patients as well as the method of estimating threshold. Finally, results that are compared with a cohort of healthy subjects, so abnormality can be expressed as a percentile considering modality, site, age, gender, and other variables. In order to simplify our discussion, no attempt will be made to comment upon all testing algorithms, techniques, or the equipment used to perform them. However, the integral role of such methodology in QST as well as the equipment used in testing still needs to be addressed. In order to do so we will base our discussion on a computer-assisted sensory examination (CASE III and IV) that we developed. A series of similar instruments have also been introduced by Lindblom and associates from the Karolinska Institute, and subsequently several instruments to measure thermal sensation. Our emphasis, however, will be on the CASE systems because they were among the first automated systems introduced and our experience relates to their use.

TABLE 1. *Cutaneous sensory receptors*[a]

Modality	Receptor	Primary afferent
Vibration	Pacinian corpuscle	Aαβ (myelinated)
Touch pressure	Meissner Corpuscle (RA)	Aαβ (myelinated)
	Merkel Cell Neurite Complex (SA I)	
	Ruffini Ending (SA II)	
Warm	?	C (unmyelinated)
Cold	Unmyelinated neurite complex	Aσ (myelinated)
Heat pain	?	C (unmyelinated)
Cold pain	Unmyelinated Neurite–Schwann Cell Complex in Basal Epidermis	Aσ (myelinated)
	?	C (unmyelinated)

[a] RA, rapidly adapting receptor: SA I, slowly adapting type I receptor; SA II, slowly adapting type II receptor.

ADVANTAGES AND INDICATIONS

Although still debated, there is considerable evidence that certain receptors, classes of sensory fibers, and cerebral association areas are involved in conveying information related to the experience of touch-pressure, vibration, cooling, or warm or heat pain (Table 1; see the article by Birder and Perl, on cutaneous sensory receptors, in this issue; and, Light and Perl, 1993). The corollary of this concept is the implication that with dysfunction of one or a combination of these fiber classes (systems) there may be selective alterations or loss of such sensory modalities. This potential for modality-specific sensory dysfunction is uniquely assessed by QST's ability to evaluate specific classes of sensory fibers. Unfortunately, clues as to the etiology of a specific pattern of sensory deficit may not always be possible on the basis of these QST results alone, but its interpretation in light of other findings does limit the possibilities. This apparent limitation is also offset by simplicity of test administration, capability for automation, its nonaversive character, and the sensitivity, specificity, and reproducibility of results that allows the use of both statistical analysis and comparison of test results.

The ability to detect and quantitate specific sensory system dysfunction does not necessarily imply that QST be used in the evaluation or follow-up of all such cases. However, there are several areas where the application of its novel capabilities are apparent. These include (a) studies that evaluate normal sensory function or its recovery and the role of various parameters (e.g., age and sex) as covariates in determining sensory perception (Dyck et al., 1993*a*; Van Boven et al., 1994). (These insights have allowed us to further understand not only normal sensory function but also to guide treatment or rehabilitation of subjects inflicted by its dysfunction); (b) epidemiologic studies applied to normal control groups and patient or disease-specific cohorts (Kahn, 1992; Dyck et al., 1992; Lundström et al., 1992; Gerr and Letz, 1993; Sosenko et al., 1987; Lipton et al., 1991; Gulevich et al., 1992); (c) evaluation of the effects of treatment with regard to halting the progression of sensory loss or in evaluating/detecting its development [the ability to detect subclinical abnormalities of sensory function offers the potential for averting permanent injury (Berger et al., 1993)]. (d) As a complementary study or in lieu of other measures of sensory nerve fiber function such as electrophysiologic and pathologic/morphometric measurements. [In some cases, poor patient toleration of these other techniques, inability to perform repeated measurements, and expense can be overcome by the substitution of QST (Dyck et al., 1985, 1987; Gerr et al., 1991; Llewelyn et al., 1991)]; (e) evaluation of small fiber dysfunction, other than ANS, which is either not adequately evaluated or incapable of being studied by other methods (Bravenboer et al., 1992); (f) the use of QST to further classify and help elucidate the cause of hypersensitivity phenomena (Hansson and Lindblom, 1992; Ochoa and Yarnitsky, 1993; Verdugo and Ochoa, 1992).

GENERAL COMMENTS

Testing Conditions and Report Generation

Because the patient must interact and be attentive to testing events, testing should take place in a quiet and comfortable setting. The subject should be alert, instructed using a preprinted and therefore uniform set of test instructions, and know how to respond. It

may be helpful to administer a detectable sample stimulus before testing to acquaint the patient with the stimulus and to establish whether they know how to respond and what is expected. Afterward the subject is instructed to provide their "best" response in lieu of "guessing" as they attempt to detect test stimuli. In those cases where null stimuli are used, a protocol as to how a positive response is treated or other inconsistencies are handled during the test needs to be established. Finally, quality control is an issue that needs to be addressed in each sensory laboratory.

When the report is generated, subject identifying features and variables (age, height, etc.) should be provided. The actual results are then given and compared with normative data or percentiles and a cut-off value for normality determined (e.g., <99th percentile). Finally, the results are interpreted and inconsistent or unusual responses commented upon.

Stimuli

Although it may appear intuitive, it is necessary that the stimuli administered be appropriate to induce one sensory experience only and no other, e.g., touch-pressure, vibration, cooling, warming, and heat-pain. In practice, it may not be possible to administer only one stimulus modality. In such cases, the additional modality to the one being tested should be present at all times, or presented in the null stimulus interval, e.g., in forced choice testing. Touch pressure, sharp or pin modalities necessitate the use of a probe that is best directed perpendicular to the site tested (Greenspan and McGillis, 1991; Mengel and LaMotte, 1990). Vibration should consist of a sinusoidal waveform at given frequencies, and temperature requires that ramps or pulses of temperature change be administered to a defined area (Stevens and Marks, 1971). In each case, the waveform needs to be precisely described or defined and should remain constant over a broad range of stimulus intensities or magnitudes. The stimuli also need to be quantifiable in appropriate units of measurement and cover a broad range of intensities. This is clearly necessary so that sensitive and relatively insensitive sites can be appropriately studied both in controls and patients. Any background conditions during stimulus administration will also need to be kept constant [i.e., with vibratory sensation the load of the transducer on the skin needs to be known and kept constant (Lowenthal and Hockaday, 1987), as does baseline temperature during temperature testing]. Finally, the testing apparatus should be periodically calibrated.

Testing Equipment

The nature of QST lends itself to automation. Beginning in 1975, we introduced systems that utilized a personal computer with keyboard and printer, an electronic controller, mechanical and thermal transducers, a visual cuing device, and a response key. The most recent version (the CASE IV) has been designed to assess vibratory (VDT), cooling (CDT), and warming (WDT) detection thresholds, and heat-pain visual analog scaling (HP VAS) of pain and fail-safe mechanisms have also been built in (Dyck et al., 1978, 1993*a*). This complement of tests allows the evaluation of both large fiber (VDT) as well as small fiber sensory function (CDT, WDT, and HP VAS). (Although the concept of testing touch-pressure at discrete grid points over the surface of the skin had been used in the CASE III system, in practice this was found to require complicated instrumentation and long testing times). This system is now produced by W. R. Medical Electronics, 123 North 2nd St., Hastings, MN 55082. In earlier reviews on QST, we listed instruments and approaches that have been available to test touch-pressure, vibration, and thermally induced sensations. (Dyck, 1975; Dyck et al., 1984).

