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Testing methods and inferences about anatomic distribution of receptors

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Article abstract—We recently found that vibratory detection threshold is greatly influenced by the algorithm of testing. Here, we study the influence of stimulus characteristics and algorithm of testing and estimating threshold on cool (CDT), warm (WDT), and heat-pain (HPDT) detection thresholds. We show that continuously decreasing (for CDT) or increasing (for WDT) thermode temperature to the point at which cooling or warming is perceived and signaled by depressing a response key ("appearance" threshold) overestimates threshold with rapid rates of thermal change. The mean of the appearance and disappearance thresholds also does not perform well for insensitive sites and patients. Pyramidal (or flat-topped pyramidal) stimuli ranging in magnitude, in 25 steps, from near skin temperature to 9 °C for 10 seconds (for CDT), from near skin temperature to 45 °C for 10 seconds (for WDT), and from near skin temperature to 49 °C for 10 seconds (for HPDT) provide ideal stimuli for use in several algorithms of testing and estimating threshold. Near threshold, only the initial direction of thermal change from skin temperature is perceived, and not its return to baseline. Use of steps of stimulus intensity allows the subject or patient to take the needed time to decide whether the stimulus was felt or not (in 4, 2, and 1 stepping algorithms), or whether it occurred in stimulus interval 1 or 2 (in two-alternative forced-choice testing). Thermal thresholds were generally significantly lower with a large (10 cm^2) than with a small (2.7 cm^2) thermode. A topographic difference of CDT, WDT, and HPDT was demonstrated, with the face and volar arms having the lowest threshold and legs and feet having the highest threshold. In healthy subjects, warm threshold varied most among different sites, followed by uncomfortably hot, and last by heat-pain threshold. Particularly in older subjects, CDT could be determined on the dorsum of the foot whereas WDT sometimes could not, the first sensation experienced being heat-pain. A low density of warm receptors, especially in the foot and leg of old people, would explain these latter findings.

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Quantitative sensory testing (QST) is used to estimate differences in sensory detection threshold with anatomic site, age, sex, and physiologic condition.[1-3] Variability of threshold might be explained by differences in thickness of tissue overlying receptors, spatial distribution of receptors, physiologic properties of receptors, impulse transmission, or central processing.[4] Detection thresholds are also used to detect and characterize the degree and pattern of sensory loss typical of different neurologic diseases and are therefore of value in medical practice.[1-3,5] Changes in threshold or in patterns of abnormality may be used as end points of severity of neuropathy in controlled clinical and epidemiologic trials.[6,7] Increasingly, QST is being used to test for and characterize such cutaneous hypersensitivity phenomena as hyperesthesia, hyperalgesia, and allodynia (pain from mechanical stimuli not normally perceived as painful).[3]

We have recently shown[8] that vibratory detection threshold (VDT) may be influenced, sometimes to a major degree, by the stimulus characteristics employed and by the algorithm of testing and estimating threshold. To illustrate: using sinusoidal oscillations at 125 cps and increasing the magnitude of displacement linearly with time to the point at which the appearance threshold is signaled by the subject's depressing a response key, thresholds are much higher when steep ramps are employed than when very slow ramps or discrete steps of

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stimulus intensity and a forced-choice algorithm are used. This overestimate of threshold with steep ramps can be attributed to a reaction time that is too slow, considering the rapid change in stimulus amplitude with time. In this report, we assess the influence of stimulus characteristics, the algorithms of testing, and estimation of thresholds for coolness (CDT), warmth (WDT), and heat-pain (HPDT). The differences in thresholds demonstrated here appear to be due to differences in methods of testing and estimating threshold and in the anatomic distribution of certain receptors.

Methods. *Computer-Assisted Sensory Examination (CASE IV) system.* The system was designed to estimate VDT as a test of large-fiber dysfunction, and CDT, WDT, and HPDT as tests of small-fiber dysfunction. The system allows the user considerable flexibility in specifying stimulus waveforms, ramp rates, and algorithms of testing and estimating threshold.

The system consists of (1) a personal computer with hard and floppy disks, and a keyboard for entry of biographic data, selection of stimulus conditions and testing options, administration of the algorithm of testing, estimation of threshold, comparison of threshold to that of control values, and printout of test results; (2) a video screen for display of program instructions, testing options, error messages, and results; (3) an electronic controller (containing power supplies, fail-safe devices, microprocessors, and circuitry) to provide different stimulus waveforms; (4) a printer (for biographic information and results); (5) a visual cueing device (to display the "get ready" yellow light, "test in progress" green light, or number 1 or 2); (6) a response key to indicate whether a stimulus was felt ("yes") or not felt ("no"), used in several algorithms of testing, appearance, or disappearance thresholds in Békésy testing, or "1" or "2" in forced-choice testing; and (7) a vibratory transducer assembly and a thermode assembly (figure 1). The software for operation of the system was written in C language.

