Sensory functions in chronic neuralgia

ULF LINDBLOM AND RONALD T. VERRILLO

From the Department of Neurology, Huddinge University Hospital, Huddinge, Sweden

SUMMARY Eleven patients with sustained neuralgia, in most cases after traumatic nerve lesion, were subjected to quantitative sensory testing with thermal and non-noxious mechanical stimuli. Measurements were made in the pain area and at a homologous site on the contralateral normal side. All patients were hypoaesthetic with raised thresholds for warm and cold or touch, or both. Thermal pain thresholds were also raised in some patients but lowered in others indicating hypersensitivity of the nociceptor system or dysaesthesia for thermal input. In six patients single mechanical stimuli produced a painful response above the touch detection threshold. Reaction time measurements indicated that this painful response was the result of a central dysfunction rather than of peripheral sensitisation. The response to suprathreshold mechanical pulses was measured by magnitude estimation as a function of stimulus amplitude. The results were fitted by power functions, as in normal skin, but with steeper slopes on the abnormal side. Suprathreshold hyperaesthesia (recruitment) may exist in the presence of normal threshold functioning.

The symptom of neuralgia which is the centre of concern for both the patient and the physician is, of course, the pain itself. Of secondary importance is the hyperalgesia and other sensory abnormalities which often occur in the painful area. Hyperalgesia literally indicates exaggerated pain, and usually includes both abnormally strong pain on noxious stimulation, such as pinch or heat, and painful responses to tactile or non-noxious thermal stimulation. The skin of the painful area may also be hyposensitive to one or more types of stimuli with raised perception thresholds and reduced sensation on suprathreshold stimulation. This hypoaesthesia, which can occur together with hyperalgesia, is usually taken as a sign of denervation of the afferent pathway.

The sensory abnormalities of neuralgic patients are often still more complex and consist of, in addition to the features already mentioned, loss of identification and localisation of stimulus, radiation of sensation, abnormal temporal summation, and after-sensations. This state, which is called hyperpathia after Foerster (1927), has been subject to much speculation about the underlying mechanism or mechanisms. Since it is difficult to imitate in animals, one has to build on what can

be observed and measured on patients and extrapolate from experimental physiological data. Among conceivable peripheral mechanisms, which have been reviewed recently by Wall and Devor (1978), are receptor sensitisation, multiplication of afferent discharges at the site of the lesion in the nerve, and ectopic impulse generation. These mechanisms are certainly operative in conditions such as skin burn and acute nerve compression. Regenerated nerve fibres with heterotypic receptor connections or pathological excitability are possible mechanisms for chronic sensory abnormalities (Trotter and Davies, 1909; Weddell *et al.*, 1948; Wall and Gutnick, 1974; Dickhaus *et al.*, 1976; Ochoa, 1977). They may account both for spontaneous pain and for some components of the hyperpathic syndrome—for example, hyperalgesia. Other features, such as radiation of sensation, seem to presuppose central mechanisms. These could be imbalance of the afferent inflow (Foerster, 1927; Zotterman, 1939; Noordenbos, 1959; Melzack and Wall, 1965), denervation hyperactivity of interneurons (Anderson *et al.*, 1971; Sunderland, 1976), central “irritation” or disinhibition (Livingstone, 1943; Melzack, 1971; Denny-Brown *et al.*, 1973).

In the search for the mechanisms of chronic neuralgias, as well as for improved therapeutic tools, it may be as important to study the sensory abnormalities as the pain itself. The primary aim

Address for reprint requests: Dr Ulf Lindblom, Department of Neurology, Huddinge University Hospital, Huddinge S-14186, Sweden.

Accepted 6 November 1978

of the present study was to examine the sensory functions in chronic neuralgia with precise methods, and to describe some of the abnormalities quantitatively as a basis for further studies of the pathophysiology. Detection thresholds for touch, cold, warmth, and thermal pain were determined, and sensations evoked by suprathreshold mechanical stimulation were quantified. Reaction time measurements were made to determine if pain resulting from tactile stimulation is the result of peripheral sensitisation of the nociceptive apparatus or of a central dysfunction.

Patients and methods

The basic data on the patients are summarised in Table 1. Trauma was the single known aetiological factor in eight cases. In case 1 the trauma was a neurotomy that had been performed because of a common trigeminal neuralgia. After the neurotomy the original neuralgia was replaced by a continuous burning pain with hyperpathia. In case 2 the lateral cutaneous rami of the caudal intercostal nerves were cut or crushed in an emergency renal operation. In case 3 trauma in the form of neurotomy was a contributory cause. It was performed because of a neuralgia which was supposed to be due to entrapment of the genitofemoral and lateral femoral cutaneous nerves, but the neuralgic condition was worsened instead of improved. In case 5 the neuralgia occurred immediately after an intramuscular injection which apparently happened to injure the lateral femoral cutaneous nerve. In case 10 a

peripheral nerve injury was not documented. The patient underwent operation on the day of the fracture with screw and cerclage fixation. The pain appeared when the effect of the anaesthetic subsided. There was no evidence of nerve injury at the operation. After three weeks there was a wound infection which healed after antibiotic therapy. When the final cast was removed, a sensory loss with patchy hyperpathia was found which covered the whole foot, except for the medial aspect, and extended laterally over the lower third of the lower leg. The distribution of the sensory loss was not compatible with a particular peripheral nerve lesion. Conduction velocities of the peroneal and sural nerves were within normal limits. On the other hand, the sensory loss remained and did not vary as a hysterical one. In case 11 the neuralgia and sensory abnormalities were confined to the lateral border of the foot. Because of the irradiating character of the pain and associated backache, myelography and laminectomy were performed without pathological findings. Neurography of the sural nerve showed normal action potential amplitude and conduction velocity.

The mean age of the patients was 47.2 years, and the median age 46.0 years with a range of 35 to 61 years. The mean and median duration of pain were 7.1 and 4.0 years respectively with a range from one to 24 years. The pain region was on the right side in six patients and on the left in five.