REQUIREMENTS FOR DEVELOPMENT OF QST ALGORITHMS

General Comments on Psychometric Tests

In general, psychophysical testing algorithms (Maurissen, 1988) have two components: (a) The stimulus test (i.e., the waveform, intensity and presentation of the stimuli) and (b) the response paradigm (i.e., how the subject is to respond to a given stimulus).

Two methods of stimulus presentation are commonly employed. The first, a *method of limits*, involves gradual changes of stimulus intensity by either (a) gradually increasing the stimulus intensity to the point of detection, (b) gradually decreasing to the point of disappearance, or (c) a combination of both (Békésy method). In the second type, or *tracking method*, the subjects themselves determine the stimulus intensities administered on the basis of their responses. For example, with every stimulus identified, the following stimulus administered would be of lower intensity, and these decrements in intensity

continue until the stimulus is no longer detected. At that time (*turnaround point*) the next stimulus would be of higher intensity. Now an incremental increase in stimulus intensities occurs and continues until the subject correctly identifies a response, when once again the process reverses itself and stimulus intensities begin to decrease. Testing continues in this manner until eventually the subject's responses fluctuate about their detection threshold. In its most simple form, this response paradigm is referred to as following a *simple up–down rule.* However, modifications whereby a certain series or combinations of correct or wrong answers determine whether the next stimulus will be of a higher or lower intensity can also be used. This manner of stimulus administration follows one of the various *up–down transformed rules* (UDTR) (Wetherill and Levitt, 1965; Wetherill et al., 1966). The actual degree of stimulus change with either the method of limits or tracking can consist of gradual changes in intensity (with varying slopes of change) or stepwise changes of either known magnitude or based on empirical studies where *just-noticeable differences* (JND) in intensity are used.

Although the foregoing suggests that testing approaches are quite standardized, regardless of which approach is used (limits, tracking, or combination), there are a large number of variables that can influence a test's performance. Therefore, it is not sufficient to indicate that threshold was estimated using the method of limits or the forced-choice algorithm. The actual threshold measured can be influenced by the time between stimuli, the ramp rate of stimulus intensity, the rate of decrement, the number of stimuli presented at a stimulus intensity, the rules that are used to determine whether the stimulus was felt or not felt at a given level, the number of turnarounds, the use of null stimuli, and how responses are evaluated to determine threshold. These events must be described in detail and the parameters of the algorithm validated by using computer simulations, or performing the test on healthy subjects and patients.

As an example of the multiple test variables that need to be defined, let us consider VDT testing. The stimulus may vary depending on the size of the stimulus disk and the load with which it rests on the part being tested. Assuming that sinusoidal oscillations are used, they may be tested at any frequency between 64 and 5,000 Hz. The intensity of the oscillations may be increased continuously or in discrete pulses or steps. The ramp rate of the increases or decreases may be linear, exponential, or other. If pulse stimuli are used, the envelope may be shaped at will. All of these variables need to be considered before their inclusion in standardized tests because each may affect the test response.

The next component of a testing algorithm is the response paradigm, which can be one of three varieties. The first is referred to as the *two-interval forced choice.* This involves stimuli that are delivered as paired stimulus events, one actual and the other a null event. Whether the stimulus is in the first or second interval is determined by chance. The ability to correctly identify the interval having the stimulus, usually defined as occurring 75% of the time, is that subject's threshold. The second method employs a *yes–no paradigm.* Now during each stimulus event an actual stimulus may or may not be present and the ability to correctly identify the stimulus event 50% of the time is considered the threshold. In such a paradigm, one keeps track of the frequency with which null stimuli were answered "yes." If this occurred too frequently, the subject is not correctly identifying the stimulus event being tested and probably needs to be further instructed. Finally, the last method is a variation of the yes–no paradigm; here, when a stimulus is perceived the subject grades its intensity along a scale. One frequently employed scale is the *visual analog scale* (VAS), which can be graded 0 (no sensation or a sensation not to be scaled) or from 1 to 10 (minimal to maximum sensation for the sensation to be scaled). Unlike the other response paradigms, this technique allows the detection of other than a threshold response, i.e., *superthreshold,* which is further defined as a sensation of a specific intensity or grade.

Testing Algorithm

For any modality evaluated, the complete testing algorithm needs to be adequately defined and validated (Dyck et al., 1993*a*; Peripheral Neuropathy Association, 1993). As previously discussed, both the stimulus and response paradigm need to be completely described. The complete algorithm of testing and finding threshold should also have been tested by computer simulation and in actual studies of healthy subjects and disease patients. The test should have then been carefully validated by demonstrating that it provides sensitive, specific, reproducible, and accurate results. To determine sensitivity and specificity, a comparable test is needed, and if not available, one may use a comparative standard, e.g., other tests of nerve dysfunction. The establishment of normative

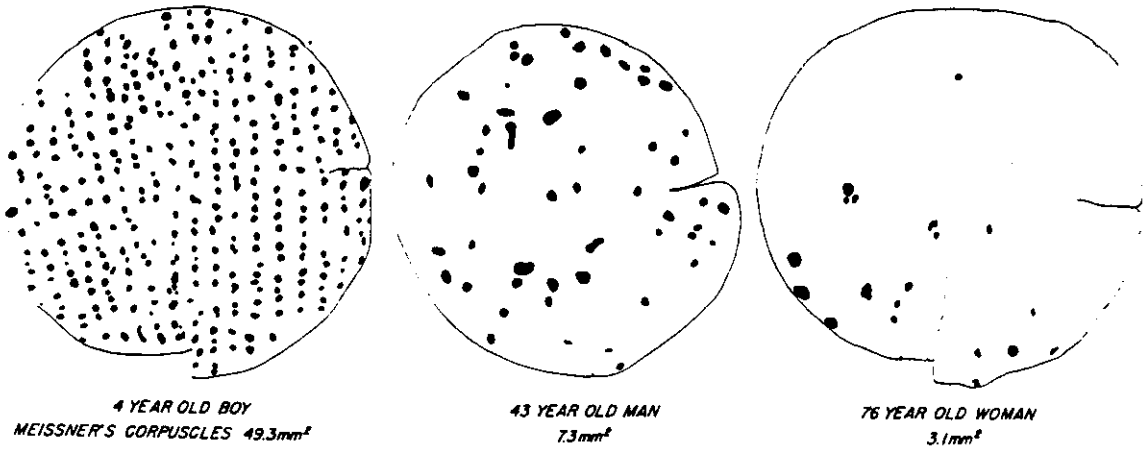

FIG. 1. Meissner's corpuscles in horizontal sections of 3-mm punch biopsy specimens of skin from the plantar surface of great toes in normal subjects (by method of superimposition of horizontal sections). The concentrations of Meissner's corpuscles are as follows: 4-year old boy, 49.3/mm^3; 43-year-old man, 7.3/mm^3; and 76-year-old woman, 3.1/mm^3. (From: Bolton CF, Winkelman RK, and Dyck PJ. A quantitative study of Meissner's corpuscles in man. *Neurology* 1966;16:1–10. Reprinted with permission.)

values is a requirement as well, so that the responses of a patient can be expressed as a percentile response. To obtain normal values for modality, site, age, sex, and co-varieties, it is necessary to study a healthy cohort and assess the influence of these variables in health. This information also needs to be available for each site tested because variation in receptor density (Fig. 1) needs to be taken into account, as do other variables such as skin thickness, receptor location, etc., (Dyck et al., 1993*c*; Greenspan and LaMotte, 1993; Klement and Arndt, 1992; Vega Bermudez and Johnson, 1991) in establishing control data (Fig. 2). Later, if a new algorithm is developed it will then be necessary to compare it with other similarly defined studies because otherwise no true "gold standard" exists for verification. Finally, it is desirable to increase the degree of automation of any such test because tester bias will then play less of a role in performance.