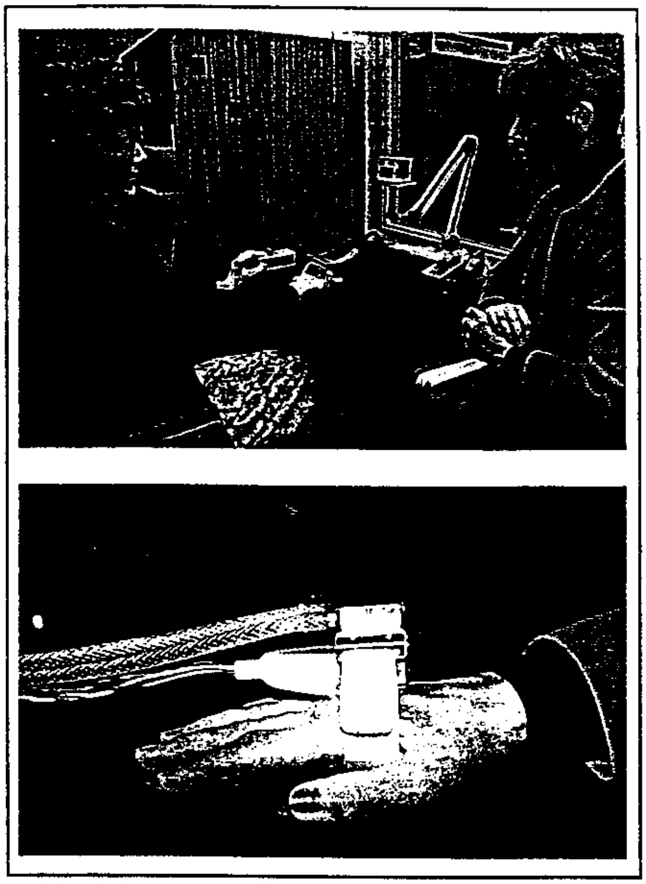

Figure 1. Use of CASE IV to assess cool (CDT), warm (WDT), or heat-pain (HPDT) detection threshold on the dorsal surface of the hand. (Upper panel) The subject is sitting on a dental chair, which can be positioned so that the hand (or foot) rests comfortably on the testing table. The thermode assembly is firmly strapped in place; the right hand of the subject activates the number 1 or 2 response key to indicate whether the sensation studied—eg, a cooling pulse—occurs during the display of "1" or "2" on the visual cueing device. The visual cueing 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 biographic 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. (Lower panel) A close-up view of the thermode assembly. The umbilical cord to the thermode has two components, electrical cords (lower) and circulating fluid hoses.

Thermodes. Two thermodes, with surface areas of 10 cm^2 and 2.9 cm^2, were fabricated, calibrated, and compared. The 2.9-cm^2 thermode was used only for comparison of altered threshold due to thermode surface areas. For all other studies, the 10-cm^2 thermode was used (figure 1).

The thermodes used here are modifications of our previously described thermode. A thermode consists of two thermoelectric units (TEUs), an intervening aluminum block, and an overlying water chamber through which water circulates. One TEU (TEU 1) rests on the skin, while the second (TEU 2) maintains the aluminum block at a constant (skin) temperature. The desired waveform (eg, of cooling) is given by providing a variable current to TEU 1. By reversing the direction of the current to TEU 1, a warming waveform is given. The thermocouples embedded in ceramic in TEU 1, when not used to heat or cool, are used to measure the temperature of TEU 1. Initially, the temperature of the skin to be tested is measured using an infrared thermometer. TEU 1 and 2 are brought to this temperature. In practice, this does not always provide a sufficiently close approximation of skin temperature; the thermode might feel slightly cold or warm. To bring the thermode precisely to skin temperature, a special subroutine is used. With the current to TEU 1 turned off (allowing the temperature to equilibrate between TEU 1 and skin), the current to TEU 2 is continuously adjusted, over approximately 2 minutes, to bring it to the same temperature as TEU 1. In practice, this appears to provide a TEU 1 temperature that does not feel cold or warm. Thereafter, the aluminum block is maintained at this steady-state skin temperature throughout the test by providing current to TEU 2 in whatever direction is needed. Current flow to TEU 1 is provided by computer instruction and hardware components to create the stimulus waveform desired.

Thermodes were calibrated periodically to meet the following performance specifications during static and dynamic events of thermal testing. When a static temperature between 10 °C and 50 °C is called for, the temperature at TEU 1 should be within ±0.5° of true temperature. At a static temperature, control of temperature in TEU 1 over 1 minute should be within ±0.05° of the desired. Dynamic events calibrated are thermal ramps (linear or exponential) and delta temperatures from baseline. Thermal ramps should essentially reproduce the rate of change called for except at the beginning or end of the ramp, where some variance from the desired is accepted. For pyramidal thermal pulses from baseline temperature, the ramp, should essentially reproduce the expected. The delta temperatures from baseline of the 25 steps of stimulus (cooling or warming) intensity provided by pyramidal thermal waveforms should be within ±0.05° for Δ° <1°; within ±0.10° for Δ° ≥1° but <2°; within ±0.15° for Δ° ≥2 but <5°; and ±0.25° for Δ° ≥5° and <20°. To test whether the system met these specifications, we first calibrated the response of a copper-constantan thermocouple (0.13-mm wire) against a high-quality mercury thermometer in a water bath for temperatures between 10° and 50 °C (accuracy, ±0.5°). The thermocouple was then taped to the surface of the thermode and used to record temperatures at static step levels or dynamically during the presentation of typical step waveforms. To provide a realistic but standard model of the thermode in situ on the hand or foot of a patient, we used a standard thermal load comparable to human flesh. Strips of pure copper, 0.5-mm thick, were placed over the stimulating surface of the thermode not occupied by the thermocouple taped to the surface of TEU 1. The static or dynamic ramps or step levels were displayed on an oscilloscope. To produce pyramidal waveforms, it was necessary to provide a constant current that determined the slope of the ramp and an initial and final (in the reverse direction) amount of current to overcome capacitance. The amount of current varied depending on the waveforms to be used.