Before quantitative sensory testing, routine neurological interview and examination were con-

Table 1 Summary of details of patients studied

Case	Sex	Age (yr)	Pain region	Injured nerve(s)	Aetiology	Duration of pain (yr)	Principal type(s) of pain
1	F	61	Face	Infraorbital	Trauma (neurotomy)	2	Burning Throbbing
2	F	45	Lumbar Abdomen	Intercostal	Trauma (neurotomy)	2	Aching
3	F	46	Abdomen Thigh	Genitofemoral Lateral femoral	Entrapment + trauma (neurotomy)	20	Aching
4	F	47	Thigh	Iliohypogastric Lateral femoral	Trauma (childbirth)	24	Aching Burning
5	F	40	Thigh	Lateral femoral	Trauma (injection)	2	Aching
6	F	43	Knee	Saphenous	Entrapment	4	Aching Burning
7	F	54	Knee	Saphenous	Trauma (car accident)	5	Aching Stabbing
8	F	56	Lower leg Foot	Sciatic	Trauma (car accident)	10	Aching Burning
9	F	54	Foot	Sural	Trauma (malleolar fracture)	4	Burning Throbbing
10	F	35	Foot	Undetermined	Trauma (malleolar fracture)	1	Aching Shooting
11	M	38	Foot	Undetermined	Unknown	4	Burning Aching

ducted on each patient to ascertain the nature and extent of the pain and to determine the gross sensory characteristics of the skin in the painful area. On the basis of this examination, sites and precise procedures were selected for further testing. The pain level was scored on a visual analogue scale before and repeatedly during and after the tests, and notes were made on the quality of pain and other sensations.

Sensory measurements were determined for two classes of physical stimuli—mechanical and thermal. Mechanical stimulation was provided by two techniques. The first consisted of single pulses delivered by a Brüel and Kjaer vibrator (model 4810). The displacement of the contactor was monitored by a capacitance meter whose output was displayed and measured on the grid of an oscilloscope. The displacement of the contactor was carefully calibrated to the output of the capacitance device by measuring the displacement optically under a microscope. The vibrator was driven by a wave-form generator (Wavetek 112) which provided single pulses with a half sinusoidal wave form at 50 Hz. The contactor was plexiglass with a round, flat surface having a diameter of 2 mm and an area of 0.03 cm². It was centred within a rigid surround with a gap of less than 1.0 mm between the contactor and the edge of the surround. This prevented the spread of the mechanical disturbance over the surface of the skin. The pulses were triggered manually by the experimenter, and the patient responded by pressing a button which operated a light whenever the stimulus was perceived. A modified method of limits was used for threshold measurements in which a 75% criterion was accepted for “yes” and “no” responses. A displacement value of 50% of the difference between these measurements was used as the threshold of detection. The patient was seated comfortably in a reclining examination chair in a position where none of the equipment was within view (for further details of the stimulation technique, see Lindblom, 1974).

With this method measurements were made of touch detection thresholds, pain thresholds when the mechanical pulses could elicit pain, and reaction times to both touch and pain. Reaction times were measured using a precision electronic timer activated by the onset of the stimulus and stopped by a switch pressed by the patient as soon as the stimulus was perceived. The median value of seven trials was taken as reaction time. The intensity of the stimulus was preset at approximately twice the detection threshold for all reaction time measurements. Psychophysical intensity functions were determined with magnitude estimation of

randomly applied suprathreshold pulses ranging from 30 to 70 dB which was the maximum output of the stimulator.

The second method used for mechanical stimulation was a standard set of von Frey hairs calibrated independently by two people in the laboratory. Thresholds at the 50% level of detection for touch and pain were determined.

Measurements of thermal sensitivity were made using the Marstock apparatus (Fruhstorfer *et al.*, 1976b). It consists of a stimulator constructed of elements operating on the Peltier principle bonded to a metal block perfused with circulating water at 30°C. It has a surface area of 1250 mm² (25 × 50 mm) in contact with the skin. The temperature at the surface of the skin was measured by a thermocouple bonded to the centre of the contact area and recorded by a pen recorder which functions like the Békésy automatic recording attenuator (Békésy, 1947). Before testing, the skin temperature was measured at the test site in the painful area and in the homologous contralateral skin area by means of a digital-readout thermocouple device.

After the stimulator was situated and taped in place on the desired site of the skin, the patient was instructed to depress a hand switch immediately upon feeling warm or, alternatively, cold sensations. Switching changes the direction of current flow within the stimulator and consequently the temperature at the surface. The temperature at the skin surface under the stimulator caused by the alternate switching by the patient is automatically recorded on a moving chart. The threshold of detection is defined as the median temperature of the warm and cold excursion limits of the pen. Approximately one to two minutes of recording time was used to establish each threshold. The difference between the warm and cold thresholds—that is, the neutral zone—was also recorded, since an expanded neutral zone has been shown to be a characteristic of neural pathology (Fruhstorfer *et al.*, 1976a).

Measurements were also made of the cold pain threshold. The patients were instructed to allow the temperature to decrease until the sensation was painful before pressing the switch. When the temperature rose to within the neutral zone, the experimenter activated a switch which caused the temperature to drop again, and the subject repeated the procedure, usually three times. After this measurement, a corresponding procedure was repeated at high temperatures to establish a heat pain threshold. Heat pain tolerance levels were measured in five patients. For this measurement the patient was asked to press the switch only

when the heat pain became intolerable. The median temperatures of the switching points recorded by the pen were taken as the cold pain, heat pain, and heat pain tolerance levels.

Mechanical and thermal sensory measurements were determined for each patient in the pain area and also at a homologous site on the contralateral, normal side. Since thresholds can vary considerably at different body sites for both mechanical and thermal stimulation, the data are expressed both as raw scores and as different levels between the abnormal and normal sides of the body (abnormal side minus normal side). This permits an evaluation of the effect of the dysfunction compared with a normal, homologous site independent of the various areas tested on different patients. The results are expressed as mean values. Measurements were often repeated to gather data for different phases of the study and to provide checks on previously obtained data. In order to insure comparability across patients, data from initial test sessions only are reported. All patients were examined at least twice over a period of six to 12 months.

Results

GENERAL CLINICAL DESCRIPTION

The pain was continuous in all cases except for one in which there were periods when it was intermittent. The pain was aggravated by physical activity, negative emotions, and environmental changes such as cold weather. The testing procedures produced an overall increase of 18%. The dominant quality of pain was aching, but most patients also experienced burning, stabbing, throbbing, shooting, radiating, tearing, or cramping pain together with the aching type or alternating with it (Table 1).

All patients reported that the painful area was numb, but that touch was unpleasant or painful, at least in certain patches. Temperatures in the range which ordinarily do not hurt were often painful and increased the resting pain. Several patients had found that firm pressure in or near the painful region temporarily reduced both pain and hypersensitivity.