QST METHODOLOGY

CASE IV System for Testing Thermoreceptors (CDT, WDT) and Nociceptor (HP VAS) Thresholds (Fig. 3)

In order to provide an adequate and quantifiable thermal stimulus, a thermode with a 10-cm^2 surface area was developed (although another size could be substituted). The thermode is a highly engineered device that can provide accurate and exquisitely controlled minute or large pulses or ramps of cooling or heating at the thermode testing surface. The heating

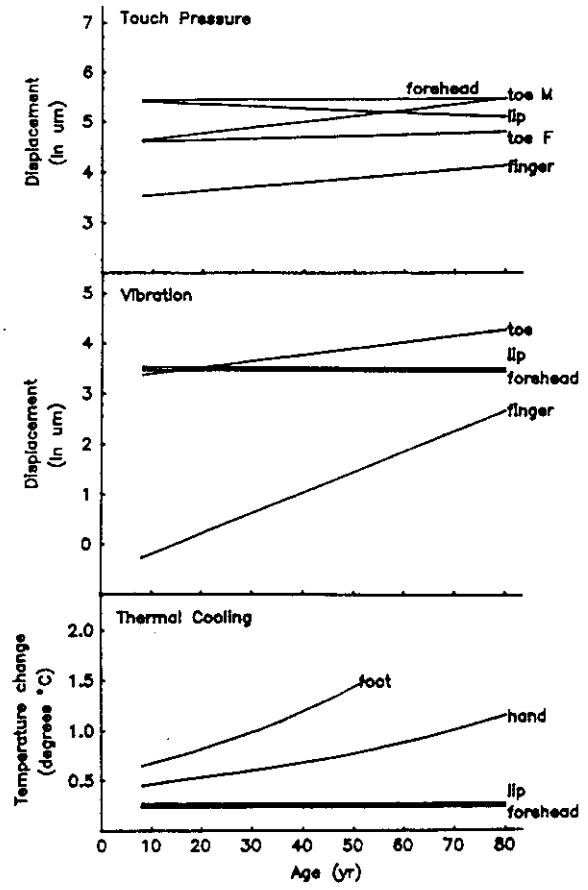

FIG. 2. Threshold regression lines with age by modality of sensation and site in health. (From: Dyck et al., 1993*a*. Reprinted with permission.)

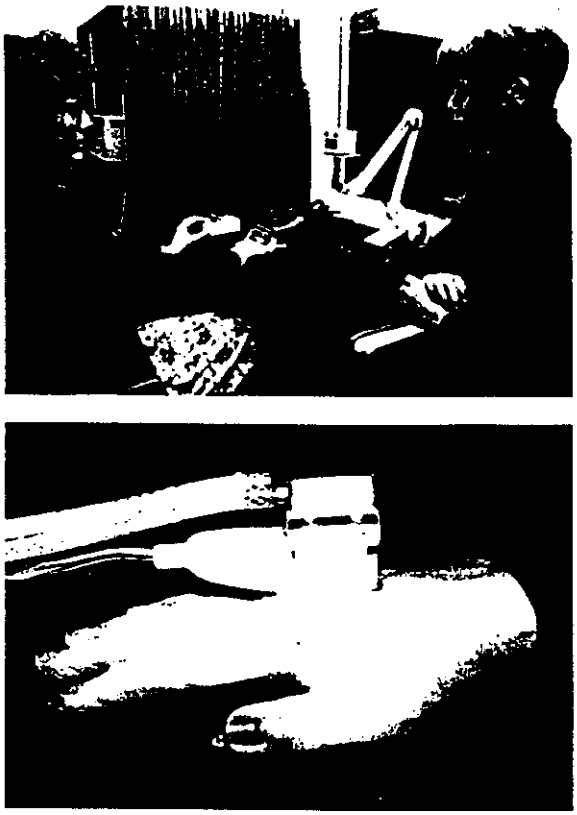

FIG. 3. Use of CASE IV to assess cool (CDT), warm (WDT), or heat-pain (HPDT) detection threshold on the dorsal surface of the hand. **Top:** The subject is sitting on a dental chair, which can be positioned so that the hand (or foot) rests comfortably on the testing table. The thermode assembly is firmly strapped in place; the left hand of the subject activates the yes or no response key during the display on the visual cuing device. The visual cuing device is mounted on a multijointed mechanical arm so that it can be positioned for comfort at eye level. In this test, the examining technician has previously entered the bibliographic and testing information and simply monitors the test to ensure that further instruction is not needed; that drowsiness, should it occur, is detected; and whether any malfunction occurs. The electronic controller, computer, and keyboard are rack mounted just beyond the testing table. **Bottom:** A close-up view of the thermode assembly. The umbilical cord to the thermode has two components: electrical cords (lower) and circulating fluid hoses. (From: Dyck et al., 1993c. Reprinted with permission.)

or cooling element is a thermoelectric unit that is a series of thermocouples in parallel. When current is applied, the temperature at the ends of the thermocouples charge in opposite direction. This Peltier effect is exploited to produce a set temperature, provide ramps of slowly increasing or decreasing temperatures, or pulses of cooling or heating. Temperature pulses (gradually increasing pyramids, or trapezoid shaped) at predefined rates and to predetermined levels can then be fashioned by computer software. In CASE IV, 25 discrete steps or stimulus magnitudes are available, and range from step 1 (smallest) to step 25 (largest). The maximum temperatures achieved are 9°C held for 10 s for CDT, 45°C for 10 s for WDT, and 49°C held for 10 s for HP VAS. The administration of these temperature stimuli involve gradual changes in temperature along a linear ramp to a preset value, and after a specified time a return to steady state following a similar but inverse ramp. Calibration of the system ensures a static temperature of ±0.5°C of the set temperature between 10 and 50°C, and on thermal ramps the final temperature will range from ±0.05°C for $\Delta < 1$°C up to ±0.25°C for $\Delta \geq 5$ to <20°C. For this modality of testing as well as the others to be reviewed, testing is performed in a mechanical chair. This allows the subject to be raised or placed in a supine position, allowing various sites (finger or toe) to be tested.

CASE IV System for Testing Vibratory (VDT) Thresholds (Fig. 4)

The stimulating probe is a 9-mm disk coated with Teflon. It is mounted by a shaft to an optical scanning motor whose displacement is proportional to current. A sinusoidal waveform at 125 Hz is employed and the envelope of a stimulus interval is increased and decreased exponentially to avoid an abrupt onset and offset. The mechanical transducer is mounted on a balance arm allowing the probe to rest with sufficient

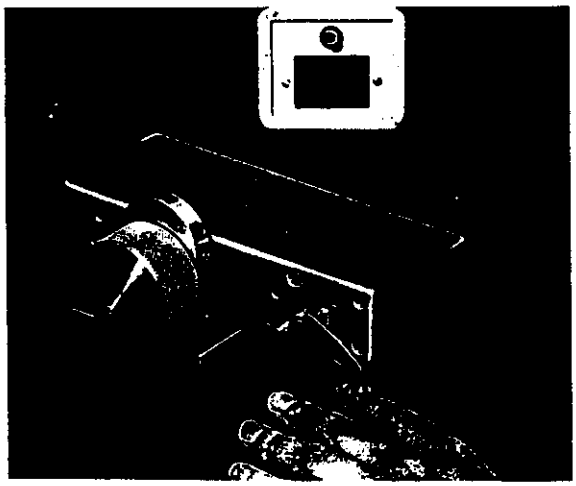

FIG. 4. The tone-arm and vibratory stimulus transducer used in computer-assisted sensory examination (CASE IV). (From: Dyck et al., 1990. Reprinted with permission.)