Waveforms and algorithms of testing. Multiple linear ramps of temperature change to appearance threshold with random null stimuli (algorithm 1):

Linear ramps, continuously decreasing (for assessing CDT) or continuously increasing (for assessing WDT) temperature change from baseline to the point at which the subject indicated, by depressing a response key, that the stimulus is felt, are used. After the response key is depressed, the temperature of the thermode is returned to baseline. In a typical test, eight or 12 thermal ramps are given. After the first stimulus, four null stimuli (no ramp during the stimulus interval) are randomly interspersed among the stimulus intervals. The threshold is the mean of the eight or 12 appearance thresholds. Depression of the response key during display of more than one null stimulus event invalidates the test. If this happens, the subject is reinstructed and the test is rerun. In practice, a "get ready" yellow light is shown, followed by the display of the number "1" and by the concomitant presentation of the stimulus or null stimulus. The maximum thermal change coincides with the midpoint of the stimulus event. The thermal ramps tested were 0.025°/sec, 0.05°/sec, 0.10°/sec, 0.25°/sec, 0.5°/sec, 1°/sec, and 3°/sec.

Multiple exponential ramps of temperature change to appearance thresholds with random null stimuli (algorithm 2):

This algorithm of testing is exactly like the one described in the preceding section except that instead of linear ramps, exponential ramps are used (eg, at one-half just noticeable difference [JND]/sec [as determined in previous experiments], 1 JND/sec, or 2 JND/sec).

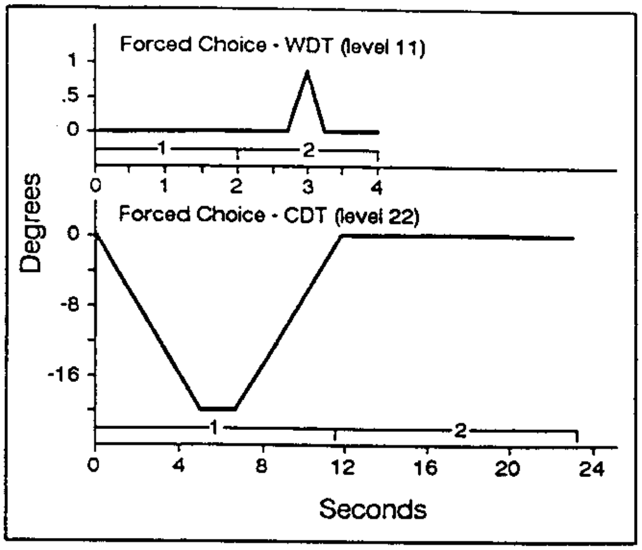

Figure 2. Shown are thermal pulses used in forced-choice; 4, 2, and 1 stepping; and operator-chosen stepping algorithms of testing described in text. In the upper frame, we show a pyramidal thermal pulse with initial warming and then cooling at 4 °C/sec. We refer to this as a "warming" stimulus because it is the initial direction of temperature change from skin temperature (shown as 0), which is the effective stimulus. Note that the apex of the pulse is positioned at the midpoint of the second testing interval. In forced-choice testing, two stimulus intervals are employed (shown here), but in other algorithms, single-stimulus intervals are used. In assessing cool or warm detection threshold by forced choice (or another algorithm of testing), 25 magnitudes of stimulus intensities (levels) are available for testing. In the lower frame, we show a cooling flat-topped pyramidal stimulus at level 23 in stimulus period 1.

Multiple exponential ramps with random null stimuli and mean of appearance and disappearance thresholds (Békésy) (algorithm 3):

This algorithm employs an exponential decrease (from skin temperature) to the point at which cooling is felt (appearance) and increase of temperature to the point at which it is not felt (disappearance) or skin temperature is reached (whichever comes first). For WDT, there is an initial increase in temperature to the point at which warming is felt, then a decrease to the point at which warming disappears or skin temperature is reached, whichever comes first. As in the first and second algorithms (described above), null stimuli are interspersed at random among stimuli. During null stimuli, the temperature is held at skin temperature for the duration of the stimulus event. The mean of the means of the appearance and disappearance thresholds is then calculated.