Most patients avoided common analgesics because they had experienced more side effects than pain relief. Three were under controlled non-narcotic analgesic and sedative therapy and, at the time when they were tested, transcutaneous nerve stimulation (TNS) had been tried by all patients with varying results. Two had good pain relief and used it on a long-term basis. In three cases the pain was aggravated by TNS. Three patients

had dorsal column stimulators, which had good effect. One patient was treated with intermittent vibration or heat stimulation. Sympathetic blocks had been performed in four patients with only short-lasting effect. Azapetin (Ildar) reduced the pain in at least three patients, but side effects hindered sustained medication.

On conventional neurological screening examination, the camel-hair brush and pinprick were felt as either numb, unpleasant, or painful. The hypersensitivity had typically a patchy or spotty distribution, and the location of the sensitive spots could change somewhat over time (cf Noordenbos (1959), p. 9). In three patients touch was painful only on stroking which implies that substantial spatiotemporal summation was a prerequisite for eliciting pain. Even when the stimuli were not painful, the sensations were different from normal touch, pinprick, cold or warmth. The abnormal quality of the sensation was often associated with loss of recognition of the stimulus and usually with radiation. The sensation produced by a pointed stimulus then had an areal distribution and might radiate widely, even outside the region of pain and sensory skin changes. Most patients had a post-stimulation painful after-sensation of 30–60 seconds duration. These qualitative sensory changes will be referred to as dysaesthesia.

By analogy with the mechanical stimulation, the response to thermal stimulation yielded both hypo- and hyperphenomena as well as dysaesthesia. In some cases moderate cold or warmth, or both, was unpleasant or painful, or was felt stronger than on the normal side. Delay of sensation occurred but was not as conspicuous as in postherpetic neuralgia (Noordenbos, 1959).

The symptoms and the results of the screening examination clearly identified the sensory disturbances with the syndrome of hyperpathia. Some of the cases could be diagnosed as causalgia, either major (case 8) or minor (cases 1–7 and 9), but we prefer the descriptive term chronic neuralgia for all cases. Causalgia has been taken to denote partly different syndromes after traumatic nerve injury and is, therefore, an ambiguous diagnosis, unless it is specifically defined (Mitchell, 1872; Livingstone, 1943; Noordenbos, 1959; Richards, 1967). Furthermore, burning pain, which is the literal meaning of causalgia, was not a prominent or constant feature in our cases.

QUANTITATIVE SENSORY TESTING

Mean raw values and mean difference values are presented in the tables. Mean difference values were obtained by first subtracting the normal side measurement from that of the abnormal side for

each patient and then taking the mean of the differences. The means of the individual differences were evaluated using a *t* test for correlated means. Comparisons between the hypo- and hypersensitive groups were made using a *t* test for uncorrelated means. Probabilities are based on a two-tailed distribution.

THERMAL STIMULATION

The mean raw score values of thermal sensitivity measurements (in degrees Celsius) for the normal and abnormal sides of all patients are presented in Table 2. The table shows that there was virtually no difference between the two sides with respect to skin temperature which indicates that there was no sympathetic reflex dysfunction at the times when the examinations were made. By inspection, it also appears that values for the abnormal side relative to the normal side reflect a loss of sensitivity to warmth and cold with an expanded neutral zone. Differences between the two sides appear to be slight with respect to measurements of heat pain, cold pain, and heat pain tolerance levels.

Table 2 Mean values* of thermal measurements

Measure	Normal	Abnormal
Skin temperature	31.5°	31.3°
Warm	37.3°	40.3°
Cold	31.5°	27.0°
Neutral zone	5.4°	13.1°
Heat pain	44.4°	43.0°
Cold pain	16.5°	16.8°
Heat pain tolerance	46.7°	45.9°

*All values in °C.

The results shown in Table 3 are expressed as the means of the individual differences between the two sides. These values provide an indication of the effect of the neural pathology or dysfunction on thermal sensitivity. It is clear from an inspection of the *t* test and probability values that the effect is significant with regard to warm and cold thresholds and the expanded neutral zone on the abnormal side. There was no thermal pain

Table 3 Mean difference values* of thermal measurements

Measure	Δ abnormal-normal	df	t	P
Warm	+2.95°	10	2.81	<0.02
Cold	-4.45°	10	2.24	<0.05
Neutral zone	+7.73°	10	2.84	<0.02
Heat pain	-1.41°	10	1.05	<0.40
Cold pain	+0.32°	10	0.10	<0.90
Heat pain tolerance	-0.75°	5	0.58	<0.60

*All values in °C.

difference between normal and abnormal sides when the patients were treated as a single group. However, closer examination of the heat and cold pain measurements showed that the total sample was comprised of two distinct groups: one with a hypersensitivity to thermal pain and another that was hyposensitive. Hypersensitivity is expressed as lower temperatures to reach heat pain thresholds, and as raised temperatures for cold pain. Hyposensitivity is reflected by the converse result.

Figure 1 shows the record of a patient who showed hyposensitivity to thermal pain, and Fig. 2 shows the typical record of a patient from the hypersensitive group. The sensory anomalies with respect to thermal pain are clearly illustrated by these examples.

Note first the greater neutral zone (ΔT) on the abnormal sides of both patients. In Fig. 1, ΔT equals 15.5° on the abnormal side compared to 6.5° on the normal side. In Fig. 2, ΔT equals 8.5° on the abnormal side and 5.5° on the normal side.

The hyposensitive patient (Fig. 1) reached a cold pain threshold (CP) at 25° on the normal side, but did not feel pain on the abnormal side when the temperature had reached the lower limit (10°) of the record. The hypersensitive patient (Fig. 2) perceived 10.5° as painful on the normal side but on the abnormal side felt 24° to be painful. Heat pain (HP) was felt at 43° on the normal side by the hyposensitive patient (Fig. 1), but at a raised temperature of 48° on the abnormal side. The hypersensitive patient (Fig. 2), on the other hand, raised the temperature to 42.5° on the normal side, while on the abnormal side pain was experienced at 39°.

Figure 3 gives a graphic representation of the individual results showing the comparison of normal (left columns) and abnormal (right columns) sides, as well as the differences between the hypo- and hypersensitive groups. One patient (case 8) did not belong clearly in either group. The tops of the cross-hatched columns indicate the thresholds for heat pain; the bottoms are the warmth detection thresholds. The tops of the hatched columns indicate the cold detection thresholds; the bottoms are the thresholds for cold pain. The clear areas between warm and cold thresholds represent the neutral zones.