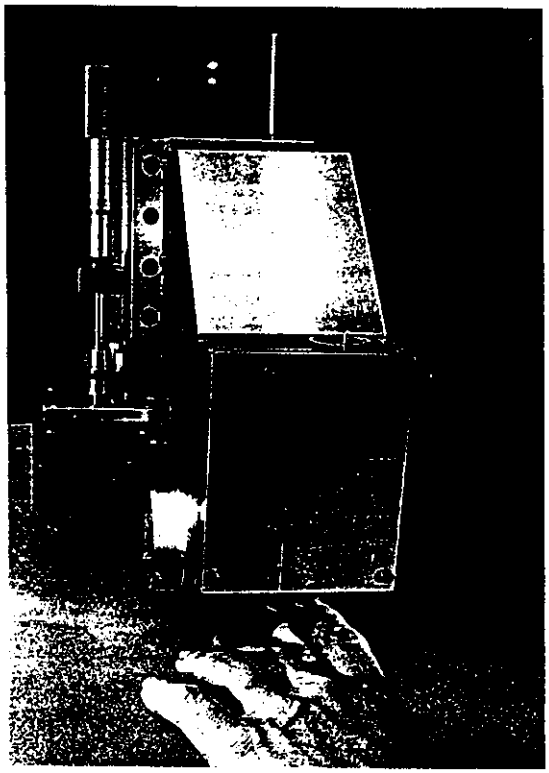

FIG. 5. Touch-pressure stimulator assembly is shown attached to the mechanical translator as touch-pressure of the index finger is being tested. The finger is cradled in clay and the stimulator stylus rests on the skin just proximal to the base of the nail. (From: Dyck et al., 1978. Reprinted with permission.)

mass (30 g) so as not to respond to rapid displacement (nonstimulus vibration), but allows slow up and down displacement from movement of the anatomic area being tested. A total of 25 discrete levels of stimulation magnitude are provided, ranging from 0.1 to 576 μm of displacement. These levels were based on estimates of just noticeable difference. Calibration is performed periodically, measuring the displacement of a laser beam after it has been reflected from the surface of a mirror mounted on the front of the stimulating probe, in contact to a finger or toe.

CASE III System for Testing Touch-Pressure (TPT) Thresholds (Fig. 5)

The CASE III system is equipped to determine TPT and does so by testing a 3 × 3 grid of nine separate points with an interpoint separation of 1 mm (Dyck et al., 1978, 1984). Each point is tested separately by using a stylus whose tip is a sphere 0.64 mm in diameter. The intensity of stimuli is controlled by a galvanometer motor to which the stylus is mounted, and the whole apparatus is affixed to an electromechanical translator. Stylus tip movement from point to point is automatic. Stimuli range from a total load of 2.9 to 1,200 mg. (If expressed as force per unit area, quite different values are achieved). To avoid impact when giving a stimulus event, the force is applied using the time constant of a discharging capacitor. Twenty-one predetermined levels of magnitude are employed. Each stimulus is superimposed on a static load of 50 mg that is exerted vertically on the skin through the stylus. Unless testing or specific evaluation of TPT is requested, we have substituted VDT as a measure of large fiber, mechanoreceptor sensory function since it can be performed rapidly and provides comparable information (Dyck et al., 1993*a*).

TEST PERFORMANCE

During the development of the CASE system, numerous modifications and changes of the testing procedure took place. We discovered that linear ramps of increasing stimulus intensity were either too time consuming, when rates of change were slow, or overestimated thresholds with fast rates of change, a direct effect of the reaction time of the test subject (Fig. 6)

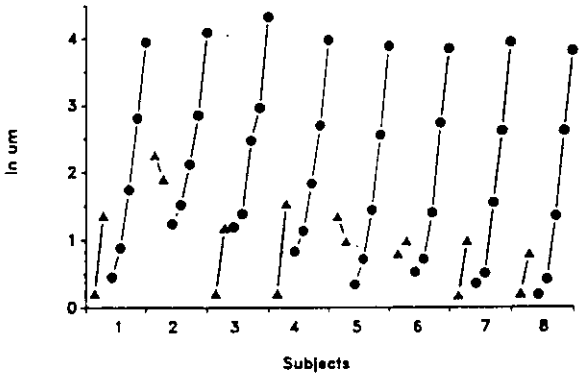

FIG. 6. Vibratory detection thresholds (VDT) for the index finger in eight subjects from a forced-interval algorithm (triangles) and "appearance thresholds" from linear ramps (circles). The VDTs based on testing with the forced-interval algorithm were performed on separate days. The first threshold value is displayed to the left of the second value. The thresholds from linear ramps at 0.08, 0.17, 0.83, 4.15, and 16.6 μm/s are joined by lines from left to right for each of the eight subjects. The thresholds from slow linear ramps (0.08, 0.17, and possibly even 0.83 μm/s) are comparable to those obtained from forced-choice testing. Slow ramps are not fast enough for testing insensitive sites, making their use impractical in automated systems. Use of fast ramps clearly overestimated threshold. This overestimation probably results from the subject's inability to stop the stimulus quickly enough because of reaction time. (From: Dyck et al., 1990. Reprinted with permission.)

(Dyck et al., 1990). Since then, other methods have been employed and validated as more efficient ways of detecting thresholds (Dyck et al., 1993*b*). These forms of testing are not influenced by reaction times, and hence allow subjects the opportunity to respond at their own pace. In addition, response paradigms that relied on forced choice were also found to be lengthy, and patient fatigue was at times a problem. For certain purposes, we have developed a yes–no paradigm or a variant that uses a graded response. In those individuals who encounter problems, one may revert to the use of forced-choice testing. Throughout the development of our new algorithms we have made use of our empiric observations, computer simulations as well as control subject and patient trials to validate each technique. In each case, the new algorithms agreed quite well with those established for CASE III.

Vibratory Threshold Determination (VDT) CASE IV Method

With CASE IV, VDT is usually estimated by a two-interval forced-choice method or by a 4, 2, and 1 stepping algorithm. In either test, 25 discrete magnitudes of stimulus intensity are available for the estimate, and the sinusoidal oscillations are at 125 Hz (Dyck et al., 1990, 1993*b*). The 4, 2, and 1 stepping algorithm employs features of the method of limits and other features of a tracking paradigm, and employs null stimuli to ensure that the subject is not supplying affirmative answers when no external stimuli are given. One begins at an intermediate magnitude of stimulus intensity and increases or decreases by 4 steps, 2 steps, and 1 step (depending on whether the stimulus was felt or not felt). To estimate threshold, the values of the turnarounds are averaged (at steps stimuli were felt or not felt) where single stepping was employed. Of the 25 such stimulus events used, five are randomly distributed null stimuli, although no more than two can occur consecutively. In addition, when the subject correctly responds to the first stimulus given, that stimulus level is repeated to ensure two consecutive correct responses before further changes take place. Threshold is defined as the mean of the observed turnaround levels, but only those where single-stepping was employed. In this as with the other forms of testing, a *supersensitive site* is defined as the subject correctly identifying stimuli of the lowest intensity during the administration of three stimuli at this same level. In the same manner, *insensitive sites* are those where the subject did not identify three separately administered stimuli of the highest magnitude.