4, 2, and 1 stepping algorithm with null stimuli (algorithm 4):

This algorithm and the forced-choice algorithm described below use 25 discrete steps of stimulus intensity over a broad range of stimulus magnitudes. The waveforms are pyramidal pulses of cooling or warming from step 1 (smallest) to step 25 (largest). For cool pulses, the temperature of the thermode decreases from skin temperature to a predetermined lower level, then returns to skin temperature. For a warm pulse, the thermode temperature increases, then decreases (figure 2). For steps 22 to 25, flat-topped pyramidal stimuli are used. For levels 22 to

24, the maximum temperature achieved is 10 °C (for CDT) and 48 °C (for HPDT), which is held for 1.5 seconds (step 22), 5 seconds (step 23), and 10 seconds (step 24). For level 25, the maximum temperature achieved is 9 °C (for CDT) and 49 °C (for HPDT), and these are maintained for 10 seconds (figure 2). For WDT, the maximum temperature is 45 °C (or another temperature set by the investigator), and this is maintained for 10 seconds (step 25). The rate of the initial ramps of the pyramidal or flat-topped pyramidal stimuli is specified from the keyboard. The ramps returning thermode temperature to baseline are the same as the ramps used to reach maximum temperatures.

The specific rules of the 4, 2, and 1 stepping algorithm with null stimuli are given in the accompanying article.[9]

The two-alternative forced-choice algorithm at 25 discrete levels (algorithm 5):

Twenty-five discrete steps of pyramidal (or flat-topped pyramidal) (steps 22 to 25) cooling (for CDT) or warming (for WDT or HPDT) stimuli are used. The operator specifies the ramp rate to be used. In our studies, 0.5°/sec, 1.5°/sec, and 4°/sec were tested.

The algorithm of testing and estimating threshold using O'Brien's specific rules, as based on the up-and-down transformed rule of Whetherhill, are described elsewhere.[1,10] The choice of the specific rules is based on extensive computer simulations to find the most efficient and accurate rules of testing.

In two-alternative forced-choice testing, pairs of stimulus events are signaled by the visual display of the number "1," then of the number "2." Only one of the stimulus events contains a pyramidal (or flat-topped pyramidal) thermal stimulus, whereas no thermal stimulus is given in the other stimulus event, the thermode remaining at skin temperature. The duration of both stimulus events is the same at a given step level. The thermode rests on the skin with a constant load, and no clue is given to identify the interval containing the stimulus. The order of stimulus events is assigned by chance from a bank of random numbers.

Operator-chosen stepping algorithm to assess warm through painfully hot thresholds (algorithm 6):

This is a modification of the 4, 2, and 1 stepping algorithm using pyramidal and flat-topped pyramidal stimuli and 25 steps of stimulus intensity to 49 °C. This algorithm is used to estimate "warm," "hot," "uncomfortably hot," and "painfully hot" thresholds. In a separate test, this same algorithm is also used to estimate the heat-pain threshold and the increase in the subjective estimate of pain magnitude when suprathreshold heat-pain stimuli are given.

In the first test, a sign with the words "not felt (0)," "warm (1)," "hot (2)," "uncomfortably hot (3)," and "painfully hot (4)" is placed before the subject. After instruction and after the "get ready" yellow light, one of the stimuli is provided during the display of the number "1." The subject chooses from among the five possible responses. The objective is to test stimulus step levels just below and to the point of eliciting each of the four defined responses. The examiner begins at low levels, trying to identify the lowest step level felt as warm, hot, uncomfortably hot, or painfully hot. Painfully hot stimuli are not repeated because they are painful and because an aftersensation is induced that may affect threshold.

For the second test, the same step stimuli and algorithm of testing are used to assess pain intensity as judged by comparison with a visual analogue scale of 1 (least) through 10 (worst).

Normal subjects. These were randomly selected volunteers from Rochester, MN, who were recruited as controls for the Rochester Diabetic Neuropathy Study (RDNS). All these patients were screened for neurologic and psychiatric disease and for diseases that predispose to neuropathy, and all had a neurologic evaluation, nerve conduction test, quantitative sensory examination, and quantitative autonomic examination.

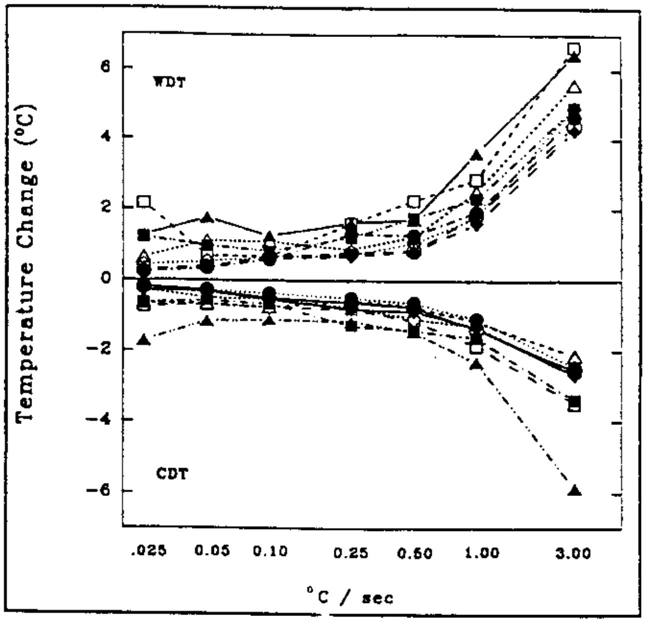

Figure 3. Appearance warm (WDT) and cool (CDT) detection thresholds (algorithm 1; described in text) on the dorsum of the hand in eight healthy subjects, using different ramps of temperature change. As compared with forced-choice thresholds, appearance thresholds below 1°/sec performed reasonably well, but rates of 1°/sec and 3°/sec overestimated threshold, as described in more detail in text.