All hyposensitive patients are characterised by higher heat pain and lower cold pain thresholds on the abnormal side. The converse is true of the hypersensitive patients. In all patients except case 5 the neutral zone is expanded on the abnormal side.

Fig. 1 Typical Marstock record from the normal and abnormal foot of a hyposensitive patient. Skin temperature (ST) and thresholds for warmth (W), cold (C), heat pain (HP), and cold pain (CP) are indicated as well as the size of the neutral zone (ΔT). Diagonal slashes on the heat pain and cold pain traces indicate the direction of the temperature change was reversed by the experimenter. Note the raised heat pain threshold and the depressed cold pain threshold on the abnormal side. The expanded neutral zone on the abnormal side is characteristic of neural pathology.

Fig. 2 Typical Marstock record from the normal and abnormal lateral thigh of a hypersensitive patient. Symbols as in Fig. 1. Note that the heat pain threshold is depressed and the cold pain threshold raised. The expanded neutral zone is apparent on the thigh with neural pathology.

Fig. 3 Individual results of Marstock measurements for the hypo- and hypersensitive groups (case 8 did not fall clearly into either group). In each case the left bar is the result from the normal side and the right bar from the abnormal side. The tops of the crossed-hatched areas indicate heat pain thresholds; the bottoms are warmth thresholds. The upper limits of the hatched areas are cold thresholds and the lower limits are thresholds for cold pain. The clear intermediate regions indicate the limits of the neutral zone.

The hypo- and hypersensitive groups are compared in Table 4 with respect to their raw score values for heat and cold pain. The mean difference scores between abnormal and normal sides (Δ A–N) for the two groups are also shown in the Table. There were five patients in each group. The patient, case 8, who clearly belonged in neither group was omitted from this analysis. The results show a highly significant difference between the abnormal sides of the two groups for heat pain ($\Delta = +9.7^\circ$; $P < 0.001$) and cold pain ($\Delta = -14.8^\circ$; $P < 0.001$). The nonsignificant differences on the normal sides for heat pain ($\Delta = +1.3^\circ$; $P < 0.30$) and cold pain ($\Delta = +3.5^\circ$; $P < 0.40$) indicate that the abnormal side differences were associated with the nature of the neural pathologies of the two groups rather than

with an intrinsic characteristic of their thermal sensitivities.

The two groups are also clearly distinguishable from their mean difference scores (Δ A–N) for both heat and cold pain. Thus, the hypersensitive group was significantly more sensitive to heat pain ($\Delta = -5.7^\circ$; $P < 0.01$) and to cold pain ($\Delta = +10.7^\circ$; $P < 0.001$) on the abnormal side. The hyposensitive group shows a significant loss on the abnormal side to heat pain ($\Delta = +2.7^\circ$; $P < 0.02$), but the results are equivocal for cold pain ($\Delta = -7.6^\circ$; $P < 0.10$). Examination of the individual cold pain data revealed two patients (cases 3 and 11 in Fig. 3) who did not experience cold pain on either normal or abnormal side. It was our experience that a criterion for cold pain was more difficult for patients to establish than a

Table 4 Comparison of hypo- and hypersensitive groups. Mean values* of heat and cold pain

Measure	Side	Hypo	Hyper	Δ hypo–hyper	df	t	P
Heat pain	Abnormal	47.8°	38.1°	+9.7°	8	10.37	< 0.001
	Normal	45.1°	43.8°	+1.3°	8	1.24	< 0.30
	Δ (A–N)	+2.7°	–5.7°				
	df	4	4				
	t	4.32	6.99				
	P	< 0.02	< 0.01				
Cold pain	Abnormal	10.1°	24.9°	–14.8°	8	9.06	< 0.001
	Normal	17.7°	14.2°	+3.5°	8	0.96	< 0.40
	Δ (A–N)	–7.6°	+10.7°				
	df	4	4				
	t	2.40	10.89				
	P	< 0.10†	< 0.001				

*All values in °C.
†See text.

criterion for heat pain. It is possible that the lack of any measurable thresholds for cold pain in these two patients was the result of a difficulty in establishing a clear criterion for their purpose. If the data are assessed omitting these patients, the mean difference increases to -12.6° with $P<0.01$. None of the other values is affected by this procedure. It is likely, therefore, that there is a significant difference in the detection of cold pain between the normal and abnormal sides of the hyposensitive group.

Tests of significance were performed for all other thermal measurements comparing the hypo- and hypersensitive groups. In addition to the thermal pain measurements, the groups were different only with respect to the threshold for warmth (Δ hypo-hyper = 6.1; $t=2.36$; $P<0.05$; $df=8$). Thus, there were no significant differences between the groups with respect to cold threshold, ΔT , or heat pain tolerance levels.

Figure 4 gives a summary of the grouped results for the normal and abnormal sides. Comparison

is shown between the total group and the hyposensitive and hypersensitive subgroups, respectively. The lack of clear differences in all measurements on the normal side is obvious. The deviations between groups as described above are conspicuous in the illustration of the abnormal side.

A further comment should be made about the heat pain tolerance measurements. The total group showed very little difference in heat pain tolerance between the normal and abnormal sides (-0.75° ; Table 3). However, when they were divided according to heat pain thresholds, the three patients of the hypersensitive group, whose heat pain tolerance was tested, measured 2.5° lower on the abnormal side with respect to the normal side. The corresponding figure for the hyposensitive group was $+2.3^{\circ}$. The tolerance levels for the hyper- and hyposensitive groups were 43.8° and 48.8° respectively on the abnormal side. On the normal side the thresholds were virtually the same (hyper = 46.3° ; hypo = 46.5°). Although none of these differences reached statistical significance, they do indicate that further tests should be made using a larger number of patients in both groups. Such tests might reveal an important diagnostic indicator which could be overlooked on the basis of our small sample.

Repeated testing, which was made at least twice on each patient over a period of six to 12 months, showed a remarkable similarity. There might be quantitative variations, but the type of sensory abnormality—for example, hypo- or hyperaesthesia—was always the same. The resting pain was only a minor hindrance during the testing. With proper care of the patients, reassurance, pauses, and so on, they performed remarkably well and gave reproducible results. There was only one exception, patient 10, whose threshold was almost normal on one occasion when her pain and hyperpathia were temporarily blocked by vibration.

MECHANICAL STIMULATION

Table 5 shows the mean values of measurements made using displacement pulses delivered through the vibrator and those made using von Frey hairs. Thresholds are given in decibels referred to $1.0 \mu\text{m}$ of peak displacement of the pulses and in grams for measurements made with von Frey hairs.