Because this type of stimulation appears to predominantly activate deeply situated Pacinian corpuscles, only one area of stimulation is used at each site tested. [CASE III used a 3 × 3 grid (a total of 9 points), which isn't necessary because the receptive field of Pacinian corpuscles is large and does not have a sharp, but rather graded, slope]. Finally, as a measure of large fiber mechanoreceptor sensory function, VDT agree well with those obtained by TPT and serves as an adequate substitute (Dyck et al., 1993*a*).

Touch Pressure Threshold (TPT) CASE III Method

A tracking method (Dyck et al., 1978, 1984) is used to administer stimuli whose intensity magnitudes consist of 21 levels based on JNDs. A forced-choice response paradigm is used and usually 35–40 pairs of stimuli events are needed to determine threshold (taken as the 75% correct detection level) at each point. A total of nine points of stimulation at each testing site is performed in a 3 × 3 grid with an interpoint distance of 1 mm. A separate threshold is determined for each point as well as the mean for all nine sites, and the number of sensitive points at any specific site is also determined. Test results are reported as the mean threshold for all sites as well as the number of sensitive sites (e.g., 8/9 indicates 8 sensitive sites or the letter A may be substituted, 7/9 indicates 7 sensitive sites or the letter B may be used, etc.).

Cold Threshold (CDT) CASE IV Method

For CDT, a tracking method employing a simple up–down technique is employed (Dyck et al., 1993*c*). Twenty-five levels of stimulus magnitude based on JNDs are used and level 25 (largest) consists of a temperature of 9°C held for 10 s. As in VDT, a 4, 2 and 1 stepping change of stimulus magnitude is used, and a yes–no response paradigm was found to be an efficient method of testing. A total of 20 stimulus events, including five random null events of which no more than two can occur consecutively, are administered. All stimulation events begin from a steady-state temperature of 32°C (although any temperature can be chosen, extremes require the reestablishment of normative percentiles). The threshold is determined as the mean of the observed turnaround levels, but only those levels where single stepping was employed.

A similar pattern of testing is also used for deter-

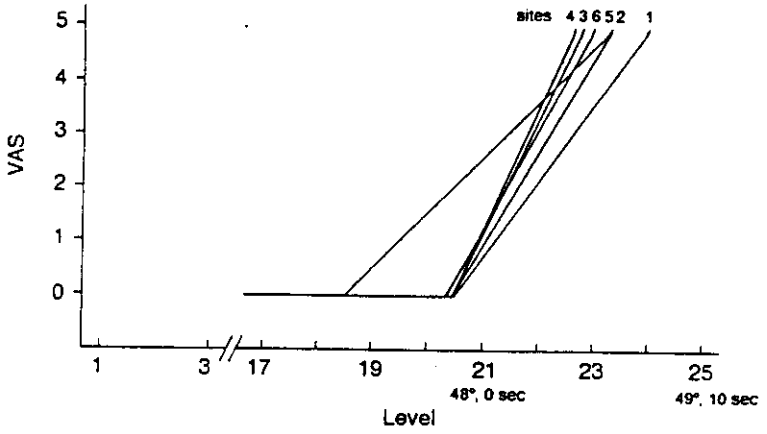

FIG. 7. Visual analogue scale (VAS) of the degree of pain (1, least and 10, most) from presentation of heat pulses of defined intensity to six anatomic regions (site 1, face; 2, volar forearm; 3, dorsal hand; 4, periumbilical; 5, lateral leg; 6, dorsal foot) in a 64-year-old healthy subject. Whereas the lowest degrees (VAS scale, 1) of discomfort was identified from stimuli at levels 18 to 20, scale 5 discomfort was identified at levels 23 to 24. In cutaneous hypersensitivity states, threshold for pain may be normal, lowered, or raised, and/or the rate of increase of the visual analogue scale lines might become steeper. (From: Dyck et al., 1993*c*. Reprinted with permission.)

mining warm thresholds. However, in evaluating normal control subjects it was found that at some sites there was a low density of such receptors, especially noticeable at the foot. In such cases, the first sensation evident was heat-pain and in view of this we preferentially look at CDT in the routine evaluation of thermoreceptor function.

Heat-Pain Threshold (HP VAS) CASE IV Method

A tracking method is employed to administer stimuli for HP VAS (Dyck et al., 1993*c*). A total of 25 levels of stimuli magnitude are available with the 25th level (largest) consisting of a temperature of 49°C that is maintained for 10 s. Levels 1 through 21 are based on JNDs, whereas 22–24 consist of a temperature of 48°C held for varying times. Testing is initiated at an intermediate nonpainful stimulus level (level 13) and null stimuli are administered at random, although usually no more than three before the subject detects a painful stimulus. All stimuli are administered from a baseline or skin temperature of 34°C. A modified yes–no response paradigm is used and consists of a VAS from 0 to 10. Zero corresponds to no stimulus or only the sensation of warm or hot, 1 is indicative of the "least" discomfort or pain and 10 is indicative of the most severe pain. Stimuli are initially given in increasing magnitudes by steps of two until a level of 20, or whenever a painful stimulus is first perceived, and thereafter in single steps until a VAS of 5 or greater is first reached or level 25 has been tested. The pain threshold is then defined as the midway point between a nonpainful (VAS = 0) and painful stimulus (VAS = 1) and referred to as VAS 0.5. Then, to serve as a midpoint in intensity of pain, a VAS of 5 is chosen and also serves as a way to terminate further increases in stimulus intensity and at a reasonable intermediate level of pain. Higher intensity stimuli or readministration of stimuli of this same magnitude are not well tolerated, and perception as well as grading may then be disturbed (Yarnitsky et al., 1992). With this restriction in regards to further increases in stimulation intensity in mind, additional stimuli at lower levels of magnitude are administered to allow the interpolation of stimulus points from threshold to superthreshold (taken or extrapolated to a VAS of 5) (Fig. 7).

A similar pattern of testing is also employed for cold pain thresholds. We have not explored CP VAS, but our initial trials seemed to indicate that thresholds might be more variable.

WHICH QST TEST SHOULD BE EMPLOYED?

For routine sensory testing, we feel that determining the VDT, CDT, and HP VAS provide an adequate spectrum of evaluations. However, the actual determination of which QST is needed in a particular circumstance is dependent on several points (Kahn, 1992): (a) the necessity for differentiating a deficit of small vs. large-diameter sensory fiber dysfunction, (b) evaluation of a polyneuropathy or a mononeuropathy, (c) screening test vs. longitudinal study, where evaluation of only a single modality may be adequate, (d) specific evaluation of small fiber function other than ANS, (e) evaluation of hypersensitivity phenomena (Verdugo and Ochoa, 1992; Ochoa and Yarnitsky, 1993).

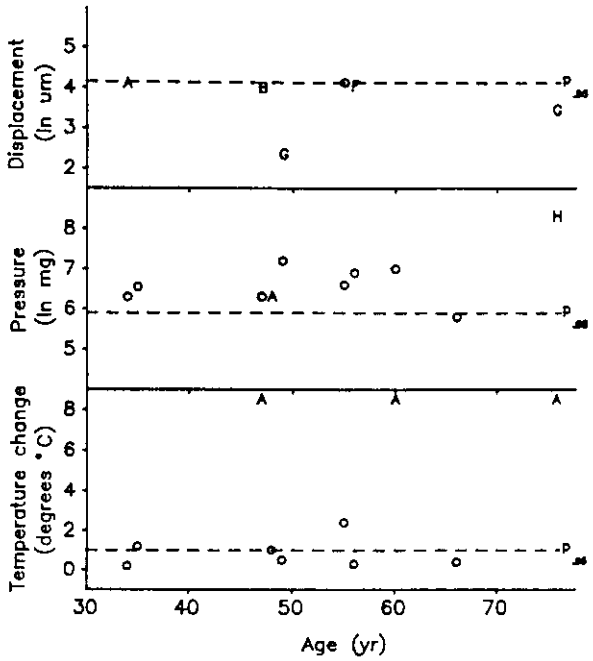

FIG. 8. Each symbol represents mean detection threshold of vibration (top), touch pressure (middle), and thermal-cooling (bottom) sensations in patients with trigeminal neuropathy and connective tissue disease. (From: Dyck et al., 1993*a*. Reprinted with permission.)