Patients. These were patients with neuropathy referred to one of us (P.J.D.) or diabetic patients with polyneuropathy in the RDNS.

Results. *Rate of thermal change and cool or warm appearance threshold (or mean of appearance and disappearance thresholds):*

Cool and warm appearance thresholds were estimated using algorithm 1 and different rates of thermal change on the dorsum of the hand in eight healthy subjects. Low rates of thermal change produced appearance thresholds similar to each other and to that obtained from forced-choice testing. A ramp rate of 1°/sec, and especially of 3°/sec, overestimated threshold (figure 3).

Exponentially increasing steep thermal ramps—eg, 2 JND/sec (algorithm 2)—also greatly overestimated both cool and warm appearance thresholds (data on request).

Use of the mean of the appearance and disappearance thresholds, using exponentially increasing thermal stimuli and null stimuli (algorithm 3), also did not perform satisfactorily in estimating cool or warm thresholds. Subjects or patients whose threshold values were near the upper range of available stimulus magnitudes frequently did not activate the response key in time, so that

Table 1. Mean cool and warm or heat-pain detection thresholds (forced-choice algorithms) from different thermode surface areas[Δ] and ramp rates tested on hand and foot (n = 7)

	Cool (CDT) detection threshold											
	Hand						Foot					
	4°/sec		1.5°/sec		0.5°/sec		4°/sec		1.5°/sec		0.5°/sec	
	[Δ]L	[Δ]S	L	S	L	S	L	S	L	S	L	S
Mean (level)*	4.5	4.4	3.2	2.9	1.9	2.9	5.6	4.0	5.1	3.6	3.0	3.7
SD	2.4	1.1	2.0	2.2	2.5	5.2	3.1	3.3	2.5	3.2	3.2	6.4
Significance	NS		NS		NS		NS		NS		NS	
Mean (Δ°C)†	0.22	0.19	0.15	0.15	0.12	0.53	0.32	0.22	0.26	0.22	0.19	0.69
SD	0.13	0.10	0.09	0.12	0.07	1.16	0.22	0.18	0.13	0.29	0.17	1.14
Significance	NS		NS		NS		NS		NS		NS	

	Warm (WDT) or heat-pain (HPDT) detection threshold											
	Hand						Foot					
	4°/sec		1.5°/sec		0.5°/sec		4°/sec		1.5°/sec		0.5°/sec	
	L	S	L	S	L	S	L	S	L	S	L	S
Mean (level)*	5.8	9.3	6.9	6.9	6.7	7.1	8.7	14.1	9.7	13.6	8.8	14.8
SD	3.1	2.7	3.3	5.4	3.3	7.2	6.6	4.3	6.0	6.4	5.0	3.9
Significance	$p = 0.005$		NS		NS		$p = 0.04$		$p = 0.06$		$p = 0.006$	
Mean (Δ°C)†	0.26	0.69	0.37	0.68	0.34	1.16	4.2	2.1	2.1	5.0	1.5	4.6
SD	0.22	0.50	0.24	0.85	0.20	1.42	4.21	4.13	4.13	5.22	2.74	4.43
Significance	$p = 0.012$		NS		NS		NS		NS		$p = 0.012$	

* Level = the step of stimulus magnitudes from 1 (lowest) to 25 (greatest).

† Δ°C = difference in °C from skin temperature thermode surface area; L = large (10 cm^2) and S = small (2.9 cm^2) thermode.

appearance thresholds remained undetermined. In such patients, it is not possible to get the mean of the appearance and disappearance thresholds.

Suitability of pyramidal waveforms for evaluation of CDT, WDT, and HPDT. Pyramidal waveforms (thermal pulses) were studied to test whether only the initial direction of thermal change from skin temperature was felt or whether the return to skin temperature was also felt. Initial studies on our own hands and feet using stimuli near threshold indicated that it was the initial thermal change that was felt. A pyramidal cooling stimulus felt like a "puff of cold air," "a cool wetness," "a trickle or drop of cool water," or simply as cooling. When cool or warm pulse stimuli greatly in excess of threshold were used, we sometimes felt not only the initial coolness or warmth (or heat or heat-pain), but also an opposite sensation of warmth or coolness after the stimulus event. Nine naive subjects were also tested on the foot. They were told that a stimulus would be given that would not be painful. From just-suprathreshold cool stimuli, nine of 12 subjects reported the stimulus as cool or cold, and none of these reported initial cooling, then warming. Three of the 12 reported the cool stimulus as warm or hot (paradoxical warm), but it was in response to the cooling phase of the stimulus. From suprathreshold warm stimuli, all the subjects reported the stimulus as warm or hot, but none reported it as warm, then cold. In separate experiments giving suprathreshold stimuli, we asked naive subjects to report the "sensations" continuously during the presentation of a stimulus waveform. Using a cooling pyramidal waveform, a typical report was "cool," "colder" and "cold," and then "it is disappearing." They did not report "cool," "cold," "colder," "warm," and "hot." It was clear that the subjects were responding to the initial thermal change from skin temperature, not the secondary thermal return to skin temperature.