It is apparent from examination of Table 5 that the patients were less sensitive to mechanical stimulation on their abnormal sides. The reaction time to touch also appeared to be longer on the abnormal side.

Fig. 4 Mean results of Marstock measurements from the normal and abnormal sides of the total, the hyposensitive, and the hypersensitive groups. The bars are explained in Fig. 3. Note the small differences between the groups on the normal side as contrasted with the same measurements on the abnormal side. An expanded neutral zone (clear areas) is evidenced on the abnormal side of all three groups.

Table 5 Mean values of tactile measurements

Stimulus	Measure	Normal	Abnormal
Pulse	Touch threshold	41.2 dB	50.9 dB
	Touch reaction time	0.29 s	0.37 s
	Pain threshold		60.6 dB
	Pain reaction time		0.48 s
von Frey	Touch threshold	0.43 g	1.06 g
	Pain threshold		3.7 g

Decibel values re 1.0 μ m of peak displacement.

When the pulse amplitude was successively increased above the detection threshold, a new threshold was reached in six patients for whom the pulse produced a painful instead of a tactile sensation. The average stimulus strength at which this occurred was 60.6 dB as compared to 50.9 dB for the touch threshold. As is also shown in Table 5, the reaction time to the painful response was slightly longer. Pain could not be elicited on the normal side of any patient by the method of pulse stimulation.

The values for touch shown in Table 6 express the mean differences of individual measurements on the normal side subtracted from those obtained on the abnormal side. The latter is shown to be significantly ($P < 0.01$) less sensitive to displacement pulses than the normal side. Although measurements made with von Frey hairs yielded results in the same direction, the difference was not significant ($P < 0.10$). The individual data for touch detection thresholds were plotted against the pain ratings from visual analogue scaling. There was no correlation between threshold elevation and pain intensity.

The difference in reaction time to pulses between normal and abnormal side was significant ($P < 0.05$) but not the difference ($+0.17$ s) between the reaction times to touch and pain on the abnormal side ($df = 3$; $t = 2.07$; $P < 0.20$).

Because the heat and cold pain measurements revealed two distinct groups, one hypo- and the other hypersensitive, we decided to examine the mechanical stimulation data according to the same division of patients in order to determine if

Table 6 Mean difference values of tactile measurements

Touch					
Stimulus	Measure	Abnormal-normal	df	t	P
Pulse	Threshold	+9.7 dB	10	3.40	<0.01
	Reaction time	+0.08 s	8	2.30	<0.05
von Frey	Threshold	+0.63 g	8	2.16	<0.10

Decibel value re 1.0 μ m of peak displacement.

a similar separation could be made on the basis of their responses to mechanical stimulation. Although differences between the two groups on their abnormal sides were generally in the direction of greater sensitivity for the hypersensitive group, the differences can be accepted only at very low levels of confidence. Thus, patients who are hypo- or hypersensitive with respect to thermal pain could not be identified on the basis of their responses to mechanical stimulation.

We noted during both the clinical and experimental testing that, although the detection threshold for mechanical stimulation was raised, the patient often reported that suprathreshold stimulation felt stronger on the abnormal side. This observation is consistent with clinical reports of "over-reaction" as well as research evidence that steeper intensity functions, commonly referred to as "recruitment," can accompany neural pathology in various sense modalities (Barlow, 1976; Franzén and Lindblom, 1976; Hallpike, 1976). A state of hypersensitivity or hyperaesthesia stands out as an essential feature of the sensory abnormalities which are associated with many neuralgias. To obtain a measure of the suprathreshold hyperaesthesia, we decided to determine the intensity functions using the mechanical pulses and the method of subjective magnitude estimation. This was made on four patients who had indicated hyperaesthesia (but not pain) for mechanical pulse stimulation. After determination of the detection threshold for single pulses, a series of suprathreshold stimuli of different intensities was presented in random order. After three presentations of each intensity, the patients were asked to assign a number which they thought represented the subjective intensity of the sensation. In order to eliminate bias in the slope values (Stevens, 1956; Hellman and Zwislöcki, 1961), no standard or modulus was given, nor was a range of numbers suggested. Each intensity was judged twice on both the normal and abnormal sides. The numbers assigned were then averaged for the two trials and plotted as a function of the physical intensity of the stimulus in decibels referred to 1.0 μ m of peak displacement. Note that the slopes of the subjective intensity curves have been computed in terms of intensity rather than amplitude of displacement. This practice is recommended for several reasons. Research in several sense modalities has shown that near the threshold of detectability there is a direct proportionality between the intensity of the stimulus and neural activity (Zwislöcki, 1974). In addition, the use of intensity values permits direct comparisons between sense modalities since intensity may be

used across all systems, whereas amplitude of displacement is limited to mechanoreceptive systems. Direct comparison of our slopes with studies which report amplitude values may be made by halving the amplitude slope values.

Graded intensity functions were obtained from both sides of all patients, and the results from two are illustrated in Fig. 5. The data in Fig. 5A are from a patient with a moderately raised threshold. The curve from the abnormal side (filled circles) is similar to that from the intact side (open circles) but is steeper and converges at the level of maximum stimulus strength. The curves from the other three patients consistently showed a more rapid growth of sensation on the abnormal side. In addition, although they showed less threshold sensitivity on the abnormal side, they demonstrated hyperaesthesia in terms of increased subjective magnitude at most stimulus strengths. The average slope of subjective magnitude for all patients was 0.51 on the normal side as compared to 0.80 on the abnormal side. Figure 5B illustrates an example of unimpaired threshold response, which is the same on both sides, but a

much more rapid growth of sensation on the abnormal side (closed circles).

Discussion

HYPOAESTHESIA

Hypoaesthesia as measured by means of conventional bedside tests like touch, pinprick, and warm and cold water has long been recognised as one of the sensory abnormalities in neuralgia associated with lesions of peripheral nerves (Mitchell, 1872; Noordenbos, 1959; and others). With recently developed quantitative methods, sensory abnormalities can be assessed with higher accuracy and graded more exactly (Dyck, 1975; Lindblom and Meyerson, 1975; Fruhstorfer *et al.*, 1976b; Goldberg and Lindblom, unpublished). The methods used in the present study enable selective measurement of passive touch, temperature, and thermal sensations. Hypoaesthesia in terms of a measurable increase in perception thresholds was found for both mechanical and thermal stimuli in practically all cases. This is in contrast to, for example, trigeminal neuralgia where the sensory

Fig. 5 Subjective intensity functions for mechanical pulses obtained by the method of magnitude estimation from two patients, one hyposensitive (A) and the other hypersensitive (B). In both cases the growth of sensation as a function of stimulus intensity is more rapid on the abnormal side even when the threshold for detection is the same for both sides (B). This illustrates that a disturbance of suprathreshold functioning may result from neural pathology although threshold sensitivity is normal.

functions are normal except for the trigger mechanism (Verrillo and Ecker, 1977). The present results also demonstrate that a low degree hypoaesthesia can be assessed even in the presence of spontaneous pain and hyperaesthesia. Using mechanical pulses it was confirmed that supra-threshold hypoaesthesia can be measured by means of magnitude estimation (Fig. 5A).