CUTANEOUS SENSORY THRESHOLDS IN DISEASE

In order to provide an adequate demonstration of QST techniques, its application to the following clinical conditions were selected (Dyck et al., 1993*a*).

Neuroses

Although test results are not given, it is best to remember that no specific pattern on QST clearly detects a nonorganic basis for a sensory complaint. Nonetheless, normal results should be expected, and inconsistent or unusual responses should always be suspect (Verdugo and Ochoa, 1992).

Trigeminal Neuropathy

Trigeminal sensory involvement can be found in various connective tissue diseases of which rheumatoid arthritis and Sjögren's syndrome are two familiar examples. Ten such patients underwent QST, but only six had TPT evaluation of the lip (Fig. 8). (The letters used for vibration and touch pressure indicate the number of insensitive points for a specific individual.) Our control data had previously indicated that any insensitive points detected at the lip is abnormal, and, because of this, VDT was abnormal for all individuals even though only one had a mean threshold at the 95th percentile. More obvious deficits are noted for TPT, and the least affected modality appeared to be CDT, where four patients showed a normal result; however, in three, no threshold was obtained. These test results clearly document this facial sensory abnormality.

Friedreich's Ataxia

The two individuals with Friedreich's ataxia that we studied demonstrated the progression of the deficit, as the older individual presented with clinically more advanced findings (Figs. 9 and 10). In both cases, no abnormalities were noted on the face; the number of sensitive points and thresholds for the younger subject were in the 30th and in the older, the 70th percentile.

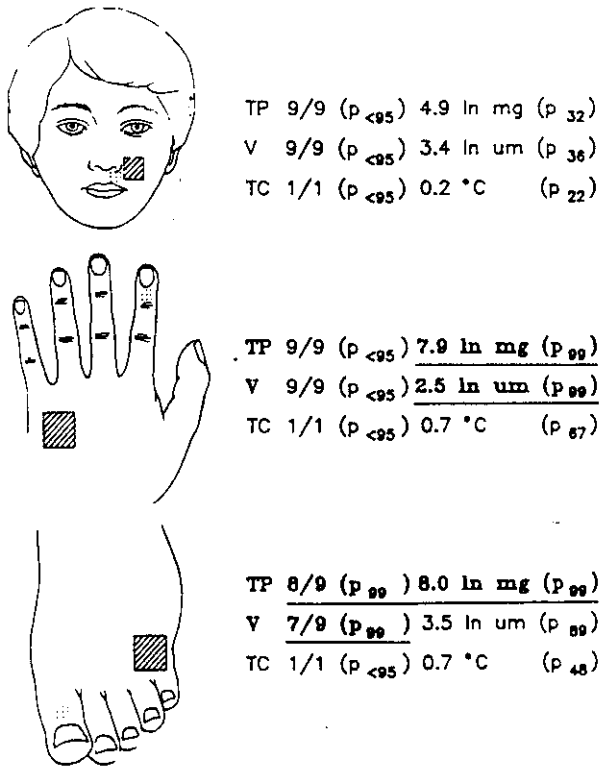

FIG. 9. The thresholds of sensation at the sites shown in a 15-year-old patient with Friedreich ataxia. On the face, thresholds fall within normal values (P_{95}). For the hand and foot, touch-pressure (TP) and vibration (V) sensations are abnormal but thermal-cooling (TC) sensation is normal. (From: Dyck et al., 1993*a*. Reprinted with permission.)

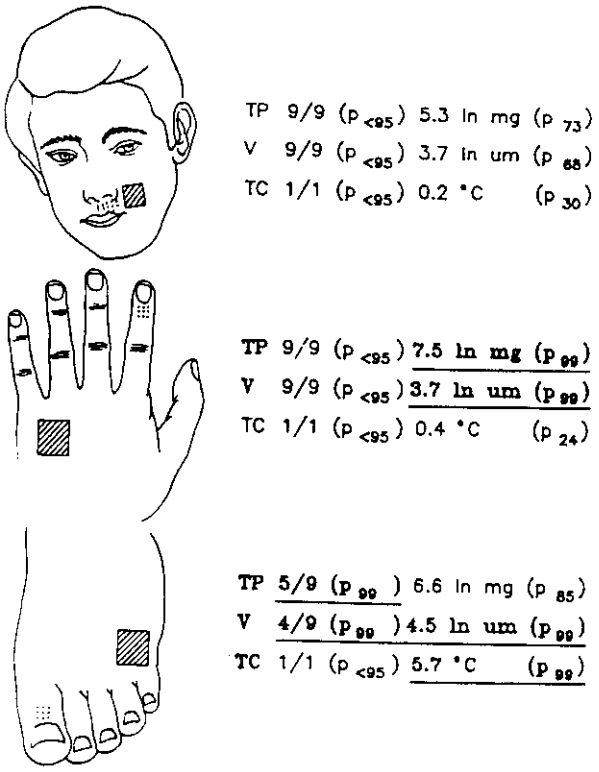

FIG. 10. Thresholds of sensation of a 30-year-old patient with advanced Friedreich ataxia. In addition to the abnormalities described in Fig. 9, this patient had an abnormality of thermal-cooling sensation of the foot. (From: Dyck et al., 1993*a*. Reprinted with permission.)

As expected, deficits of TPT and VDT were found in finger and toe, and in the older individual CDT were also abnormal at the foot. This preferential involvement of touch-pressure and vibratory sensations fits well with the selective involvement of Aα afferent neurons in this disorder.

Adult Onset Tangier Disease

Tangier disease is a disorder of plasma lipid transport characterized by a deficiency of plasma high-density lipoprotein (HDL) as well as tissue deposition of cholesterol esters, and is also associated with a neuropathy. Although the neuropathy may be manifested as one of several types, one characteristic pattern resembles the sensory loss found in syringomyelia. In Fig. 11, such a case is demonstrated where TPT, VDT, and CDT are abnormal for the hand, only VDT is abnormal at the face, and no abnormalities are noted on the foot.

Hereditary Motor-Sensory Neuropathy (HMSN) Type I

In Figs. 12 and 13 the results of testing a man and his daughter affected by HMSN I are shown. Facial sensory testing was normal and the hand demonstrated only an elevated VDT (CDT was absent in the father). In both, severe abnormalities predominantly involving TPT and VDT were noted in the feet, predominantly on the basis of insensitive points of stimulation. Similar patterns of abnormalities of QST have also been shown in the feet of patients with HMSN type I (Fig. 14). In these cases, a loss of sensitive points or elevated thresholds were often detected and abnormalities of CDT are less frequent.

Motor Neuron Disease

Despite its clinical limitation to the motor system, subclinical deficits of sensory function can also be detected in motor neuron disease. In 80 cases of sporadic motor neuron disease, QST was performed (Fig. 15).