Thermode surface area and ramp rates on CDT, WDT, or HPDT (pyramidal stimuli and forced-choice algorithm). Eight healthy subjects had assessment of CDT and WDT (or heat nociception detection threshold [HPDT]; these were arbitrarily identified as WDT when the final temperature did not exceed 40 °C and as HPDT when the temperature exceeded 40 °C). Both dorsal hand and dorsal foot were studied using large (10 cm^2) and small (2.9 cm^2) thermodes and ramp rates of 4°/sec, 1.5°/sec, and 0.5°/sec. In this small series of subjects, the size of the thermode was not found to significantly affect CDT for the two sites and three ramp rates tested (table 1). By contrast, for WDT (or HPDT), in four of six comparisons (two sites and three ramp rates), threshold was significantly lower with use of the large thermode. For each comparison of thermode size and rate of thermal change, and for cooling and warming (or heat nociception), the threshold was higher in the foot than in the hand.

Warm, hot, uncomfortably hot, and painfully hot thresholds (eight healthy subjects, 10 anatomic sites, and the operator-chosen stepping algorithm). Even for this small number of subjects, differences were found among sites (table 2) with the face having the lowest threshold, followed by volar forearm, then by other sites, and finally by leg and foot sites. The differences among sites for a healthy subject aged 64 years are shown in figure 4. For the foot, warmth was not felt. The first stimulus experienced at this site was pain.

Table 2. The mean temperatures[*] for warm, hot, uncomfortably hot, and painfully hot detection thresholds in various regions of the body (operator-chosen stepping algorithm, eight healthy subjects)

	Site[*]										Mean of means
	1	2	3	4	5	6	7	8	9	10	
					Warm						
Mean	33.7	34.6	34.3	33.8	32.5	32.7	32.9	33.6	33.8	33.3	33.5
SD	1.9	2.9	2.5	1.6	1.1	1.4	1.1	1.4	1.0	1.3	0.71
					Hot						
Mean	39.0	40.7	40.0	38.1	36.5	37.0	36.4	39.0	37.6	35.0	37.8
SD	5.0	4.2	0.8	2.0	2.8	3.0	2.6	2.0	3.2	1.6	1.74
					Uncomfortably hot						
Mean	43.7	44.3	45.6	42.6	41.1	43.1	40.0	41.9	41.7	39.0	42.3
SD	3.6	3.0	1.9	3.4	4.2	3.3	4.4	4.1	4.4	3.0	1.99
					Painfully hot						
Mean	44.7	46.9	46.1	46.0	45.5	46.8	43.5	45.3	44.9	43.0	45.3
SD	3.6	1.1	2.7	3.2	2.9	2.1	4.4	4.0	3.7	4.5	1.30

[*] 1 = dorsal foot; 2 = sole of foot; 3 = lateral leg; 4 = medial leg; 5 = anterior thigh; 6 = dorsal hand; 7 = volar forearm; 8 = lateral shoulder; 9 = periumbilical; and 10 = maxillary face.

The means of mean values are significantly different ($p < 0.001$) between warm, hot, uncomfortably hot, and painfully hot.

Table 3. Warm and painfully hot thresholds at different anatomic sites (operator-chosen algorithm, eight healthy subjects)