Hypoaesthesia is usually taken as a sign of denervation through the nerve lesion, and tactile and thermal loss indicate injury of coarse and fine nerve fibres, respectively (Dyck *et al.*, 1971). Histological studies in postherpetic neuralgia (Noordenbos, 1959) have revealed a preferential loss of large fibres which led to the assumption that pain may result from loss of inhibitory large fibre input. In the present study, as judged by the sensory tests, both large and fine fibre functions were impaired. There was no correlation between the degree of tactile hypoaesthesia and the intensity of the neuralgia. Considerable pain, as well as hyperaesthesia, occurred together with only minute changes of the tactile threshold. Thus, lack of large fibre afferent inhibition did not seem to be important for the development of the neuralgia in the cases studied.

Although hypoaesthesia most often can be taken as a sign of neural pathology, the diagnosis of a peripheral nerve lesion should preferably, as in most cases in this study, be based on other evidence than the result of sensory testing. One has to consider that a functional block at spinal or higher levels associated with the pain state may produce hypoaesthesia. Such a mechanism was seemingly operative in one of our patients (case 10) in whom evidence of a persistent peripheral nerve lesion was lacking. Considerably improved sensory functions were recorded on one occasion when she was temporarily relieved of her pain and typical hyperpathia by vibration. Otherwise the threshold changes were unrelated to the pain level, and it was repeatedly confirmed that they were not caused by distraction due to pain and paraesthesias.

HYPERAESTHESIA

Two measures of hyperaesthesia were obtained: one was decreased thresholds for thermal pain and the other augmented sensation on supra-threshold mechanical stimulation. Five patients showed decreased thermal pain thresholds, in most cases for both warm and cold stimuli (Fig. 3). Since the thresholds for warm and cold were raised simultaneously, the ranges of thermal sensation were compressed from both ends in this group. This indicates steeper intensity functions for both

warm and cold than on the normal side. In the hyposensitive group the ranges for warm and cold sensation were comparable on both sides (Fig. 4).

One possible explanation for the decreased thermal pain threshold would be sensitisation of the nociceptors for heat and cold pain. We would then be concerned with increased sensitivity of a normally nociceptive system, and the condition would best be described as thermal hyperalgesia, or noxious thermal hyperaesthesia. Another possibility is that the painful responses which were evoked by non-noxious warm and cold stimuli are mediated by warm and cold fibres. Recent reaction time measurements indicate this possibility (Fruhstorfer and Lindblom, unpublished). Discharges in such nerve fibres normally evoke thermal sensations. If they instead produce pain, we would be concerned with an abnormal quality of sensation. Dysaesthesia would then, as discussed below, be a more adequate description of these responses, which could be specified as painful thermal dysaesthesia. Goldscheider (1926), citing Schilder's (1913) observations on cold hyperaesthesia, has previously discussed the option of hypersensitivity of the thermal sense versus increased sensitivity of "pain points" to thermal stimulation.

Although three of the four patients we tested for sensation magnitude were hypoaesthetic at threshold on the abnormal side and one had equal thresholds on both sides, all of the magnitude estimates could be fitted by a power function with significantly higher slopes on the abnormal side (Fig. 5). This is consistent with similar measurements for hearing (reviewed by Hallpike, 1976), vision (Barlow, 1976), and touch (Franzén and Lindblom, 1976). The phenomenon of steepened sensation-magnitude functions associated with elevated thresholds is generally called "recruitment." The importance of testing at supra-threshold levels is underlined by the results illustrated in Fig. 5B which show that hyperaesthesia at suprathreshold levels of stimulation may exist in a patient with normal threshold. This phenomenon has been demonstrated in experimental hyperalgesia (Hardy *et al.*, 1952).

No theory has been advanced that will adequately explain the recruitment phenomenon in any sense modality. However, for vibro-tactile sensitivity it has been demonstrated that the slopes of functions in normal skin are inversely related to the sensitivity of the stimulated region (Békésy, 1957, 1959; Stevens, 1959; Verrillo and Chamberlain, 1972). Verrillo and Chamberlain (1972) demonstrated that the steeper growth rate in areas of reduced sensitivity is probably related to the

fewer number of neural units excited rather than to a reduced receptor density as proposed by Békésy (1957, 1959). This finding was later corroborated by Franzén and Lindblom (1976) on patients with peripheral nerve lesions. Thus, we may suggest that the increased slope of the subjective intensity function in patients with elevated thresholds is governed by a central integrating mechanism in which the "gain" is affected by the number of receptor inputs. An alternative explanation of the recruitment would be central disinhibition allowing transmission and perception of the mechanoreceptive discharges at a higher "gain." A third hypothesis would invoke an enhanced responsiveness in the individual primary afferent fibres. This mechanism would imply that the responsible mechanoreceptors have an abnormally high excitability as a result of the nerve lesion. It should be possible to test this hypothesis by performing percutaneous micro-neurography on patients and studying the characteristics of single afferent units.

DYSAESTHESIA

Dysaesthesia literally means "bad sensation" and the term would, therefore, denote various kinds of somatosensory disturbances including hyperpathia. Operationally, however, dysaesthesia refers more to qualitative than to quantitative changes and indicates an abnormal sensation which is more or less unpleasant because it is painful or unfamiliar. To the extent that the sensory abnormalities can be defined as hypo- and hyperaesthesia, as they are in this study, it seems appropriate to use these more descriptive terms and let dysaesthesia denote the array of primarily qualitative changes for which more precise words are not yet available. One such change which will be discussed here is the painful response to tactile stimulation which is usually called hyperalgesia.