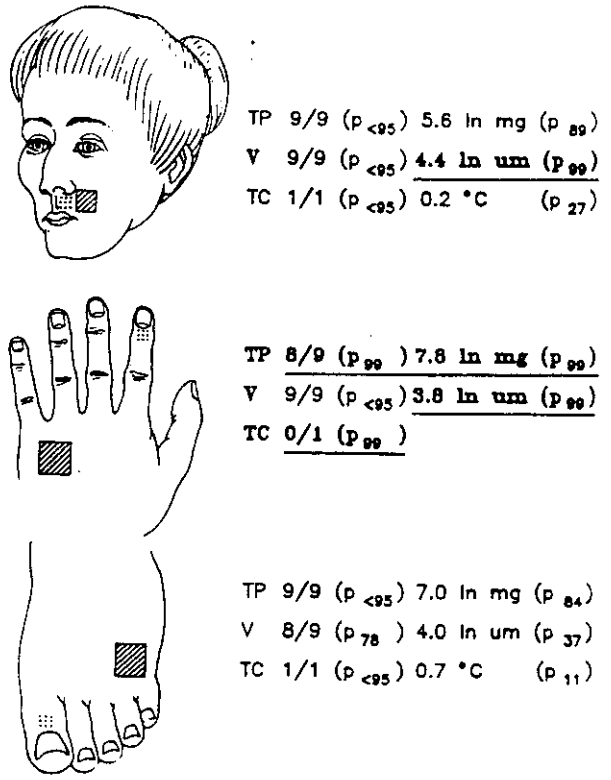

FIG. 11. The distinctive pattern of sensation abnormality encountered in adult-onset Tangier disease. (From: Dyck et al., 1993*a*. Reprinted with permission.)

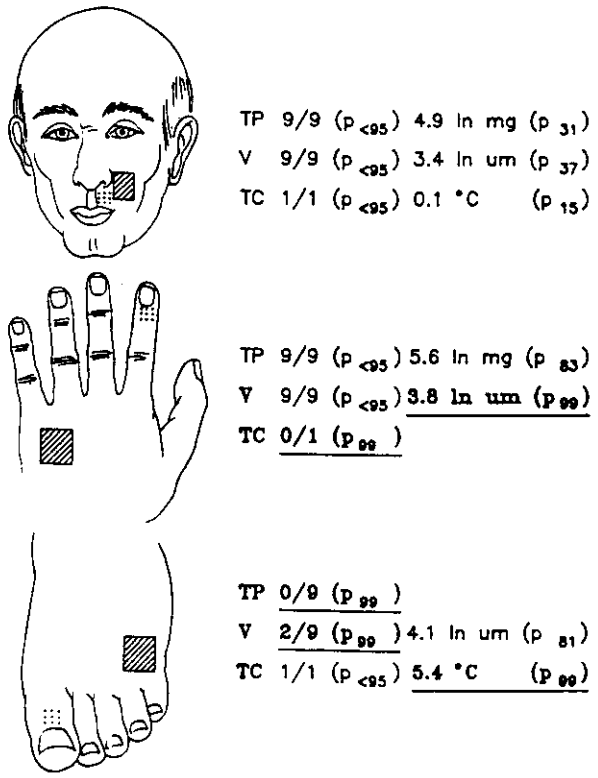

FIG. 12. Thresholds for sensation on face, hand, and foot of a 39-year-old man with HMSN type I. (From: Dyck et al., 1993*a*. Reprinted with permission.)

Of these individuals, 14 had an abnormality of VDT (elevated mean thresholds, insensitive points, or both), five of TPT, and 8 of CDT. Although TPT and CDT otherwise appear to have a normal distribution, VDT was more frequently elevated than in controls, suggesting the presence of a mild sensory abnormality for vibration.

Monitoring Drug Therapy

Multiple examples exist of various drug treatments being associated with the development of overt or subclinical nervous system involvement. Recently, Berger et al. (1993) have shown the usefulness of QST in a trial of 2',3'-dideoxycytidine (ddC) in HIV-infected patients with either AIDS-related complex or AIDS. In those individuals receiving either high or intermediate doses of ddC, QST abnormalities either preceded or coincided with the development of sensory symptoms that were indicative of a polyneuropathy (Fig. 16). Although further studies are planned, the capability of early detection of neuropathic side effects may allow their prevention by modification of drug dosage or perhaps substitution of a less toxic therapy.

Diabetic Polyneuropathy

It was in the area of diabetes that QST underwent one of its first widespread applications, helping to detect subclinical peripheral nerve involvement as well as assisting in its staging (Dyck et al., 1987, 1992; Sosenko et al., 1987). Its success resulted in its application to many other systemic disorders. Recently, for example, Lipton et al. (1991), identified the presence and type of sensory dysfunction that may exist in patients with cancer, providing further insight into the extent and variety of its remote effects.

FUTURE DIRECTIONS FOR QST

Although the future of QST is difficult to predict, certain developments are likely to occur. First, the study of pain using QST will continue. Already, such

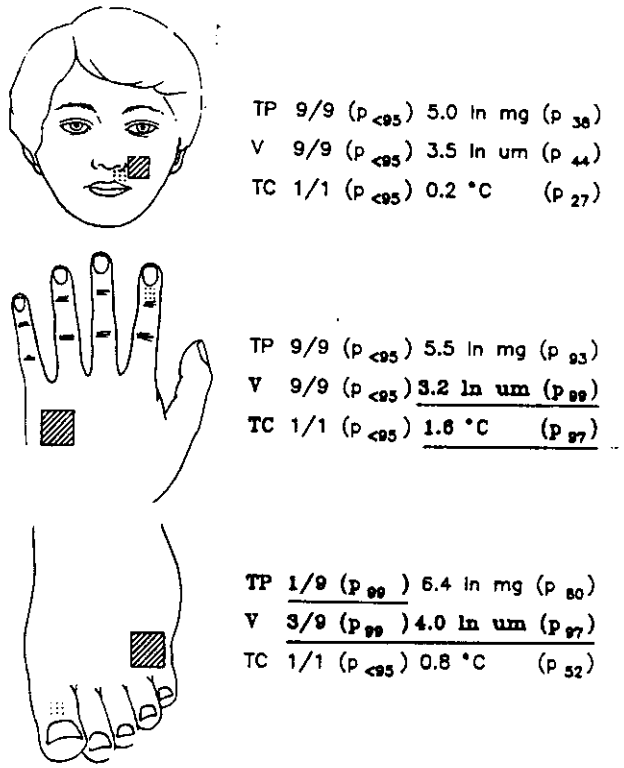

FIG. 13. Thresholds for sensation of face, hand, and foot of a 14-year-old girl, daughter of the man whose values are given in Fig. 12. (From: Dyck et al., 1993*a*. Reprinted with permission.)

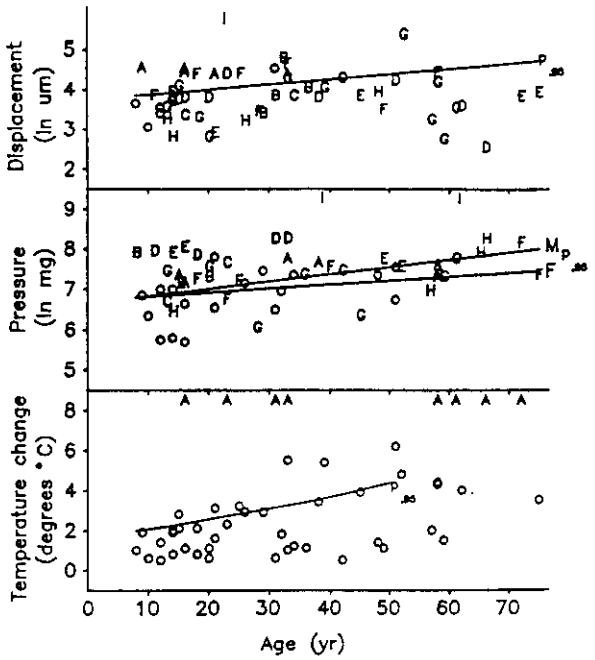

FIG. 14. Threshold values of the foot for vibration (top), touch-pressure (middle), and thermal-cooling (bottom) sensations of patients with HMSN type I. (From: Dyck et al., 1993*a*. Reprinted with permission.)

studies are being used to characterize and understand the mechanisms underlying hypersensitivity phenomena (Ochoa and Yarnitsky, 1993; Verdugo and Ochoa, 1992) and attempts have been made to identify specific syndromes (Ochoa and Yarnitsky, 1994). However, much remains to be learned about the physiology, pharmacology, and psychology of human pain experience, and standardized tests of induced pain may help, both in research and practice.