	Dorsum, foot	Sole foot	L-5 leg	L-4 leg	Thigh	Dorsum, hand	Volar arm	Deltoid	Periumbilical	Face
					Warm					
Mean (levels)	15.3	14.6	14.8	14.3	11.4	10.7	9.3	13.2	12.4	5.4
SD	1.7	3.3	3.0	1.3	1.7	1.3	3.0	2.4	2.3	2.0
Dorsum, foot	—	NS	NS	NS	*0.006*[*]	*<0.000*	*0.010*	**0.083**[†]	*0.003*	*0.001*
Sole foot	—	—	NS	NS	*0.043*	*0.031*	*0.007*	NS	NS	*0.000*
L-5 leg	—	—	—	NS	*0.031*	*0.041*	*0.003*	NS	**0.086**	*0.000*
L-4 leg	—	—	—	—	*0.003*	*0.001*	*0.010*	NS	NS	*0.000*
Thigh	—	—	—	—	—	NS	NS	NS	NS	*0.001*
Dorsum, hand	—	—	—	—	—	—	NS	**0.075**	**0.098**	*0.002*
Volar arm	—	—	—	—	—	—	—	*0.031*	*0.035*	*0.000*
Deltoid	—	—	—	—	—	—	—	—	NS	*0.000*
Periumbilical	—	—	—	—	—	—	—	—	—	*0.000*
					Painfully hot					
Mean (levels)	20.88	21.63	21.31	21.13	21.13	21.81	20.25	21.25	20.88	19.88
SD	1.69	0.83	1.31	1.41	1.30	1.44	2.12	1.98	1.60	2.52
Dorsum, foot	—	NS	NS	NS	NS	**0.075**	NS	NS	NS	NS
Sole foot	—	—	NS	NS	NS	NS	NS	NS	NS	NS
L-5 leg	—	—	—	NS	NS	NS	NS	NS	NS	NS
L-4 leg	—	—	—	—	NS	NS	NS	NS	NS	NS
Thigh	—	—	—	—	—	NS	NS	NS	NS	NS
Dorsum, hand	—	—	—	—	—	—	*0.034*	NS	*0.035*	*0.040*
Volar arm	—	—	—	—	—	—	—	*0.019*	NS	NS
Deltoid	—	—	—	—	—	—	—	—	NS	*0.034*
Periumbilical	—	—	—	—	—	—	—	—	—	**0.090**

[*] Values presented in italic type are statistically significant (two-tail).

[†] Values presented in boldface type are statistically significant (one-tail).

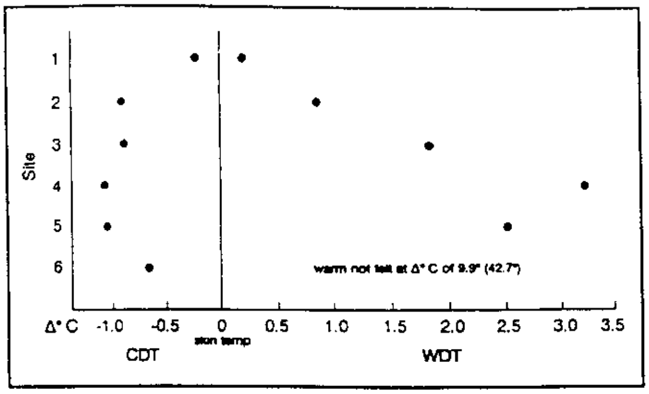

Figure 4. Cool (CDT) and warm (WDT) detection threshold at six anatomically distributed sites (1 = face, 2 = volar forearm, 3 = dorsal hand, 4 = periumbilical, 5 = lateral leg, and 6 = dorsal foot) in a representative 64-year-old healthy man. For both CDT and WDT, the lowest Δ°C (from skin temperature) threshold values are for the face. Especially for WDT, intermediate values are found for upper limb, trunk, and proximal lower limb. For the foot (site 6), a WDT could not be obtained; the first sensation experienced was that of heat-pain. The greater variability of WDT as compared with CDT or HPDT over the surface of the body is explained by the low density of warm receptors, especially over the feet and legs of older persons.

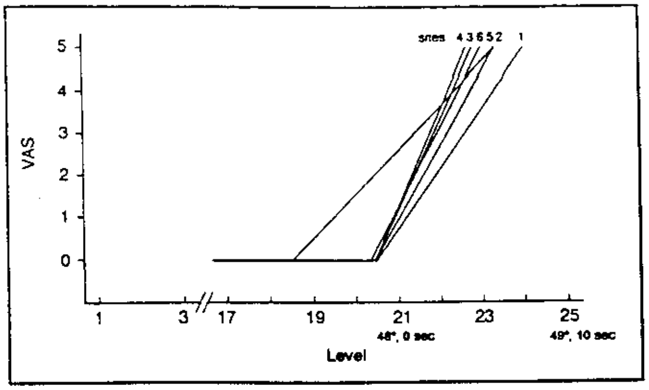

Figure 5. Visual analogue assessment (VAS) of the degree of pain (1 = least and 10 = most) from presentation of heat pulses of defined intensity to six anatomic regions (the sites are given in figure 4) in a 64-year-old healthy subject. Whereas a lowest degree (scale 1) of discomfort was identified from stimuli at levels 18 to 20, scale 5 discomfort was identified at levels 23 to 24. The stimulus at level 23 achieves a temperature of 48 °C and is held for 5 seconds; at level 24, 48 °C is held for 10 seconds. 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.

In table 3, we show statistically significant differences between threshold of warmth (or heat-pain) of the foot and other anatomic sites. Similar tables were prepared for hot and uncomfortably hot, and are available on request. These results indicate that thresholds are different among sites. Statistically significant differences in warm, hot, uncomfortably hot, and painfully hot thresholds were not found in the dorsal hand and dorsal foot of eight healthy persons (table on request). Furthermore, the results show that there is more variation among sites for WDT than for HPDT.

Visual analogue scale (1 to 10) assessment of pain stimuli. Subjects were asked to grade pain from 1 (least) to 10 (most severe) from heat-pain stimuli. In figure 5, we show the responses for six sites in one patient. It appeared that the steps of stimulus intensity were appropriate for such studies.