It was confirmed in this study that the same mechanical stimuli never evoke a painful sensation in normal skin. We are thus concerned with an abnormal quality of sensation, painful instead of tactile, and it may be more appropriate to call the condition painful tactile dysaesthesia. This response was obtained in six patients, four of whom belonged to the thermally hypersensitive group. In all six cases the detection threshold was lower than that of the painful response. Thus, there was always a range, although it might be small, in which the mechanical stimuli below the pain threshold evoked only tactile sensations. These were both hyper- and dysaesthetic but their existence shows that the tactual sense was in some way retained.

We wanted to investigate the pathophysiological mechanism of the painful response to non-noxious mechanical pulses. The first step was to characterise the afferent pathway by reaction time measurements. The reaction time to the painful response was on average 0.48 s. This is clearly too short to allow for conduction in C fibres (Zotterman, 1933; Fruhstorfer, 1976). The times were longer than those to the tactile response evoked from contralateral normal skin. It is possible that the afferent pathway consists of A-delta nociceptive fibres with an abnormal excitability after regeneration, perhaps through heterotypic receptor connections. Such an arrangement would allow them to be fired by the non-noxious mechanical pulses. With retained central connections such fibres would then mediate painful sensations evoked by innocuous stimuli. However, outgrowing fibres have a remarkable ability to resume their normal function (Burgess and Horch, 1973), and the reaction times to the painful sensation were similar to the reaction times to the tactile responses evoked below the pain threshold. It is, therefore, most likely that the afferent pathway is the tactile fibres, and that the abnormal painful character of the sensation is due to central mechanisms. This is in agreement with the blocking experiment of Wallin *et al.* (1976) in a patient with hyperalgesia to touch and cold stimulation. The hyperalgesia disappeared simultaneously with the touch and cold sensation while the C fibres were still conducting. It is appealing to speculate that the convergent dorsal horn cells which respond to both low threshold mechanical and noxious stimulation are involved. These cells are a conspicuous and numerous population. They project to a large extent to higher levels but their exact physiological role is unknown. Normally, the cells are suppressed by a descending tonic inhibition (for references see Albe-Fessard and Fessard, 1975). If it is assumed that the cells are disinhibited in the pathological state of neuralgia, and that their activity can produce a sensation, this would have the character of the painful tactile dysaesthesia. Other components of the hyperpathic syndrome such as radiation of sensation and after-sensation may also be explained by disintegrated central inhibition. This is still a hypothesis, however, and direct evidence can probably only be obtained in experiments with chronic nerve lesions in animals. Clinical observations may give interesting information. For example, multiple sclerosis patients with demyelinating lesions involving the spinal grey matter may suffer from painful seizures (Shibasaki and Kuroiwa, 1974) which are evoked by tactile stimuli

and have a similar pattern of radiation and after-sensation as is seen in the neuralgia patients.

Some general comments may be made on the value of quantitative sensory testing in pain patients. Such testing can be a valuable aid in the diagnosis of a nerve lesion where conventional methods are too crude. Furthermore, the course of a disease can be followed by repeated measurements in the same patient. Wider application in the clinic will probably help to classify various painful and other sensory disturbances which are now grouped under various headings such as neuritis (Wartenberg, 1958). An important point is whether spontaneous pain and the sensory abnormalities, especially hyperalgesia, may have the same pathophysiology. If so, a further close study of the sensory dysfunction may provide evidence about pain mechanisms and perhaps contribute to the search for new and more affective remedies. On the other hand hyperpathia is often seen without spontaneous pain during nerve regeneration (Head *et al.*, 1905) and in patients with various neuropathies. The converse is also true, namely that pain may occur without disturbed sensation as in trigeminal neuralgia. Deductions about pain mechanisms from the characteristics of the sensory abnormalities should, therefore, be made with caution.

We are indebted to Dr Björn Meyerson and the Department of Neurosurgery, Karolinska Sjukhuset, for offering patients for study, and to Mrs Berit Lindblom for excellent technical assistance and patient care. The study was supported by the Swedish Medical Research Council (B77-14X-04256-04B) and Karolinska Institutets fonder and by grant NS-09940 from the National Institutes of Health, US Department of Health, Education, and Welfare.

References

- Albe-Fessard, D., and Fessard, A. (1975). Recent advances on the neurophysiological bases of pain sensation. *Acta Neurobiologica Experimentalis*, **35**, 715-740.
- Anderson, L. S., Black, R. G., Abraham, J., and Ward, A. A. (1971). Neuronal hyperactivity in experimental trigeminal deafferentation. *Journal of Neurosurgery*, **35**, 444-452.
- Barlow, R. B. (1976). Brightness sensation and pupil reflex in normals, rod monochromats and patients with retinitis pigmentosa. *Association for Research in Vision and Ophthalmology, Abstracts*.
- Békésy, G. von (1947). A new audiometer. *Acta Otolaryngologica*, **35**, 411-422.
- Békésy, G. von (1957). Neural volleys and the similarity between some sensations produced by tones and by skin vibrations. *Journal of the Acoustical Society of America*, **29**, 1059-1069.
- Békésy, G. von (1959). Neural funneling along the skin and between inner and outer hair cells of the cochlea. *Journal of the Acoustical Society of America*, **31**, 1236-1249.
- Burgess, P. R., and Horch, K. W. (1973). Specific regeneration of cutaneous fibers in the cat. *Journal of Neurophysiology*, **36**, 101-114.
- Denny-Brown, K., Kirk, E. J., and Yanagisawa, N. (1973). The tract of Lissauer in relation to sensory transmission in the dorsal horn of spinal cord in the Macaque monkey. *Journal of Comparative Neurology*, **151**, 175-200.
- Dickhaus, H., Zimmerman, M., and Zotterman, Y. (1976). The developments in regenerating cutaneous nerves of C-fiber receptors responding to noxious heating of the skin. In *Sensory Functions of the Skin in Primates*, pp. 415-423. Edited by Y. Zotterman. Pergamon Press: Oxford.
- Dyck, P. J., Lambert, E. H., and Nicholas, P. C. (1971). Quantitative measurement of sensation related to compound potential and number and sizes of myelinated and unmyelinated fibers of sural nerve in health, Friedreich's ataxia, hereditary sensory neuropathy, and tabes dorsalis. In *Handbook of Electroencephalography and Clinical Neurophysiology*, volume 9, pp. 83-118. Edited by W. A. Cobb. Elsevier: Amsterdam.
- Dyck, P. J. (1975). Quantitation of cutaneous sensation in man. In *Peripheral Neuropathy*, pp. 465-479. Edited by P. J. Dyck, P. K. Thomas, and E. H. Lambert. W. B. Saunders: Philadelphia.
- Foerster, O. (1927). *Die Leitungsbahnen des Schmerzgeföhle*. Urban and Schwarzenberg: Wien.
- Franzén, O., and Lindblom, U. (1976). Tactile intensity functions in patients with sutured peripheral nerve. In *Sensory Functions of the Skin in Primates*, pp. 113-118. Edited by Y. Zotterman. Pergamon Press: Oxford.
- Fruhstorfer, H. (1976). Conduction in the afferent thermal pathways of man. In *Sensory Functions of the Skin in Primates*, pp. 355-365. Edited by Y. Zotterman. Pergamon Press: Oxford.
- Fruhstorfer, H., Goldberg, J. M., Lindblom, U., and Schmidt, W. G. (1976a). Temperature sensitivity and pain thresholds in patients with peripheral neuropathy. In *Sensory Functions of the Skin in Primates*, pp. 507-517. Edited by Y. Zotterman. Pergamon Press: Oxford.
- Fruhstorfer, H., Lindblom, U., and Schmidt, W. G. (1976b). Method for quantitative estimation of thermal thresholds in patients. *Journal of Neurology, Neurosurgery, and Psychiatry*, **39**, 1071-1075.
- Goldscheider, A. (1926). Temperatursinn des Menschen. In *Handbuch der normalen und pathologischen Physiologie*, volume 11, pp. 161-164. Edited by A. Bethe, G. von Bergmann, G. Emden, and A. Ellinger. Springer-Verlag: Berlin.
- Hallpike, C. S. (1976). Sensori-neural deafness and derangements of the loudness function: their