Second, QST probably will be used to follow sensory system injury and recovery. Longitudinal studies are needed of how sensation becomes altered with injury or disease and of how recovery occurs and what deficits remain. In addition to primary modalities of sensation, complex sensory perceptions such as directionality of movement, texture, or form need to be studied. Much more attention needs to be given to understanding how the cerebral association areas can adjust (plasticity) to nerve or tract injury. If the afferent pathway is either anatomically [i.e., nerve injury (Van Boven and Johnson, 1994)] or physiologically (i.e., Guillain–Barre syndrome) disrupted, the return of modality-specific function is then dependent on both the redevelopment of functional innervation densities, which are appropriate to the constraints imposed by the mechanics of the skin (Phillips and Johnson, 1981), and normal physiologic activity. The CNS's reliance on the faithful transmission of this sensory information is dramatically demonstrated in animals, as prominent changes of the cortical sensory map can also occur as it is actively remodeled based on the sensory input it receives (Merzenich and Jenkins, 1993). Although this plasticity reflects the CNS's dynamic responsiveness to its sensory input, it also reflects its dependence on the accurate portrayal of these stimuli by the afferent limb of the sensory system. Therefore, a disturbance in a particular afferent system/receptor could preferentially not affect one sensory perception, whereas another that requires further or more extensive processing by the CNS may be disturbed. Therefore, in those cases where nerve injury is followed by "faculty reinnervation," an individual's symptoms and degree of recovery may reflect not only peripheral nerve dysfunction, but the CNS's attempts to deal with "inaccurate" sensory information. Although these issues have been addressed in experimental animals, there are almost no studies in man, especially with age.

A possible third direction, already mentioned above, is the need for the development of QST meth-

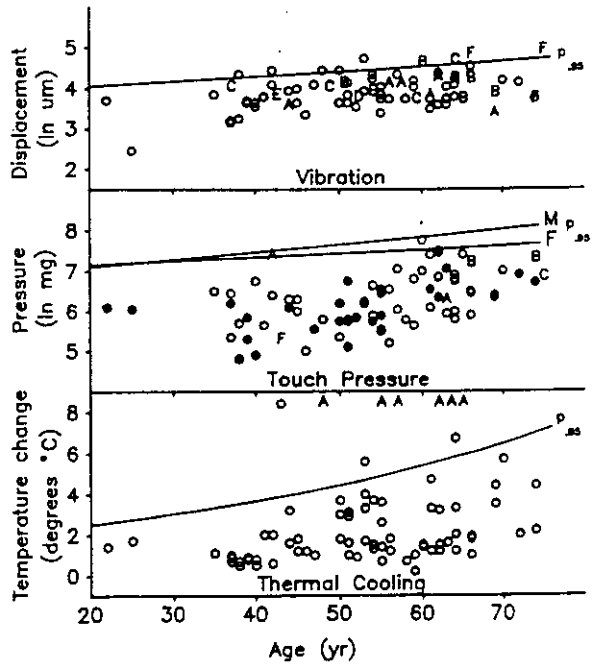

FIG. 15. Mean detection thresholds of vibration (top), touch-pressure (middle), and thermal-cooling (bottom) sensations in motor neuron disease. (From: Dyck et al., 1993*a*. Reprinted with permission.)

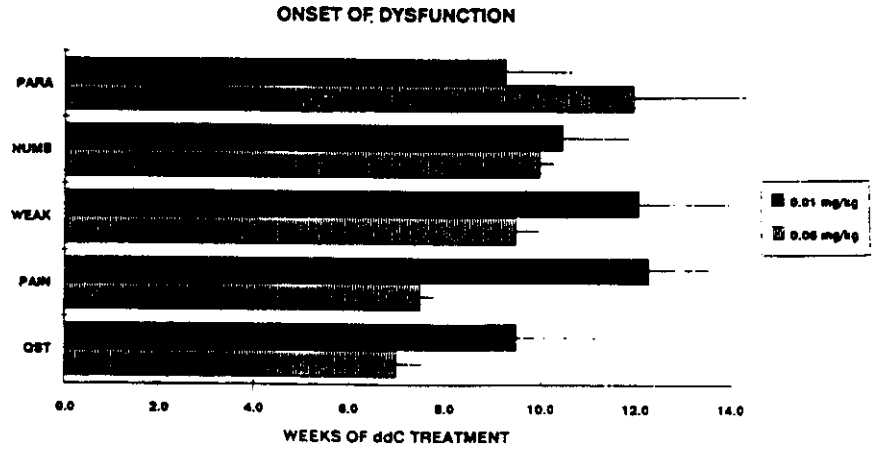

FIG. 16. A comparison of the timing of initial neuropathic manifestations in patients receiving high-dosage (0.06 mg/kg every 4 h) and intermediate-dosage (0.01 mg/kg every 4 h) ddC. QST, quantitative sensory testing; Numb, numbness; Para, paresthesias. (From: Berger et al., 1993. Reprinted with permission.)

ods assessing spatial and pattern recognition. Already there is research on recognition of directionality of movement and orientation of grating ridges. In conjunction with information supplied by microneurography, cortical recordings, and perhaps other techniques, it will be possible to elucidate mechanisms underlying sensation in health and disturbed sensation in disease. When such a multimodality approach to sensory perception was applied to the hand, it demonstrated that each group of mechanoreceptors supplied specific sensory information (Johnson and Hsiao, 1992; Hsiao et al., 1993). The slowly adapting type I (SA I) group were found to be crucial to the routine interpretation of both texture and form perception. The Pacinian corpuscle afferents played a role in the perception of forces or movements that occurred through other objects (i.e., tools). Finally, the rapidly adapting receptor (RA) system showed itself to be best suited for the detection of movement that occurred between the skin and a surface (i.e., slipping); or if surface variation was too small to activate the SA I system, it could also determine tactile or texture characteristics. The contributions of all these different mechanoreceptor afferent systems resulted in the realization of these complex perceptions. It would certainly appear that part of the future application of QST and psychometric techniques includes their use as a method of further analyzing these and other complex sensory perceptions.

The fourth major development that we anticipate is the expansion of standardized QST for use in epidemiologic and controlled clinical trials. QST provides meaningful information regarding sensory loss that is directly related to unsteadiness in walking, plantar ulcers, and Charcot joints. In malnutrition, infection (leprosy and HIV infection), intoxication (industrial or medicinal), endocrine diseases (diabetes mellitus), and mechanical injury sensory loss and its complications are primary events that need to be followed. QST is the best approach to follow these events. In order to do so, all events of testing and estimating threshold must be ideal and standardized. In this review, we have emphasized the characteristics of systems and procedures that are needed for quality QST.

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