Discussion. CDT, WDT, and HPDT may be used to detect disordered function or structure of a class of receptors and nerve fibers (small myelinated and unmyelinated sensory fibers) not adequately testable in the EMG examination.[11,12] A variety of approaches, instruments, and systems have been described and used to assess thermal sensations.[13-19] QST has not been as broadly used in neurologic practice as it perhaps should have been, in part because adequately designed systems were not commercially available, standard quantified stimuli were not used, and testing methods were not adequately standardized. Comparison among medical centers was not generally possible. Now that improved systems are becoming available and standardized tests are available, the use of QST in neurologic practice can be defended because these tests actually measure sensory loss—a neurologic complaint of patients. We have previously published information on sensitivity, specificity, accuracy, and reproducibility of detection thresholds measured by computer-assisted sensory examination (CASE III or IV) in community diabetics with and without neuropathy.[8,20]

The present study addresses the broad issue of how to assess CDT, WDT, and HPDT using quantitative psychophysical approaches. As we previously found for VDT, so also for CDT and WDT (or HPDT): use of linearly or exponentially increasing ramps to the point that cold or warmth is felt (appearance threshold) consistently overestimates threshold when rapid thermal changes are used in testing. Very slow linear or exponential thermal ramps give acceptable results as compared with estimates from forced-choice algorithms, but considerable time is needed for insensitive sites or patients. One could argue that the use of the mean of the appearance and disappearance thresholds (Békésy) would result in an approximately equal overestimate in both directions and thus provide a good estimate of threshold. In fact, we found this approach to be impractical, especially for insensitive sites or persons, because too frequently appearance thresholds are not registered and threshold cannot therefore be estimated. There are other problems with the use of ramps whose increase is stopped when the subject or patient depresses a response key. The time needed to make a decision is quite variable among patients, with some responding quickly while other, more deliberate, persons may wish to take more time. Furthermore, patients with neurologic disease may not be able to respond quickly. Such slow responses spuriously elevate thresholds.

By contrast, algorithms that utilize defined levels of stimulus magnitudes distributed in steps over a broad range perform well and are appropriate for use in several algorithms (eg, forced-choice and the 4, 2, and 1 stepping algorithm). Use of defined stimulus levels allows one to repeat the test at a given stimulus magnitude and, depending on response, to step to a higher or lower level. The subject or patient can be given whatever time is needed to make a judgment. The only disadvantage of defined steps of stimulus intensity is that sophisticated systems are needed to provide the discrete steps of stimulus intensity needed. It is also more complex to ensure accurate calibration of waveform and its magnitude. On the other hand, as we have shown, this degree of sophistication is now possible.

We find that the pyramidal or flat-topped pyramidal waveform of thermal change is ideal for the assessment of CDT, WDT, or HPDT, using 25 steps of increasing stimulus magnitude and a computer-assisted sensory examination system such as CASE IV. The active physiologic component of the waveform is the initial thermal change from skin temperature and not the return to skin temperature. A flat-topped pyramidal stimulus provides a greater stimulus than does a pyramidal waveform. In testing near the threshold level, only the initial direction of thermal change from baseline is felt. This observation is also supported by single-unit electrophysiologic recordings: trains of impulses are associated with the initial thermal change but not with the return of temperature to baseline.[21] Among the algorithms tested, the forced-choice algorithm is theoretically the preferred one because it has the least subject and observer bias, and it has been validated extensively. Its two disadvantages are that it is time-consuming, and it probably should not be used to test heat nociception because repeated testing in the nociceptive range is not well tolerated and threshold may alter with repeated testing.

Although we did not study algorithms in which the temperature of the thermodes changes from the perception of cold to warm or hot or heat-pain and does this repeatedly, we believe there are compelling reasons not to use such algorithms. First, the fast linear ramps employed overestimate threshold. Second, the algorithm does not allow separation of coolness from warmth or from heat-pain thresholds. There is considerable evidence that there are separate receptors and fibers for CDT, WDT, and HPDT.[4]

Our study also addresses the practical issues of thermode surface area, ramp rates, and ranges of temperature that should be used to assess CDT, WDT, and HPDT. In the small group of subjects studied, statistically significant differences in thresholds were found among sites, between thermode sizes, and among thermal ramps. This underscores what we have found in our previous studies, that normative data must be available for the modality, specific test of threshold, site, age, and sex.

In eight healthy subjects, we found quite striking differences in WDT among topographically distributed sites over the body but much less difference for CDT or HPDT. This is of both theoretical and practical interest. It seems likely that this variability relates to the low and variable distribution of warm receptors as compared with the denser and more generalized distribution of cold and pain receptors.[4] The low density of warm spots was extensively documented by early investigators[21,22] and supported much later by single-unit recordings.[22,24-27] Even normal subjects may experience a slight burning discomfort without having felt any warm sensation at some sites such as the foot, leg, or hand. Because of the low density of warm receptors at some sites, estimating WDT may not be as useful as estimating CDT or HPDT in detecting neuropathy because threshold values may be quite variable in control subjects.

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