- nature and clinical investigation. In *Handbook of Sensory Physiology, V/3. Auditory System*, pp. 1–35. Edited by W. D. Keidel and W. D. Neff. Springer-Verlag: Berlin.
- Hardy, J. D., Wolff, H. G., and Goodell, H. (1952). *Pain Sensations and Reactions*, pp. 173–215. Williams and Wilkins: Baltimore.
- Head, H., Rivers, W. H. R., and Sherren, J. (1905). The afferent nervous system from a new aspect. *Brain*, **28**, 99–115.
- Hellman, R. P., and Zwislocki, J. (1961). Some factors affecting the estimation of loudness. *Journal of the Acoustical Society of America*, **33**, 687–694.
- Lindblom, U. (1974). Touch perception threshold in human glabrous skin in terms of displacement amplitude on stimulation with single mechanical pulses. *Brain Research*, **82**, 205–210.
- Lindblom, U., and Meyerson, B. A. (1975). Influence on touch, vibration and cutaneous pain of dorsal column stimulation in man. *Pain*, **1**, 257–270.
- Livingstone, W. K. (1943). *Pain Mechanism*, pp. 100–113. Macmillan: New York.
- Melzack, R. (1971). Phantom limb pain: implications for treatment of pathologic pain. *Anesthesiology*, **35**, 409–419.
- Melzack, R., and Wall, P. D. (1965). Pain mechanisms: a new theory. *Science*, **150**, 971–979.
- Mitchell, S. W. (1872). *Injuries of Nerves and their Consequences*. J. B. Lippincott: Philadelphia.
- Noordenbos, W. (1959). *Pain*. Elsevier: New York.
- Ochoa, J. (1977). Neuralgia and hyperalgesia from local nerve lesions: pathophysiology. *Electroencephalography and Clinical Neurology*, **43**, 597.
- Richards, R. L. (1967). Causalgia. *Archives of Neurology (Chicago)*, **16**, 339–350.
- Schilder, P. (1913). Zur pathologischen Physiologie der Hautsinne. *Zeitschrift für die gesamte Neurologie und Psychiatrie*, **14**, 631–646.
- Shibasaki, H., and Kuroiwa, Y. (1974). Painful tonic seizure in multiple sclerosis. *Archives of Neurology (Chicago)*, **30**, 47–51.
- Stevens, S. S. (1956). The direct estimation of sensory magnitude loudness. *American Journal of Psychology*, **69**, 1–25.
- Stevens, S. S. (1959). Dynamics of sensory intensity. *Journal of Experimental Psychology*, **57**, 210–218.
- Sunderland, S. (1976). Pain mechanisms in causalgia. *Journal of Neurology, Neurosurgery, and Psychiatry*, **39**, 471–480.
- Trotter, W. B., and Davies, H. M. (1909). Experimental studies on the innervation of the skin. *Journal of Physiology*, **38**, 134–246.
- Verrillo, R. T., and Chamberlain, S. C. (1972). The effect of neural density and contractor surround on vibration sensation magnitude. *Perception and Psychophysics*, **11**, 117–120.
- Verrillo, R. T., and Ecker, A. D. (1977). Effects of root or nerve destruction on vibrotactile sensitivity in trigeminal neuralgia. *Pain*, **3**, 239–255.
- Wall, P. D., and Devor, M. (1978). Physiology of sensation after peripheral nerve injury, regeneration, and neuroma formation. In *Physiology and Pathobiology of Axons*, pp. 377–388. Edited by S. G. Waxman. Raven Press: New York.
- Wall, P. D., and Gutnik, M. (1974). Ongoing activity in peripheral nerves: the physiology and pharmacology of impulses originating from a neuroma. *Experimental Neurology*, **43**, 580–593.
- Wallin, G., Torebjörk, E., and Hallin, R. (1976). Preliminary observations on the pathophysiology of hyperalgesia in the causalgic pain syndrome. In *Sensory Functions of the Skin in Primates*, pp. 489–499. Edited by Y. Zotterman. Pergamon Press: Oxford.
- Wartenberg, M. D. (1958). *Neuritis, Sensory Neuritis, Neuralgia*. Oxford University Press: London.
- Weddell, G., Sinclair, D. C., and Feindel, W. H. (1948). An anatomical basis for alterations in quality of pain sensibility. *Journal of Neurophysiology*, **11**, 99–109.
- Zotterman, Y. (1933). Studies in the peripheral nervous mechanism of pain. *Acta Medica Scandinavica*, **80**, 1–64.
- Zotterman, Y. (1939). The nervous mechanism of touch and pain. *Acta Psychiatrica et Neurologica*, **14**, 91–97.
- Zwislocki, J. J. (1974). A power function for sensory receptors. In *Sensation and Measurement*, pp. 185–197. Edited by H. R. Moskowitz and B. Scharf. Reidel: Dordrecht and Boston.